University of Glasgow

Characteristics and consequences of antenatal exposure to selective serotonin reuptake inhibitors

Tom Everett Julyan

BSc MBChB DGM DRCOG MRCPsych PGDip(CBP)

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Abstract

Depression is a common condition, affecting around one in 20 people worldwide. It is challenging conceptually and clinically, with treatment being ineffective for many, and significant consequences for individuals and societies alike. Depression is particularly problematic during pregnancy, where it is no less common, but poses additional difficulties. Both depression and its pharmacological treatments are associated with a range of short- and longer-term sequelae for offspring, and current data is insufficient to allow fully informed decisions to be made by mothers, midwives, or doctors.

Research is affected by practical, ethical, and methodological issues, and a myriad of confounding factors, which combine to increase uncertainties over the risks and benefits of prescribing (or not). Retrospective and prospective observational studies accompany epidemiological data linkage and meta-analyses involving millions of subjects, in contributing to both current knowledge and testable hypotheses to inform future directions for research, while clinical and preclinical studies with smaller sample sizes provide invaluable and complementary details. However, significant gaps remain, not least in delivering optimal care to each individual mother and baby.

While the overall emerging picture appears reassuring to some, others acknowledge that we do not even possess all the pieces of the puzzle yet. There remains an urgent need for more comprehensive and relevant data. This thesis presents the findings from a series of pilot studies on evaluating the characteristics and consequences of antenatal exposure to selective serotonin reuptake inhibitors. Up to one in 10 women in the general Scottish population may be exposed to an antidepressant at some point during pregnancy, but adverse outcomes may be related more to underlying maternal depression, rather than its pharmacological treatment. We highlight areas of both intelligence and ignorance, and make proposals for future research.

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Preface

The various components of this project were presaged in August 2006, when my Supervisor, Professor Jonathan Cavanagh (then Senior Lecturer in Psychiatry at the University of Glasgow), invited the new Higher Trainees in Psychiatry (of which I was one) to speak to him if they were interested in research.

After doing so I agreed to process data on antenatal prescribing for patients receiving care via the local specialist Perinatal Mental Health Service, with a view to establishing baseline characteristics and informing clinical care. Through subsequent collaboration with various colleagues in the University of Glasgow and the University of Columbia, and in light of existing concerns about the potential sequelae of early exposure to pharmacological perturbation of serotonin-mediated processes, we progressed to imaging neonates via magnetic resonance, in an attempt to identify neurodevelopmental consequences of exposure to antenatal antidepressants, specifically selective serotonin reuptake inhibitors.

I registered as a doctoral student in October 2008, with the aim of completing the scanning as a pilot study. However, circumstances intervened (e.g. scanning was stopped in early 2012 by a change in local NHS services), and our pilot became a feasibility study instead. Concurrently we had been reanalysing the data on antenatal exposure to antidepressants in the specialist Perinatal Mental Health Service, and extended our methodology to a local general maternity service, thus allowing more representative characterisation of prescribing patterns in the population. We then expanded this work to include both a check on accuracy of our existing data, and to identify what data on early clinical outcomes could be established.

This thesis presents our findings.

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I wish to thank the following family, friends, and colleagues, without whom this thesis would remain incomplete:

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Dr Alison MacRae, my colleague, for providing cover during study leave;

And lastly, Sarah, my wife, for being longsuffering and gracious, especially through her illness.

Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Signature _____

Printed name Tom Everett Julyan

Definitions/abbreviations

ACOG	American College of Obstetricians and Gynecologists
AD	Antidepressant
ADD	actual delivery date, i.e. neonatal date of birth
AMU	Ayrshire Maternity Unit
AP	Antipsychotic
BadgerNet	neonatal electronic database
BDNF	brain-derived neurotrophic factor
BJOG	British Journal of Obstetrics and Gynaecology
CMHT	Community Mental Health Team
DOB	Date of birth
DSM	Diagnostic and Statistical Manual
DTI	diffusion tensor imaging
Eclipse	obstetric electronic health record and database
EDD	estimated delivery date (by ultrasound scan)
FACE	mental health electronic health record and database (Functional Analysis of Care Environments)
ICD	International Classification of Diseases

ISD	Information Services Division of NHS Scotland
MAOi	monoamine oxidase inhibitor
MHA	Mental Health (Care and Treatment) (Scotland) Act 2003
MLS	Maternity Liaison Service
MR	magnetic resonance
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MS	mood stabiliser
NAA	N-acetyl aspartate
NARI	noradrenaline reuptake inhibitor
NaSSA	noradrenergic and specific serotonergic antidepressant
NHS	National Health Service (UK)
NICE	National Institute for Health and Clinical Excellence
NNU	neonatal (special baby care) unit
PMHS	Perinatal Mental Health Service
RIMA	reversible inhibitor of monoamine oxidase A
RCOG	Royal College of Obstetricians and Gynaecologists
RCPsych	Royal College of Psychiatrists

SAMS	addictions electronic database
SBR	Scottish Birth Record
SERT	serotonin transporter
SGH	Southern General Hospital, Glasgow
SGHMU	SGH Maternity Unit
SIGN	Scottish Intercollegiate Guidelines Network
SSRI	selective serotonin reuptake inhibitor
T0	Preconception (variably defined in context)
T1	Trimester 1
T2	Trimester 2
T3	Trimester 3
T4	The postnatal period (variably defined in context)
TCA	tricyclic antidepressant
TOP	termination of pregnancy
UK	United Kingdom
USA	United States of America

Chapter 1 - Perinatal depression: An overview

"Depression is the cruelest disease in the world."

"Postpartum depression is a stunning example of its cruelty."

Phil Baumann

Depression is pandemic.

Recently described in *Nature* as "the biggest blight on human society — bar none", that "hits people with a double-whammy" of the suffering caused by the "agony of the symptoms", as well as "the way in which those symptoms interfere with how the person would otherwise like to live", depression remains under-diagnosed, under-treated, and stigmatised compared with other conditions, with treatment being underfunded (Nature, 2014; Smith, 2014). This is related to depressive disorders being poorly understood, and research underfunded, too, particularly in contrast with cancers (Ledford, 2014). At worst, depression has been perceived as lacking both validity as a medical diagnosis and effective treatments (attitudes not without empirical support), and has certainly lacked the level of advocacy witnessed in cancer (Hyman, 2014; Ledford, 2014). Comparisons with cancer are commonplace, with those who have suffered both making statements such as, "Depression is worse than cancer", and "I would rather have terminal cancer than depression", on the grounds that depression has no guaranteed end, friends and family withdraw rather than rally round, and one feels dead already, even while still alive (Goddard, 2008; lonesomeroad, 2014). Professor Lewis Wolpert famously described his experience of depression as a "dark destroyer", admitting with shame that, "It was the worst experience of my life. More terrible even than watching my wife die of cancer" (Wolpert, 1999; Wolpert, 2010).

According to the World Health Organization (WHO) (2012), depressive disorders are one of the leading direct causes of disability worldwide, and major contributors to the global burden of disease, including that attributable to ischaemic heart disease and suicide (WHO, 2012; Ferrari *et al.*, 2013). They are "responsible for more 'years lost' to disability than any other condition", due to both their prevalence and chronicity (Smith, 2014). Estimated to affect more than 350 million people internationally (~5% of the world's population), unipolar depression is associated with greater ill health than other major chronic diseases such as ischaemic heart disease and diabetes, and is projected to become the leading contributor to the global burden of disease by 2030 (Moussavi *et al.*, 2007; WHO, 2011). It is well established that women are affected disproportionately and, due to complex gene-environment interactions, are at around twice the risk of suffering depression than men (Kessler, 2003; Kendler *et al.*, 1995). Lépine and Briley (2011) provide a helpful review of the prevalence and consequences of depressive illness.

As a poorly understood complex acute and chronic brain condition, depression poses a multiplicity of challenges to researchers as well as sufferers and carers. Firstly, in addition to the practical problems associated with its prevalence and impact, depression is challenging conceptually. In the broadest sense depression is a ubiquitous human experience, such that it would be highly abnormal for anyone never to experience low mood, albeit usually appropriate to the external environment. There appears to be no satisfactory answer to the critical question, when does unhappiness become a clinical condition? In particular, context, psychopathology, pragmatism, and/or severity, cannot be used to determine thresholds or criteria for diagnosis, nor can response to treatment even demonstrate the validity or presence of depression as a diagnosable illness, as it appears that it is the minority of those with recurrent episodes who achieve remission as traditionally defined (Trivedi *et al.*, 2006; Parker, 2009; Maj, 2011). While the term "major depressive disorder" is frequently employed to signify a syndrome of sufficient severity to require clinical intervention, the word "depression" will be used hereafter to refer to all depressive experiences, both "major" and "minor", in light of the difficulties of more precise definition.

Depressive illness is formulated as a mental disorder characterised by dysthymia, anhedonia and anergia, with these core features being accompanied by a range of other psychological and physical problems (WHO, 1992; American Psychiatric Association, 2013). However, despite the term being used as if it is a well-circumscribed unitary phenomenon, it is acknowledged that depression is a neurocognitively-mediated clinical syndrome, a heterogeneous group of disorders associated with a complex array of biological, psychological and social factors, with unclear boundaries (Parker, 2000; Antonijevic, 2006; Horwitz & Wakefield, 2007). Depression is not simply a singular shared experience directly attributable to one discrete neuropathology, and therefore cannot be conceptualised in a reductionist manner. Some have pointed out that depression is analogous to other clinical phenomena with a range of aetiologies such as pain or fever, explaining why categorisation and treatment remain suboptimal (Parker, 2009; Ledford, 2014). Nevertheless, despite these challenges to elucidating the neurobiological correlates of depressive psychopathology for the purpose of identifying specific targeted therapies, safe, (broadly speaking) effective, and (reasonably) well-tolerated pharmacological interventions for treating major depressive disorder have been available for several decades; arguably, however, there have been no radical advances since the 1950s (Bauer *et al.*, 2002a; Bauer *et al.*, 2002b; Cleare *et al.*, 2015; Hyman, 2014).

Secondly, depression remains challenging clinically. Perhaps closely related to the underlying conceptual and aetiological uncertainties, acute depressive illness not infrequently progresses to recurrent and chronic depressive illness, accompanied by the phenomena of "kindling" and increasing treatment resistance, particularly in those with genetic risk factors and stressful life events (Kendler, Thornton & Gardner, 2000; Kendler, Thornton & Gardner 2001; Monroe & Harkness, 2005). It is well recognised that outcomes for patients can be poor, with perhaps less than 50% achieving sustained remission and recovery (Trivedi *et al.*, 2006; Pigott *et al.*, 2010). And, like other conditions, depression of any severity is associated with increased mortality, both directly via suicide, and indirectly via medical comorbidities (Miret *et al.*, 2013; Cuijpers *et al.*, 2013). It is significant to note that depression is known to place a disproportionate burden on those in the age range 15-44, i.e. women of childbearing potential (WHO,

2013). The usual morbidity and mortality of untreated depression are complicated in pregnancy by additional risks to the developing fetus such as intrauterine growth retardation, low birth weight, preterm delivery, and longer-term educational and neurocognitive difficulties (American College of Obstetricians & Gynaecologists [ACOG], 2008; Stein *et al.*, 2014).

And thirdly, depression is also challenging with regards to its costs to the individual sufferer, his or her family, health services, and society, in terms of personal identity and wellbeing, years lived with disability, care, healthcare interventions, and financial issues related to employment and benefits. Nowhere are these issues more apparent than when depression affects young women in the perinatal period, when the "double" becomes at least a "triple whammy", with immediate and longer term consequences on offspring, too (Centre for Maternal and Child Enquiries, 2011).

Perinatal mental health problems

Although traditionally thought of as protective against mental disorder (including suicide), pregnancy and in particular the postnatal period are now recognised to be associated with significant mental health problems, including psychotic, affective, and neurotic disorders (Oates, 2003). Postpartum psychosis, a condition that affects between one and two per thousand women, was described by Hippocrates almost 2,500 years ago, but it was not until the 19th century that Marcé published his classic treatise (Doyle, Carballedo & O'Keane, 2015). Over 100 years later Kendell *et al's* seminal study demonstrated a striking increase in the risk of admission to psychiatric hospital due to mental illnesses in the early puerperium, with the risk being greatest for psychotic illness, in primiparous women, in the first 30 postnatal days (relative risk 35.0) (Kendell *et al.*, 1987). These findings have recently been replicated, confirmed, and extended in Scotland, and similar admission patterns for non-psychotic major depression in perinatal women reported in Australia (Xu *et al.*, 2012; Langan Martin *et al.*, 2016).

Postnatal maternal admission to psychiatry is not the most concerning risk associated with perinatal mental illness, however. Suicide, although mercifully rare, is also a significant risk associated with perinatal mood disorders (Oates, 2003). Alongside several high profile tragedies involving acutely psychiatrically unwell mothers killing their infants along with themselves (e.g. Daksha Emson, a consultant psychiatrist with bipolar affective disorder), the recent heightened awareness of perinatal mental health issues was also driven by the serial Confidential Enquiries into Maternal and Child Health (CEMACH), now conducted via the Centre for Maternal and Child Enquiries (CMACE) (North East London Strategic Health Authority, 2003; Jones & Craddock, 2005). The CEMACH/CMACE reports identified suicide as the leading cause of maternal death during pregnancy and within the first postnatal year from the Fifth Report (covering 1997-99) until the Seventh Report (2003-5) (Lewis & Drife [eds], 2001; Lewis [ed], 2004; Lewis [ed], 2007) (Table 1-1). These findings were based on careful analyses of data not hitherto included in such projects, and included deaths up to one year postpartum, taking account of so-called late maternal deaths, including those due to indirect (psychiatric) causes. The reports made and precipitated numerous recommendations regarding the provision of specialist services for women suffering from mental illnesses in the perinatal period, including the National Institute for Health and Clinical Excellence (NICE), the Royal College of Obstetricians and Gynaecologists (RCOG), and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines. (NICE CG45, 2007 [updated 2014]); RCOG, 2011; SIGN, 2012). Perinatal mental health care, including via mother and baby units, became a national priority in Scotland, enshrined in the Mental Health (Care and Treatment) (Scotland) Act (MHA) 2003 (Lewis [ed], 2004). In particular, Scottish Health Boards became obligated to provide mothers of children less than one year old who require inpatient care "such services and accommodation as are necessary to ensure that the woman is able, if she wishes, to care for the child in hospital" (so long as this "is not likely to endanger the health or welfare of the child"), whether detained or not (MHA, 2003 p14: Part 4, Chapter 1, S24). Given that psychiatric admissions in the puerperium are likely to be required soon after delivery (especially for puerperal psychosis, which peaks within the first postnatal week), that separating babies from their primary care-giver is likely to adversely affect attachment, and that

such separation may well feed in to any persecutory maternal delusions, it is desirable that mothers can continue to care for their infants as much as possible.

Table 1-1 – Maternal death rates and suicides

	Maternal mortality		Suicides	
	Rate per 100,000 maternities[1]	(N)	Rate per 100,000 maternities	(N)
2000-2	13.07	(261)	1.10	(22)
2003-5	13.95	(295)	0.95	(20)
2006-8	11.39	(261)	1.27	(29)

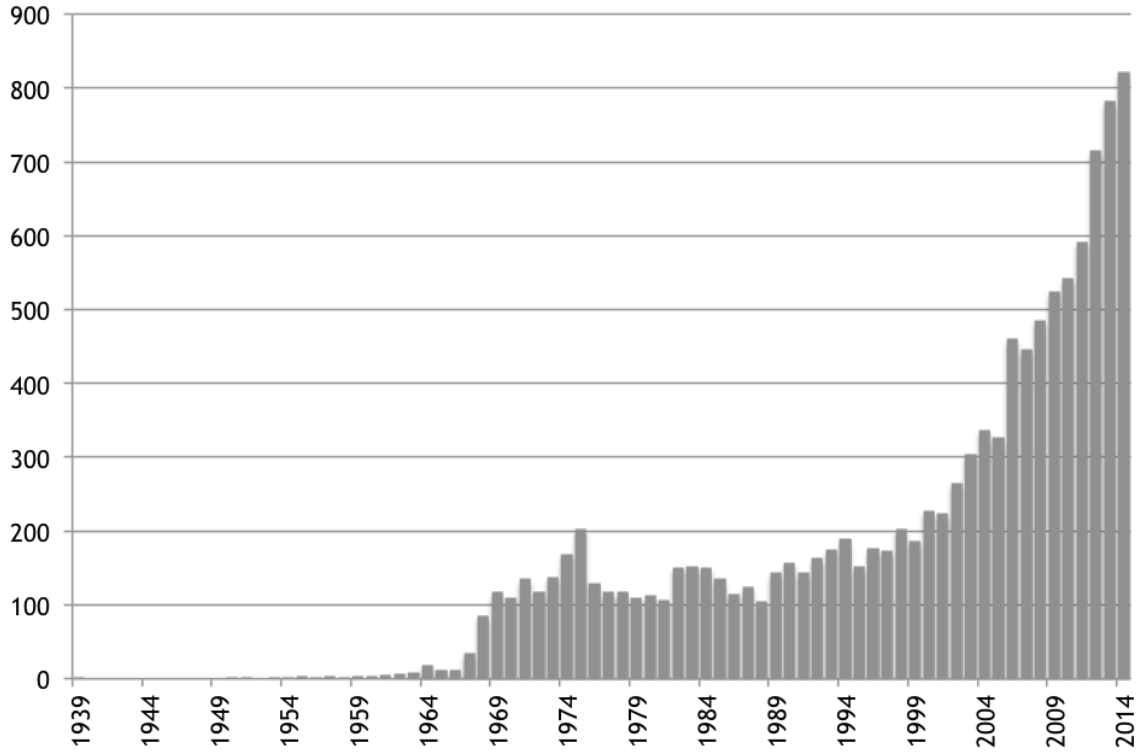
[1] Direct and indirect causes combined

However, despite the seriousness of postpartum psychosis, perinatal depression may be considered to pose equal if not greater problems, in terms of both prevalence and potential sequelae for mothers and progeny. Moreover, new onset depression during pregnancy can herald the start of persisting or chronic recurrent illness, with around two thirds of women experiencing more than one episode (Rahman & Creed, 2007; Pawlby *et al.*, 2009; Reay *et al.*, 2011; Woolhouse *et al.*, 2014). Perinatal anxiety disorders are common, too, and neurotic and stress-related symptoms share similarities with perinatal depression, with overlapping obstetric and offspring consequences, being frequently comorbid (Ross & McLean, 2006; Alder *et al.*, 2007; Kingston, Tough & Whitfield, 2012). In addition to the clinical concerns, recent analyses concluded that perinatal mental health problems cost British society more than £8 billion per annual birth cohort in the long term, with more than two thirds of this attributable to sequelae for the child (Bauer *et al.*, 2014). To put this in context, it is estimated that one episode of postnatal depression costs the United Kingdom's (UK) National Health Service (NHS) around £74,000 on

average, equating to approximately £10,000 for every single UK birth. Using complex modelling, maternal and offspring lifetime costs of perinatal depression (due to health and social care, education, health-related quality of life losses, productivity losses, parents' out-of-pocket expenditure, criminal justice, crime victim costs) are estimated to be largely attributable to the children's adverse outcomes (pre-term birth, infant death, emotional problems, conduct problems, special educational needs, and leaving school without qualifications) (Bauer, Knapp & Parsonage, 2016). Unfortunately, and despite the financial motivators to provide clinically effective interventions for perinatal depression, significant uncertainty remains about cost effectiveness, mainly due to the lack of adequate research (Morrell *et al.*, 2016). Moreover, an investigation into NHS service provision for postnatal depressions services by The Patients Association via a Freedom of Information request demonstrated widespread failings, with the majority of Primary Care Trusts who responded acknowledging that they did not even know the incidence of postnatal depression in their region (The Patients Association, 2011). Notwithstanding these challenges to addressing the economic challenges, recent recommendations and commitments to invest in perinatal mental health services are welcome (National Maternity Review report, 2016; BBC, 2016).

The increasing awareness of the significance of the characteristics and consequences of perinatal depression is reflected by the exponential growth in associated research and publications. A PubMed search for "[*natal OR pregnan* or *partum] AND depression" in September 2015 yielded more than 12,000 results, increasing from one paper published in 1939 to 822 in 2014 (Figure 1-1). However, these include numerous studies of small sample size and varying methodologies reporting an array of inconsistent findings (Wisner *et al.*, 2009; Howard *et al.*, 2014).

Figure 1-1 – Number of publications on perinatal depression by year

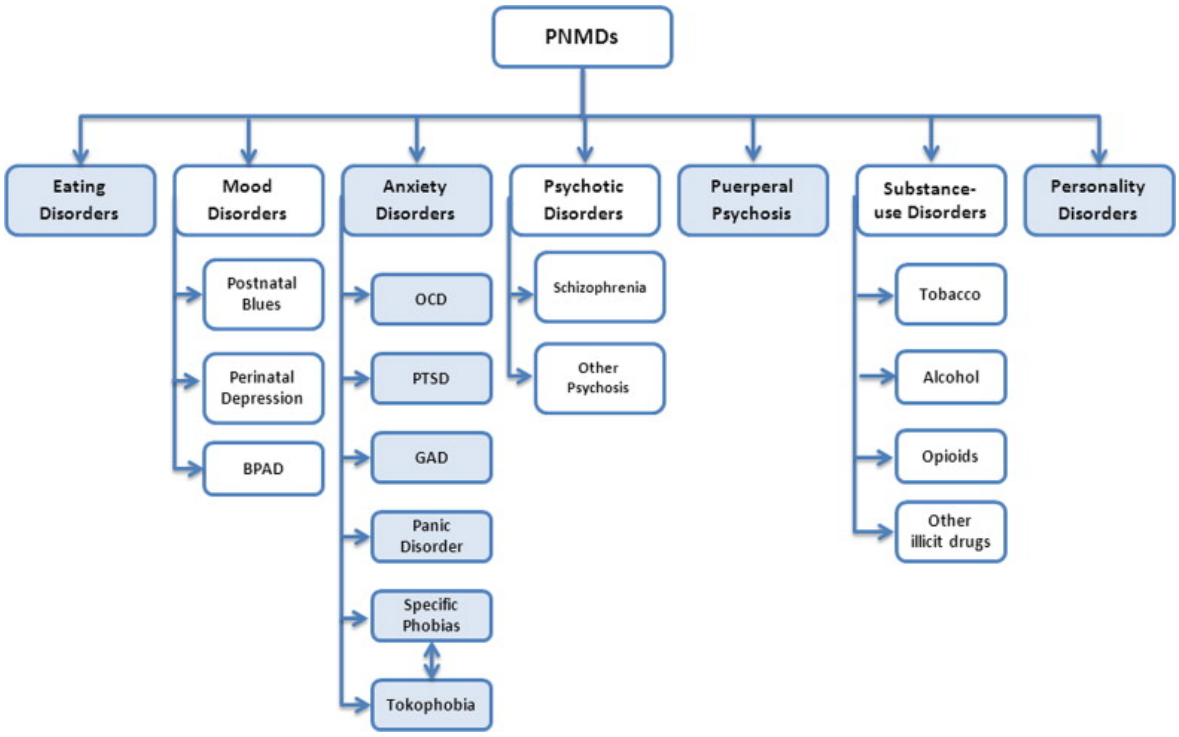


Perinatal depression

Perinatal mental illness is defined as those psychiatric disorders occurring during pregnancy and up to one year postpartum (O'Hara, Wisner & Asher, 2014). Historically, clinical and research focus has been on postnatal psychosis and depression, with more recent characterisation of other disorders both antenatally and postnatally (Waters *et al.*, 2014). Paschetta *et al.* (2014) classify common perinatal mental disorders as depicted in Figure 1-2, indicating that both new onset and relapse in existing illness are included. At least in part due to the close temporal relationship between childbirth and low mood, postnatal depression was originally suspected to be nosologically distinct from depressive illness outwith the puerperium, a notion now largely abandoned, although uncertainties remain (Di Florio & Meltzer-Brody, 2015). On behalf of the Nosology Working Group of the Perinatal Section of the Royal College of Psychiatrists, Jones and Cantwell (2010) made five recommendations on the

classification of perinatal mood disorders with regards to potential future revisions to both DSM and ICD, seeking to harmonise the challenges in emphasising continuity with illness episodes outwith the perinatal period, while acknowledging the distinct timing and characteristics of antenatal and postnatal elation and depression.

Figure 1-2 – Classification of common perinatal mental disorders



Reprinted from American Journal of Obstetrics and Gynecology, Volume 210; Elena Paschetta, Giles Berrisford, Floriana Coccia, Jennifer Whitmore, Amanda G Wood, Sam Pretlove, Khaled MK Ismail; Perinatal psychiatric disorders: an overview, Pages 501-509.e6, Copyright Mosby, Inc. (2014), with permission from Elsevier.
https://www.sciencedirect.com/journal/american-journal-of-obstetrics-and-gynecology

Distinguishing between puerperal psychosis and perinatal (antenatal and postnatal) non-psychotic depression is critical, as despite similarities there are significant differences in epidemiology, clinical management, risks, outcomes, and aetiology. For example, while there is no time in a woman's life that she is more at risk of developing affective psychosis than immediately after delivery, particularly if she has a personal or family history of significant mental illness, the risk of significant new onset or relapse in pre-existing illness may be reduced during pregnancy itself (Kendell *et al.*, 1987; Wieck *et al.*, 1991; Robertson *et al.*, 2005; Xu *et al.*, 2012). In contrast, depressive symptoms (although not necessarily depressive illness) appear to be common both antenatally and postnatally, with up to 70% and 84% of women affected, respectively (Henshaw, 2003; ACOG, 2008). Discriminating between antenatal and postnatal depression is not straightforward, as the two are closely related (approximately half of postnatal depressive episodes begin during pregnancy and, empirically as well as logically, antenatal episodes persist postpartum), and they pose overlapping risks to mother and offspring in both the short and longer term (Robertson *et al.*, 2004; Rahman & Creed, 2007; Reay *et al.*, 2011; Parker *et al.*, 2015).

Risk factors for perinatal depression

Numerous biological, psychological, and social factors are associated with increased risk of both antenatal and postnatal depression. Howard *et al.* (2014) summarise key findings from 12 systematic reviews in their recent overview of non-psychotic perinatal psychiatric disorders, comparing and contrasting the overlapping and discrete profiles of depression during and following pregnancy. They lament the quality of the data available, highlighting the relative lack of systematic reviews, and the rarity of studies based on valid diagnoses, longitudinal perspectives, comparison groups, and representative population samples from which meaningful generalisable and ultimately clinical useful inferences can be reached. Notwithstanding, a number of relevant papers, including original research and review articles, report consistent conclusions, summarised helpfully in the systematic review by Lancaster *et al.* (2010) and

presented in Table 1-2 (Logsdon & Usui, 2001; Robertson *et al.*, 2004; Howell *et al.*, 2005; Ryan, Milis & Misri, 2005; Leigh & Milgrom, 2008; Pearlstein *et al.*, 2009; Ross & Dennis, 2009; Paschetta *et al.*, 2014).

Not all factors are specific either to discrete disorders, nor the perinatal period, and several are strongly interrelated and/or demonstrate a bidirectional relationship with depression. For example, maternal age is linked with socioeconomic status and social/partner support, and personal mental illness is associated with family history, substance misuse, and unintended pregnancy. Moreover, absence of evidence is not evidence of absence – it would seem odd if immigrant status or substance misuse were not associated with antenatal as well as postnatal depression. Risks are also culture-sensitive – while there is no association between offspring gender and postnatal depression in western populations, paternal negativity towards having a baby girl may be linked with postnatal depression in some populations (Robertson *et al.*, 2004).

Table 1-2 – Risk factors for perinatal depression

	Antenatal depression	Postnatal depression
Physical abuse/violence/trauma	✓	✓
Sexual abuse		✓
Stress/negative life events	✓	✓
Socioeconomic deprivation	✓	✓
Poor social support (including relationship with partner)	✓	✓
Unintended pregnancy	✓	✓
Immigrant status		✓
Ethnicity		✓
History of psychiatric disorder (especially depression)	✓	✓
Anxiety during pregnancy	✓	✓
Depression/unhappiness during pregnancy		✓
Personality traits (including trait neuroticism)	✓	✓
Substance misuse		✓
Family history of psychiatric disorder		✓
Young maternal age (<18)	✓	
Previous miscarriages	✓	
Hyperemesis gravidarum	✓	
Multiparity		✓
Multiple births		✓
Chronic illness		✓
Medical comorbidity	✓	✓
Preterm birth		✓
Low birthweight		✓
Premenstrual tension/dysphoria		✓
Neonatal complications		✓
Infant temperament/ childcare stress		✓

The prevalence of antenatal and postnatal depression

There appears to be no clear or final answer to the question, how common is perinatal depression? The prevalence of perinatal depressive illness, a term encompassing both antenatal (prenatal) and postnatal depression, has been reported to be comparable to that of depression at other times of life, affecting around one in ten women, while other studies suggest increased rates in the childbearing years (Cooper & Murray, 1998; Kessler *et al.*, 2003). However, attempts to more clearly delineate the incidence, point prevalence, and period prevalence of depression during and after pregnancy have been affected by the conceptual and methodological limitations of diagnosis, and the time periods studied: reported figures have been based on various approaches, ranging from retrospective self-reports to structured interviews and rating scales, for different perinatal stages and intervals (Gaynes *et al.*, 2005; O'Hara *et al.*, 2014). In light of how common perinatal depressive features are, discriminating between symptoms and illness, and estimating severity, are clearly vital in reaching meaningful conclusions, and making relevant recommendations.

Due to the huge volume of studies and publications on perinatal depression alone (with an average of one new paper indexed every 12 hours), high quality, relevant, and up-to-date systematic reviews are invaluable in informing valid inferences with regards to the prevalence and consequences of perinatal depression.

Two systematic reviews of studies on the extent of perinatal depressive illness reached important conclusions; Bennett *et al.* (2004a), and Gavin *et al.* (2005). Bennett *et al.* (2004a) concluded from 21 studies of 19,284 pregnant women from the general population (including more than 12,000 from one English study) that rates of depression (defined as either reaching cut-off scores on the Beck Depression Inventory [BDI or BDI-II] or Edinburgh Postnatal Depression Scale [EPDS], or diagnosed via structured clinical interview [SCI]) were 7.4%, 12.8%, and 12.0% in the first, second, and third trimesters, respectively (Evans *et al.*, 2001). Interestingly, it appeared that studies using the BDI/BDI-II reported higher rates of depression, while those using the EPDS and SCIs were

comparable, despite both the EPDS and BDI having been validated in obstetric populations (Murray & Cox, 1990; Holcomb *et al.*, 1996). It should be noted that studies used different cut-off scores, ranging from >12 to ≥15 for the EPDS, and >9 to ≥16 for the BDI/BDI-II.

Holcomb *et al.* (1996) specifically recommended using a higher cut-off point of >16 for the BDI during pregnancy, to avoid false positives. However, Ji *et al.* (2011) concluded that while the BDI and EPDS are suitable instruments to screen for depression during pregnancy (as compared to the "gold standard" Hamilton Rating Scale for Depression [HRSD] for rating severity, and the Mood Module of the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID] for diagnosing), different cut-off points are required at different time points for optimal sensitivity and specificity (Table 1-3) (Hamilton, 1960; First *et al.*, 2002). Remarkably, although specificity reduces during pregnancy (as they predicted, due to the increasing somatic symptoms of pregnancy that overlap with those of depression), lower cut-off scores are indicated. They suggested that this could be due to women's own interpretation of the aetiology of their symptoms, i.e. not rating symptoms that they attributed to pregnancy rather then depression when completing the rating scales. (Consistent with this, one additional finding of interest was that multigravida women scored more highly than primigravida during the third trimester, and consequently required higher cut-off points to maintain adequate sensitivity – this may be explained by their previous experiences of pregnancy informing more nuanced interpretations of physical symptoms as not due to pregnancy, and hence increased reporting, and not a direct effect of multiparity *per se*.)

Gavin *et al.* (2005) reported from 28 studies (including three with a comparison group) of 14,835 patients that the combined rate of minor and major depression (diagnosed via SCIs either during pregnancy or within the 12 months following delivery) was 19.2% in the first three months after delivery, although significantly less at 7.1% for major depression only. While they were unable to provide accurate estimations of incidence or period prevalence for the trimesters of pregnancy, point prevalence for combined depression (major

depression only) was 11.0% (3.8%), 8.5% (4.9%), and 8.5% (3.1%) for the first, second, and third trimesters, respectively.

Table 1-3 – Optimal cut-off points for screening for the BDI and EPDS

	BDI	EPDS
Preconception	17	18
Trimester 1	15	12
Trimester 2	13	9
Trimester 3	12	15
Early postpartum	14	11
Late postpartum	14	12
Overall	13	11

Gavin *et al*. (2005) noted that their reported rates were slightly lower than those of others, attributing this to their methodology of including only recent studies of "higher quality" (associated with lower prevalence of depression), excluding studies based on patient-reported screening measures, differentiating between major and combined major/minor depression, and using point rather than period prevalence. (However, their second trimester rate was still higher than that found by Andersson *et al*. [2003], who reported the point prevalence of major depression as 3.3%, using the DSM-IV-based PRIME-MD structured clinical interview and patient questionnaire in 1,734 consecutive women attending for routine care.) Gavin *et al*. (2005) also observed that there were no statistically significant differences between the rates of depression in perinatal and non-pregnant control subjects, save for one paper reporting a three-fold increased risk of developing depression of any severity in the first five weeks postpartum (Cox, Murray & Chapman, 1993). However, they drew attention to

the inconsistencies in the published literature, as illustrated by the wide confidence intervals, advising caution in interpreting their conclusions, and highlighting a number of challenges in comparing the identified studies. In particular, they raised the issue of potential confounders, such as higher rates of minor depression in more socioeconomically deprived populations, and differences in the specific SCIs used – further research using bigger samples (to allow subgroup analyses), more representative populations (to include ethnic and racial heterogeneity), and comparator control groups of non-pregnant women is warranted.

More recently, Woolhouse *et al*. (2014) conducted a prospective cohort study of 1,507 pregnant nulliparous women, using a cut-off of EPDS ≥13 to define depressive symptoms. They found rates of perinatal depression similar to Gavin - *et al*. (2005), but follow-up at four years postnatally yielded a prevalence of depressive symptoms of 14.5%, higher than at any point during the first postnatal year. Women with one child at four years reported the highest rates of depressive symptoms (22.9% versus 11.3% for those with two or more children), an intriguing finding which suggest that environmental adversity contributed greater risk than multiparity with or without recurrent episodes of perinatal depression.

Of relevance to estimating rates of perinatal depression is the recent paper by Parker *et al*. (2015). They "diagnosed" 756 pregnant women in the third trimester and again at three months postnatally using both a SCI (the MINI International Psychiatric Review, which assesses DSM-IV criteria for major depression), and the EPDS with a cut-off of ≥10, yielding rates of antenatal depression "diagnosed" via the MINI and the EPDS of 3.2% and 18.5% (respectively), and 6.5% and 15.4% postnatally, comparable to those reported by Gavin *et al*. (2005) for major depression only, and combined major and minor depression. In other words, estimating perinatal depression prevalence is strongly influenced by the measure used, and as the EPDS is a quantitative dimensional rating of depressive symptomatology rather than a qualitative categorical discriminator of "caseness", using a cut-off score risks both false positives and negatives – lower cut-off points sacrifice specificity for sensitivity,

and vice-versa. Moreover, the EPDS includes items that relate more to anxiety and general distress, thus diluting its ability to discriminate between depression and related but distinct phenomena.

However, in addition to the concerns over the limitations of the EPDS in accurately "diagnosing" perinatal depression, the validity of using DSM criteria has also been questioned. Matthey and Ross-Hamid (2011) used the MINI in 118 women in the second and early third trimesters, establishing a rate of DSM-IV major depressive disorder of 6.8%. However, when they asked those meeting criteria for major depression if they thought that their symptoms were due to pregnancy or mood, 66% attributed them to pregnancy, reducing point prevalence to 1.7%. This study suggests that establishing rates of depression using even SCIs and DSM operational criteria may not be accurate in the perinatal period due to including the physical symptoms associated with pregnancy, leading to artificially inflated estimates of point prevalence. Assuming that women's attribution of symptoms to pregnancy rather than mental illness was correct even half the time, this study suggests that we may be in danger of being "ridiculous", and "pathologising women for being pregnant". They note the potential harm associated with current screening practices, particularly given that rating scales used (e.g. the EPDS) are also validated with reference to DSM criteria, and suggest that the low utilisation of clinical care following screening positive for depression may reflect women's attribution of their symptoms as being due to pregnancy, and not indicative of a significant psychiatric disorder (Sit *et al.*, 2009). Matthey and colleagues have explored related concerns in other studies, noting that around half of pregnancy women who screen "high" for emotional distress (i.e. depressive or anxiety symptoms) on the EPDS no longer do so within two weeks, indicating transient distress resolving spontaneously, rather than severe and enduring mental illness requiring intervention; and that the EPDS appears to rate symptoms of anxiety and not just specifically depression, concluding that diagnosing and treating perinatal depression after one high score on a self-reported rating scale has the potential to over-pathologise, and result in unnecessary clinical activity (Matthey, 2010; Matthey & Ross-Hamid, 2012; Matthey, Fisher & Rowe, 2013).

Notwithstanding, Matthey *et al*. acknowledge that mothers who score >13 on the EPDS, either antenatally or in the early postnatal period, continue to self-report distress up to two years later, associated with poorer relationships with their partners and mother-infant relationships, particularly those who screened positive on more than one occasion (Reay *et al.*, 2011). Despite concerns about over-pathologising, it is noteworthy that normalising depressive symptoms during pregnancy has reported to be a barrier to women accessing mental health services (Kingston *et al.*, 2015).

Overall, despite the challenges and uncertainties in establishing how common perinatal depression actually is, the summary by Oates and Cantwell bears repeating:

> *"The majority of women who develop mental health problems during pregnancy or following delivery suffer from mild depressive illness, often with accompanying anxiety. Such conditions are probably no more common than at other times. In contrast, the risk of developing a serious mental illness (bipolar disorder, other affective psychoses and severe depressive illness) is reduced during pregnancy but markedly elevated following childbirth, particularly during the first 3 months."* (CMACE, 2011.)

Nevertheless, whether or not depression within the perinatal period differs qualitatively or quantitatively from that without, it remains clear that a significant proportion of mothers and babies are exposed to depressive symptoms, which are in turn linked with significant sequelae for both, both immediately and over time. In this regard, it is significant to note that even "unhappiness during pregnancy" has been reported to be a risk factor for postnatal depression, with all its associated consequences (Ramchandani *et al.* 2009).

Consequences of (untreated) perinatal depression

For many years it has been known that maternal depression in the postnatal period can have adverse effects on offspring, in addition to negative maternal effects (Murray & Cooper, 1997). However, although historically clinical concern was focused on postnatal depression and its consequences, more recently there has been increasing awareness of antenatal depression, too, not least as a major predictor of postnatal depression (Lee *et al.*, 2007; Waters *et al.*, 2014).

Again, the literature on outcomes for those "diagnosed" with antenatal and postnatal non-psychotic depression is voluminous and growing, and defies simple summary. Several reviews, both systematic and narrative, reach similar, overlapping, and complementary conclusions. In addition to the usual personal biopsychosocial consequences of untreated depression outwith pregnancy, a myriad of maternal, obstetric/fetal, neonatal, and long term sequelae for offspring have been established, with some reported adverse outcomes being inconsistently replicated (Wisner *et al.*, 2009; Hanley & Oberlander, 2014). This is unsurprising, given the twin challenges of diagnostic heterogeneity, and the multitude of known and unknown confounding factors.

Maternal correlates of untreated perinatal depression include subjective suffering and negative cognitive biases; poor self-care and worse general health; poor nutrition and reduced maternal weight gain; obesity; increased use of tobacco, alcohol and substances; reduced use of antenatal care; social isolation; reduced breastfeeding; bonding, parenting, and childcare deficits; and even suicide and infanticide (Pearlstein *et al.*, 2009; CMACE, 2011; O'Hara & McCabe, 2013; Epstein, Moore & Bobo, 2014; Paschetta *et al.*, 2014). Obstetric/fetal features span spontaneous and elective abortion; placental abnormalities; reduced fetal growth; pre-eclampsia and eclampsia; pre-term and earlier deliveries; operative deliveries; low birthweight; DNA methylation abnormalities; congenital abnormalities; and stillbirth (Field, Diego & Hernandez-Reif, 2006; ACOG, 2008; Ban *et al.*, 2012; Ban *et al.*, 2014; Hanley & Oberlander, 2014; Gentile, 2015; Staneva *et al.*, 2015). Neonatal problems have been reported as low APGAR scores; respiratory distress; persistent pulmonary

hypertension of the newborn; increased rates of admission to neonatal care units; and perinatal death (ACOG, 2008; Ban *et al.*, 2014; Epstein, Moore & Bobo, 2014). Longer term sequelae for offspring include neuroendocrine dysregulation and physiological abnormalities; attachment difficulties, temperament and personality; neurodevelopmental delay and deficits; socio-emotional, psychomotor, cognitive, academic, intellectual, and behavioural problems; general health complications; and increased risks of childhood/adolescent/adulthood psychopathology and mental health problems, including depression (Grace, Evindar & Stewart, 2003; Murray *et al.*, 2006; Deave *et al.*, 2008; Pearlstein *et al.*, 2009; Murray *et al.*, 2010; Murray *et al.*, 2011; Davalos, Yadon & Tregellas, 2012; Kingston, Tough & Whitfield, 2012; O'Hara & McCabe, 2013; Pearson *et al.*, 2013; Csaszar, Melichercikova & Dubovicky, 2014; Suri *et al.*, 2014; Waters *et al.*, 2014; Gentile, 2015).

Two key reviews of the literature on the consequences of antenatal depression are those provided by Field, Diego & Hernandez-Reif (2006), and Waters *et al.*, (2014), which, in addition to contributing to the findings summarised above, highlight several important points.

Field, Diego & Hernandez-Reif (2006) reviewed fetal and neonatal sequelae of exposure to antenatal depression. They draw attention to the obvious conclusion that as fetuses exhibit abnormalities, at least some adverse effects of exposure to maternal depression commence *in utero*. They discuss possible mechanisms, including that some consequences of exposure to antenatal depression may be mediated via elevated maternal cortisol and norepinephrine, which are associated with persisting hypothalamic-pituitary-adrenal (HPA) axis and sympatho-adrenal hyperactivation in offspring, in addition to structural brain abnormalities (Weinstock, 2001). They acknowledge, however, that potential confounders include maternal anxiety and stress, as antenatal depression, anxiety and perceived stress interact in complex ways with one another and other risk factors for adverse outcomes, to exert direct and indirect effects on pregnancy outcomes (Weinstock, 2008; Woods *et al.*, 2010; Staneva *et al.*, 2015).

Waters *et al*. (2014) performed a systematic review of publications on antenatal depression and longer term developmental outcomes. They observe that prenatal maternal stress can have long lasting adverse effects on offspring, and explore potential mechanisms as per Field, Diego & Hernandez-Reif (2006). With regards to neuroendocrine dysregulation, although the influences of HPA axis dysregulation and overactivation on the developing fetus are not fully understood, Water *et al's* conclusions resonate with the aphorism that "a stressed mum equals a stressed baby" (Davis *et al.*, 2011). However, Waters *et al*. (2014) point out that hypercortisolaemia and antenatal depression are often independently linked with offspring outcomes. They highlight the possible contribution of epigenetic phenomena, including altered DNA methylation and histone modification. Moreover, they suggest that changes in placental gene expression and endocrine function may mediate the fetal consequences of antenatal maternal stress. They also note that aspects of the postnatal environment may act to accentuate or indeed buffer the effects of stress *in utero* on offspring. Importantly, they emphasise that associations do not establish causality, and that exposure to antenatal depression is heavily confounded by a variety of interrelated biopsychosocial prenatal and postnatal risk factors.

In summary, therefore, not only is perinatal depression common, it is associated with a wide range of significant adverse outcomes for both mothers and progeny.

Characteristics and consequences of antenatal antidepressants

It is in this context that the pharmacological treatment of perinatal psychiatric disorders has attracted greater attention over the last few years, with regards to clarifying issues surrounding the safety and efficacy of antenatal psychotropics, particularly antidepressants, and especially selective serotonin reuptake inhibitors (SSRIs), given the extent of their use (e.g. Oberlander *et al.*, 2008; Udechuku *et al.*, 2010; Grzeskowiak, Gilbert & Morrison, 2011; Bromley *et al.*,

2012; Malm, 2012; Bourke, Stowe & Owens, 2014; El Marroun *et al.*, 2014; McDonagh *et al.*, 2014; Forray, Blackwell & Yonkers, 2015; Robinson, 2015). It appears clear from a number of studies that a significant proportion of women in the UK are prescribed antidepressants during their childbearing years, including during pregnancy. Margulis, Kang & Hammad (2014) reported that 4.7% were prescribed an antidepressant, mostly SSRIs, before pregnancy, falling to 2.8% in the first trimester, and 1.3% thereafter, returning to 5.5% postpartum. However, these figures were averaged for pregnant women over a period of 22 years (1989-2010), and as antenatal prescribing of SSRIs has been reported to have increased significantly during this time, it seems likely that recent rates of exposure may be higher. Petersen *et al.* (2011) described similar period prevalence before and during the trimesters of pregnancy (4.8%, 2.4%, 1.0%, and 1.0%, respectively), noting however that overall exposure rates during pregnancy increased more than fourfold from 0.8% in 1992 to 3.3% in 2006. This trend suggests that recent exposure rates during pregnancy may have increased further in the past 10 years, and be closer to American estimates of 13.4% in 2003 (Cooper *et al.*, 2007).

Charlton *et al.* (2015) recently compared perinatal rates of SSRI prescribing in six European populations between 2004 and 2010, and found these to be highest in the UK, especially in Wales. While 4.5% of Welsh women were prescribed an SSRI during pregnancy, the average for the six regions was 2.3%, with rates of 1.2-1.6% in Italy, and 2.3% in Denmark and the Netherlands. The relatively high rates of antenatal exposure in the UK were attributed to the higher pre-pregnancy prescribing rates (8.8-9.6% versus 3.3-4.4% in other areas), leading to increased first trimester exposure in particular. Most studies converge on reporting a "J-shaped" curve, of exposure reducing markedly from periconception through the first and second trimesters, before returning to/exceeding pre-pregnancy levels following delivery. Characteristics of exposure to antenatal psychotropics in the UK are discussed in more detail in Chapters 2 and 4.

Given that many women are prescribed antidepressants in their fertile years, and that a significant proportion of pregnancies are unexpected, it follows that a

sizeable number of fetuses are at risk of unintended exposure in the first trimester. Early concerns centred on congenital malformations due to first trimester exposure, but progressed to include short term maternal/obstetric and fetal/neonatal risks following exposure later in pregnancy (Chambers *et al.*, 1996; Wisner *et al.*, 2009). Although accumulating data reassuringly suggests that exposure to many commonly used antidepressants during organogenesis in the first trimester is not clearly linked with clinically significant major congenital malformations, it is acknowledged that current evidence remains inadequate to allow informed decisions, particularly given the extent and potential consequences of perinatal depression and its antenatal pharmacological management (McDonagh *et al.*, 2014; Ornoy & Koren, 2014; Furu *et al.*, 2015). Moreover, uncertainties about the longer term neurobehavioural consequences of both untreated depression and antidepressants on the developing brain remain, despite recent reassurances (Grzeskowiak *et al.*, 2015).

One major challenge in this area is the lack of randomised controlled trials of interventions, due to the ethical issues involved, leaving observational and epidemiological database linkage studies to fill the gap, with all their associated limitations, including inability to establish causal relationships (Grzeskowiak, Gilbert & Morrison, 2011; Einarson, Egberts & Heerdink, 2015). Notwithstanding, the volume of literature available suggests that inferential quantity has been substituted for empirical quality. Barbui and Ostuzzi (2014) observe that "antidepressants are the most studied drugs during pregnancy, with more than 30,000 neonatal outcomes following exposure . . . documented in the peer-reviewed literature". Although no consistent associations between commonly used antidepressants and major congenital malformations have been demonstrated, different studies have linked drugs with a variety of adverse pregnancy outcomes (Ban *et al.*, 2012; Andrade, 2014; Ban *et al.*, 2014; Jimenez-Solem, 2014; Furu *et al.*, 2015; Reefhuis *et al.*, 2015). These include, but are not limited to, spontaneous and elective abortion, obstetric complications, teratogenicity and birth defects, pre-term delivery and low birth weight (both independently associated with long term health problems), neonatal adaptation syndrome, feeding difficulties and failure to thrive, specific

uncommon conditions such as persistent pulmonary hypertension of the newborn, and structural brain abnormalities (Simoncelli, Martin & Bérard, 2010; Grigoriadis *et al.*, 2014; Knickmeyer *et al.*, 2014; Huybrechts *et al.*, 2015). However, although statistically significant associations between antenatal exposure to antidepressants and sequelae have been reported, these are not always clinically significant (Ray & Stowe, 2014).

The robustness and finality of the conclusions based on the current literature is weakened by several factors. One major problem is heterogeneity. The definitions of exposure vary from study to study with regards to drug type, timing, and duration, and consequences have frequently been lumped together, with the potential for true associations to be obscured via dilution. For example, Reefhuis *et al.* (2015) found clear associations between specific birth defects and certain SSRIs, illustrating that drugs (even SSRIs) are not all the same (Gentile, 2015). This suggests that proportionately greater exposure to "safer" drugs (e.g. Sertraline) may mask the effects of less commonly used "riskier" SSRIs (e.g. Paroxetine), if analysed together as a single exposure. Furthermore, the overlap with consequences of exposure to antenatal depression is at least partially explained by the observation that not all studies take account of underlying illness type, timing, duration, and severity, nor known confounding factors (Grzeskowiak, Gilbert & Morrison, 2011). Research has increasingly taken account of theses issued over the past 20 years, and initial reports of consequences of antenatal exposure to antidepressants have not infrequently been refined and/or negated by improved methodology, e.g. propensity score matching (Oberlander *et al.*, 2008; Margulis *et al.*, 2013; Bourke, Stowe & Owens, 2014).

Despite the generally reassuring data and clinical experience accrued over decades, and millions of exposures worldwide, the potential impact of antenatal antidepressants on neurodevelopment and later functioning remains largely unknown, and therefore complacency is ill-advised. Findings from preclinical animal studies indicate that fetal brain exposure to drugs with monoaminergic effects has a range of anatomical and functional correlates (Kiryanova, McAllister & Dyck, 2013). Hermansen and Melinder (2014) consider that prenatal

SSRI exposure may have latent deleterious effects on cognition and behaviour that studies with only short-term follow-up may miss. Kepser and Homberg (2015) reviewed neurodevelopmental effects of early exposure to antidepressants in rodents and humans, concluding that pharmacological perturbation of serotonin-dependent neurodevelopmental processes may be associated with mood disorder in adulthood. A critical question emerges – in an attempt to reduce adverse outcomes for both mother and baby, could treating maternal depression during pregnancy with antidepressants actually increase the risks of later depression and anxiety for offspring? Despite the rodent data, Gur, Kim and Eperson (2013) opine that while the existing literature indicates the urgent need for further research, nevertheless it should not dissuade from the appropriate use of antenatal SSRIs, given the known risks of untreated antenatal depression.

SSRIs and the developing brain

Kepser and Homberg (2015) note that consequences of exposure are time-sensitive, with both shared and differential outcomes for prenatal, early postnatal, and late postnatal exposure. In light of this, it is noteworthy that there has also been widely publicised concern over the potential dangers of prescribing antidepressants for children and adolescents, particularly with regards to increased suicidality (Stone *et al.*, 2009; Wijlaars, Nazareth & Petersen, 2012). However, a more recent analysis of the data did not support this association (Gibbons *et al.*, 2012). It remains unclear exactly if and when the developing brain may be especially vulnerable to SSRIs, but it is plausible that there may be critical periods of neurodevelopment when altered serotonergic function results in potentially long-term undesirable consequences (Olivier *et al.*, 2011).

It is well-established that SSRIs not only cross the placenta in humans, they are also present in amniotic fluid and the fetal circulation, rendering the immature central nervous system vulnerable to neurobiological toxicity from exogenous

drug exposure during the prenatal and early postnatal periods (Ababneh, Ritchie & Wesbter, 2012; Bourke, Stowe & Owens, 2014; Ray & Stowe, 2014). A significant proportion of infants born to mothers taking SSRIs during pregnancy do display signs of a putative neurochemically-mediated initial antidepressant withdrawal syndrome, the "neonatal adaptation syndrome", in keeping with concerns that the fetus is exposed to neurobiologically relevant doses of these drugs (Sanz *et al.*, 2005). Oberlander *et al.* (2005) reported alterations in pain sensitivity and heart rate variability in infants exposed to SSRIs *in utero*, suggesting abnormal autonomic neurodevelopment, as well as increased risk of low birth weight and respiratory distress.

Findings from genetic and pharmacological studies indicate that serotonin signaling during early life is critically involved in regulating the development of brain circuits that modulate adult emotional behaviour (Whitaker-Azmitia, 2001). Rodent work indicates that neonatal exposure to SSRIs can disrupt the normal maturation of the serotonin system, and alter serotonin-dependent neuronal processes, including the regulatory pathways in the ascending serotonin projections (Maciag *et al.*, 2006a). These effects are mediated via the serotonin transporter (see below). Other rodent studies have shown that early exposure to serotonergically-active antidepressants are associated with persistent neurobehavioural abnormalities in adults (Kepser & Homberg, 2015). These data all add weight to the hypothesis that disrupted serotonergic function during neurodevelopment are related to structural and functional brain abnormalities in the adult brain (Oberlander *et al.*, 2012).

SSRIs and the serotonin transporter

The exact mechanism(s) via which SSRIs are therapeutic in depression remain as unclear as the pathophysiology of the disorder itself (Walker, 2013). Notwithstanding, one of their major effects is blockade of the presynaptic membrane protein known as the serotonin transporter (SERT). SERT blockade precipitates a transient increase in serotonin in the synaptic cleft, leading to an

early net reduction in serotonergic transmission, due to activation of presynaptic inhibitory autoreceptors. This results in desensitization of the presynaptic receptors and upregulation of the postsynaptic receptors, phenomena that emerge over days to weeks. Consequently, enhanced activation of G-protein-coupled postsynaptic receptors increases intracellular messaging, gene expression, and the production of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), which has been linked with the clinical response to antidepressants via hippocampal neurogenesis and synaptic plasticity (Krishnan & Nestler, 2008; Haase & Brown, 2015).

The SERT gene is located on the short arm of chromosome 17 (17q11.2), and has several allelic variants. The best know, and perhaps most clinically important, is a polymorphism in the promoter region (5-HTTLPR), consisting of a 44 base pair insertion or deletion, referred to as long (L) and short (S), respectively. This polymorphism is linked with varying degrees of reduced SERT expression and function. When compared to the long allele, the short allele is associated with less efficient transcription of the SERT, and less than half the basal activity and serotonin uptake. Adults with one or more short alleles appear to be more prone to trait neuroticism, anxiety and depression, in addition to other phenotypic abnormalities (Murphy *et al.*, 2008). Complementary studies have suggested that the short allele mediates an increased risk of depression in response to stressful life events and physical illness, and is associated with attenuated response to SSRIs and increased side-effects, although findings are conflicting (Serretti *et al.*, 2007; Kato & Serretti, 2010; Karg *et al.*, 2011; McGuffin, Alsabban & Uher, 2011; Queirazza & Cavanagh, 2014).

The "serotonin paradox"

This appears counterintuitive. If individuals with reduced endogenous SERT function are at increased risk of depression, why should SSRI-induced SERT blockade be therapeutic? In other words, there is an apparent "serotonin paradox", in that while iatrogenic pharmacological inhibition of the SERT in the

adult brain can be antidepressant, genetically-mediated SERT stultification may have contrary effects (Homberg, Schubert & Gaspar, 2009).

Serotonin and neurodevelopment

Healthy adults carrying one or more "S" alleles (or variants with comparable functionality) have been found to have significantly reduced amygdalar and hippocampal volumes, compared to those homozygous for the long allele (Frodl *et al.*, 2008a; Frodl *et al.*, 2008b). Moreover, possessing one or more "S" alleles is associated with smaller hippocampal volume, which is in turn linked with increased risk of developing depression in adolescence (Little *et al.*, 2014). Pezawas *et al.* (2005) and Kobiella *et al.* (2011) also described reduced amygdalar volumes in "S" carriers, in addition to associated functional abnormalities, with a dysregulated over-sensitive "fear response" circuit. In other words, congenital SERT hypofunction is associated with structural and functional limbic abnormalities that may result in excessive prolonged fear responses during neurodevelopment, resulting in trait neuroticism and susceptibility to depression (Hariri & Weinberger, 2003; Keightley *et al.*, 2003).

Ansorge *et al.* (2004) found that transient exposure of mice to an SSRI during a neurodevelopmental period corresponding to the third trimester and neonatal period in humans mimicked the emotionally abnormal phenotype of mice carrying one or more short alleles. This suggests that perturbation of serotonergic function during critical phases of early neurodevelopment, whether mediated genetically or pharmacologically, adversely affects the maturation of the neural circuitry responsible for emotional regulation in the adult brain.

Ansorge *et al.* (2008) further reported that it is the SERT and not the noradrenaline transporter (NAT) that is relevant with regards to pharmacological effects on neurobehavioural development. However, other studies using different models of depression report somewhat contradictory findings, implicating the dopamine transporter (DAT) more than either the SERT or NAT

(Perona *et al.*, 2008). Interestingly, Maciag *et al.* (2006b) reported that chronic adult administration of the SERT/NAT inhibitor imipramine reversed the neurobehavioural consequences of neonatal exposure to the SSRI citalopram in rats. A comprehensive account of the relationships between monoamines and neurodevelopment, SERT, NAT and DAT genotypes, early exposure to serotonergically-, noradrenergically- and dopaminergically-active ligands, and subsequent affective dysregulation remains elusive.

Despite the difficulties in reconciling the apparently discordant findings, it appears clear that timing is important. The adverse effects of SERT inhibition appear to be dependent on early life exposure as evidenced by the observation that the effects of SERT inhibition on behaviour were not maintained if this inhibition occurred at a later time period (Ansorge *et al.*, 2008). Taken together, these findings indicate that the effects of SSRI-mediated inhibition of the SERT on neural circuitry are not merely sustained withdrawal phenomena. Rather, they are dependent on the timing of treatment, representing a "critical period" in neurodevelopment.

Imaging the neurodevelopmental consequences of antenatal SSRIs

Given that early exposure to Fluoxetine mimics the "S/S" genotype in mice, and structural and functional brain abnormalities are associated with "S" genotypes in otherwise healthy human adults, can similar findings be demonstrated in human infants exposed to antenatal SSRIs?

Detailed neuroimaging studies of the developing human brain remain rare, and any exploring the effects of antenatal exposure to maternal depression or SSRIs are yet to be published. This is due in large part to the difficulties in performing scans on neonates and young children (see Chapter 5). Notwithstanding, several such projects have been undertaken, including Knickmeyer *et al.* (2008) completing structural magnetic resonance imaging (MRI) on infants from two weeks to two years postpartum, Choe *et al.* (2013) reporting on serial scans

between three and 13 months, and Holland *et al*. (2014) presenting findings from the first three postnatal months. Two review articles provide a synthesis of findings to date, with the main findings being that there is significant early postnatal growth mainly due to grey matter, with total brain volume more than doubling in the first year alone (Silk & Wood, 2011; Dennis & Thompson, 2014). The cerebellum grows more and faster than other regions, more than doubling in volume in the first three postnatal months, and increasing in size by 240% over the first two years of life. Although Gilmore *et al*. (2012) and Holland *et al*. (2014) were able to evaluate the hippocampus, reporting a slow rate of growth in the first 12 months compared to other regions, Knickmeyer *et al*. (2008) were unable to identify the hippocampus reliably in neonates, and only presented findings from the second year of life. Guo *et al*. (2014) outline the technical and methodological challenges in imaging the hippocampus in the early postnatal months, discussed further in Chapter 5.

It is theoretically possible, therefore, to look for structural abnormalities in the brains of neonates exposed to depression and SSRIs *in utero*. However, it is crucial to finalise which regions of the brain to evaluate, not least due to heterogeneity in the rates of neonatal brain development and the difficulties in measuring subcortical nuclei. For example, limbic structures with rich serotonergic innervation involved in mood regulation such as the amygdala and hippocampus are obvious targets for comparative neuroimaging in adults, but their small size in the neonatal brain limits their usefulness for this purpose. Other structures such as the cerebellum are therefore worthy of study.

Neonatal neuroimaging and the cerebellum

Human brain growth begins antenatally, peaks at term and continues beyond 30 months postnatally (Dobbing & Sands, 1973). In addition to an increase in brain mass, synaptogenesis and glia proliferation in humans begin during the second and third trimesters and continue throughout childhood and adolescence (de Graaf-Peters & Hadders-Algra, 2006). Although the relationship between

anatomical volume and cognitive function is neither clear nor necessarily linear, size can influence performance of modality-specific behaviour (Leingärtner *et al.*, 2007). The cerebellum grows faster and proportionately more than other brain regions, and its long term functions increasingly have become the focus of attention (Knickmeyer *et al.*, 2008; Holland *et al.*, 2014). It is now established that, in addition to its traditionally understood contributions to motor and sensory activity, the cerebellum is important in a wide variety of cognitive tasks, including planning, abstract reasoning, and visuospatial organisation (Baillieux *et al.*, 2008). This is unsurprising as the cognitive regions of the cerebellum are known to have reciprocal connections with non-primary frontal, occipito-parietal and temporal cortical associative areas (Bugalho *et al.*, 2006).

The cerebellum is also implicated in mood disorders, with the cerebellar-cognitive-affective syndrome described by Schmahmann, and reduced cerebellar volume, increased cerebellar activity, and abnormal connectivity being reported in depression (Gordon, 2007; Tavano *et al.*, 2007; Phillips *et al.*, 2015). In light of this, it is noteworthy that serotonin plays roles in cerebellar development and functioning, albeit poorly understood (Oostland & van Hooft, 2013; Saitow, Hirono & Suzuki, 2013). Due to its exponential growth and development over the first year of postnatal life, the cerebellum is potentially especially vulnerable to environmental insults. Consistent with this, Gilmore *et al.* (2010) reported that, of all brain regions studied in twins, the heritability of cerebellar volume is significantly lower than the others. Interestingly, Knickmeyer *et al.* (2014) found that around one in five children exposed to SSRIs in utero develop a Chiari I malformation, where the cerebellar tonsils herniate through the foramen magnum during the first decade of life. Together, these observations make the cerebellum a potential area of interest for comparative structural neuroimaging. In particular, diffusion tensor imaging (DTI) studies of developing connections between the cerebellum and other brain regions may also help shed light on potential areas of abnormality at an early stage in life.

Research proposals

Significant numbers of fetuses are exposed to maternal depression and/or SSRIs, whose long-term consequences remain insufficiently characterised to allow fully informed clinical decisions. Evidence suggests that, in addition to clinical outcomes, both antenatal maternal depression and its pharmacological treatment may be associated with structural brain differences, which could serve as biomarkers for future risk. We therefore proposed to complete a series of pilot studies, intended to explore some of the issues discussed above.

We undertook to investigate early neurodevelopmental consequences of exposure to depression/SSRIs via structural MRI, DTI, and magnetic resonance spectroscopy (MRS), a significant body of work presented in Chapter 7. Concurrently, in preparation for neuroimaging, and as the consequences of antenatal exposure to SSRIs are intimately related to its characteristics, we completed a systematic review on characteristics of antenatal exposure to SSRIs in the UK, detailed in Chapter 2. We also reviewed local records in a general maternity unit, and two specialist perinatal mental health services, to establish details of medication usage during pregnancy, subsequently evaluating the utility and accuracy of the clinical records in comparison with national epidemiological data (Chapters 3 and 4). Thereafter we investigated select outcomes of exposure in the general maternity unit and one specialist service (Chapter 5). Chapter 6 outlines key methodological challenges in researching characteristics and consequences of antenatal exposure to SSRIs, and Chapter 8 provides a synthesis of our findings, with discussion and recommendations for future research.

Chapter 2 - Characteristics of antenatal exposure to SSRIs in the UK: A systematic review

Within the last 10 years, the American College of Obstetricians and Gynecologists (ACOG) stated that "an estimated one third of all pregnant women are exposed to a psychotropic medication at some point during pregnancy" (ACOG, 2008). This projection was made with reference to a 30 year old study of 168 mums-to-be receiving care from a university teaching hospital in Florida, USA (Doering & Stewart, 1978). This study also reported that all patients consumed at least two drugs during pregnancy, with over 90% taking five or more drugs, and an average of 11 drugs being used per participant. (13.2% used illicit drugs, mainly Marijuana.) Doering and Stewart based their findings on patients' retrospective accounts of their drug use, and included over-the-counter medicines and nutritional supplements such as iron and vitamins, which may explain the concerningly high rates of antenatal exposure to drugs in general. However, it is not clear from Doering and Stewart's paper, nor from the ACOG report, to which psychotropics the ACOG estimate refers.

Assuming that psychotropic medication indicates mainly antidepressants, mood stabilisers, and antipsychotics, the ACOG conclusion seems at odds with current clinical practice and experience in the UK. In 2008, anecdotal evidence indicated that a more likely figure for our local population would be ~1 in 20, i.e. ~5% of women in the West of Scotland are exposed to a psychotropic medication during pregnancy, as found during an audit at the Queen Mother's Hospital in Glasgow in the early 2000s (Dr Roch Cantwell, personal communication). However, a subsequent retrospective analysis of the records of women attending the specialist Glasgow Perinatal Mental Health Service (PMHS) did find that 57.3% (118/206) were documented as receiving at least one antidepressant, mood stabiliser, or antipsychotic drug at some point during pregnancy, with 50.8% (60/118) of these exposed to SSRIs (59.4% of those

exposed to antidepressants [60/101]), i.e. 29.1% (60/206) of the total sample (Julyan, Cavanagh & Cantwell, 2009).

Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) suggest that (in the UK at least) more than 80% of women take prescribed medication (other than nutritional supplements) at least once during pregnancy, while more recent American studies indicate that up to one in eight fetuses may be exposed to antidepressant medication (Headley *et al.*, 2004; Cooper *et al.*, 2007; Yonkers *et al.*, 2009). Reports from both sides of the Atlantic raise concerns that rates of antidepressant prescribing during pregnancy have risen recently, up to fourfold in the UK (Cooper *et al.*, 2007; Andrade *et al.*, 2008; Petersen *et al.*, 2011; Jimenez-Solem, 2014). Mirroring patterns in the non-pregnant population, and as per guidelines, the bulk of prescriptions for antenatal psychotropics are for SSRIs (Margulis, Kang & Hammad, 2014; NICE, 2014).

As outlined in Chapter 1, the short, medium and long term advantages and disadvantages for both mothers and babies of using antidepressants to treat perinatal depressive disorders require careful consideration. In particular, the numerous potentially significant sequelae of fetal exposure to SSRIs must be weighed against those of untreated ante- and post-natal depression. Clarifying current patterns of perinatal prescribing is a critical prerequisite for evaluating outcomes, and therefore informing future practice to minimise risks and maximise benefits for mothers and babies. Key characteristics to note include the frequency of prescriptions for SSRIs during pregnancy, and for which drugs, at what doses, when, for how long, and for what indications, in addition to types and severity of maternal illness, and the myriad of known and unknown confounding factors. We therefore undertook a systematic review to address this gap in the literature.

Research question

What are the characteristics of antenatal exposure to SSRIs in the UK, with specific reference to prevalence, type, dose, timing, and duration?

Methods

Search strategy and study selection

We used PRISMA criteria for conducting a systematic review, and a professional librarian (JW) working in the local mental health library within NHS Ayrshire & Arran advised on and ran the search strategy (Moher *et al.*, 2009). Electronic databases (including MEDLINE®, EMBASE, the Cochrane Database of Systematic Reviews, the PROSPERO International Prospective Register of Systematic Reviews, the Web of Science/Knowledge, Trip and OpenGrey) were searched from their respective inceptions to 7 October 2016.

Keyword combinations utilised included: selective serotonin reuptake inhibitors or SSRIs, citalopram or cipramil, dapoxetine or prilegy, escitalopram or cipralex, fluoxetine or prozac or oxactin, fluvoxamine or faverin, paroxetine or seroxat, sertraline or lustral, pregnan*, fetal or fetus or foetal, pr*natal or ant*natal, and in utero or intr*uterine (see Appendix 1 for full details). A filter was applied to limit results to UK studies.

Inclusion and exclusion criteria

We included English language publications reporting original data from observational studies on the UK population (or representative samples) that directly addressed the research question. Papers that indirectly covered relevant data were also included, e.g. those stating prevalence and characteristics of antenatal exposure to SSRIs *en route* to reporting outcomes.

We excluded interventional trials and case-control studies, as well as review and educational articles, abstracts, conference proceedings and unpublished data, although employed these in identifying subsequent peer-reviewed publications.

Data extraction and analysis

Three psychiatrists (EJ, TK and AS) independently screened the titles and abstracts of all studies identified through the search strategy, identified pertinent papers, and obtained the full text of each for more detailed analysis. Articles likely to contain references to other relevant publications were also accessed.

We extracted data from each included study into an Excel® worksheet under the following headings: date range, data source, number of pregnancies, inclusion criteria, exclusion criteria, definition of antenatal exposure to SSRIs, and characteristics of exposure. This allowed the prevalence of antenatal exposure to SSRIs in the UK to be calculated, including more detailed estimates of exposure rates preconception, in each trimester and postnatally.

Contributors

EJ (consultant psychiatrist) planned, supervised and contributed to each part of the systematic review, including defining the research question, planning the search strategy, reviewing all titles and abstracts, reviewing references in relevant articles, extracting and analysing data, and writing up. JW (professional librarian) advised on and ran the search strategy, and acquired copies of relevant articles. TK (speciality psychiatric trainee) and AS (core psychiatric trainee) independently reviewed all titles and abstracts, reviewed references in relevant articles, and extracted data, with support from EJ as required.

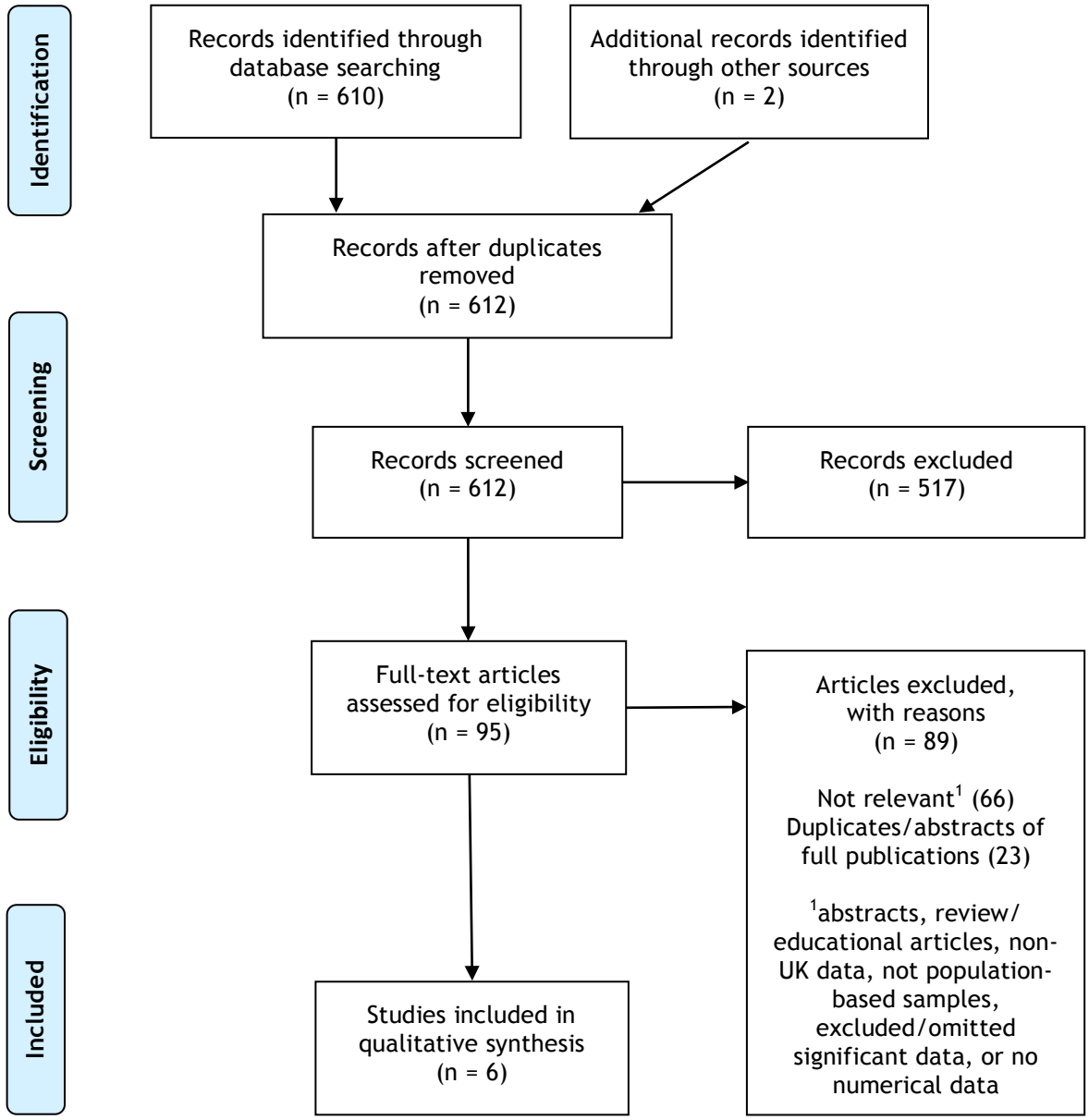
Following electronic removal of duplicates, our search strategy identified 587 publications across the medical databases Figure 2-1). The "grey literature" search yielded no relevant articles, and PROSPERO identified 23 registered systematic review protocols. Ninety-three articles were selected as potentially relevant by the three reviewers, with five meeting the inclusion criteria (Table 2-1 studies 1-4 & 6), and hand-searching of references identified two further papers, one of which was relevant (Table 2-1 study 5). Two of the studies primarily and directly (albeit partially) addressed our research question (Margulis, Kang & Hammad, 2014; Charlton *et al.*, 2015), with a third focusing on antidepressant discontinuation during pregnancy (Petersen *et al.*, 2011). The others reported briefly on antenatal SSRI prescribing rates in the context of their primary aims of exploring outcomes of fetal exposure to antidepressants, and are included for completeness (Table 2-1, studies 2-4 & 7) (Ban *et al.*, 2012; Margulis *et al.*, 2013; Ban *et al.*, 2014). None of the studies identified via PROSPERO met inclusion criteria.

Table 2-1 – Studies meeting inclusion & exclusion criteria

Study	Authors (year)	Date range	Data source	Number of pregnancies
1	Petersen *et al.* (2011)	1992-2006	THIN	145,532
2	Ban *et al.* (2012)	1990-2009	THIN	512,574
3	Margulis *et al.* (2013)	1996-2010	CPRD	149,464
4	Ban *et al.* (2014)	1990-2009	THIN[1]	349,127
5	Margulis *et al.* (2014)	1989-2010	CPRD	421,645
6a (UK)	Charlton *et al.* (2015)	2004-2010	CPRD[2]	182,920[3]
6b (Wales)			SAIL[4]	58,106[5]

[1]The Health Improvement Network; [2]Clinical Practice Research Datalink; [3]excluding subjects registered with GPs in Wales; [4]Secure Anonymised Information Linkage Databank; [5]Welsh subjects only

Figure 2-1 - PRISMA flow diagram

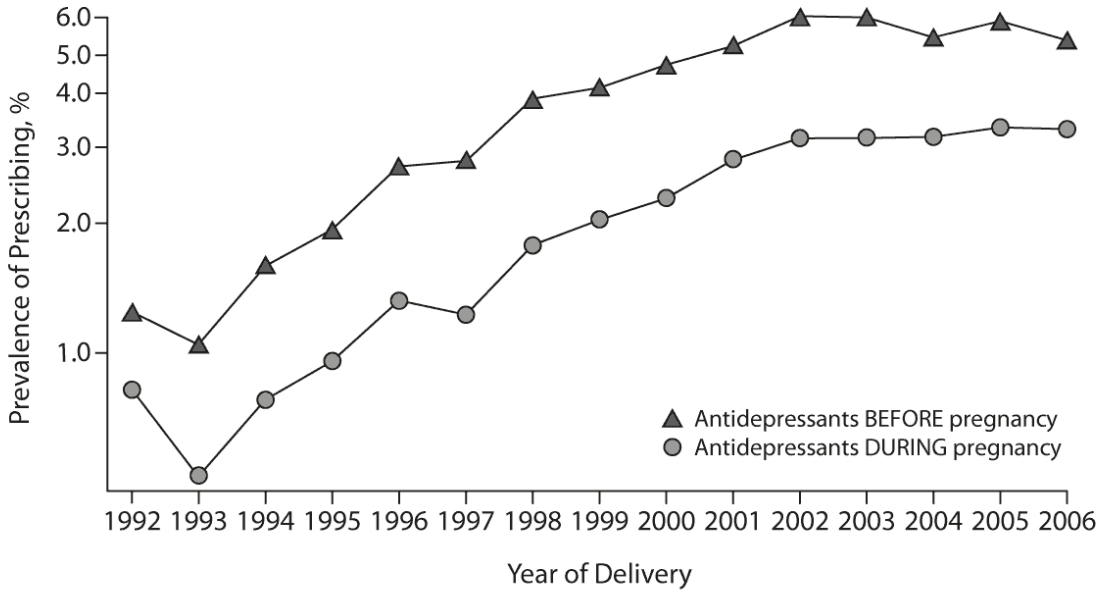


One of the final six studies also reported on data from outwith the UK: Charlton *et al*. (2015) compared data from UK-wide and Welsh databases with data from four other European areas (Denmark, the Netherlands, and two Italian regions). All seven studies utilised either THIN (The Health Improvement Network) or CPRD (the Clinical Practice Research Datalink [formerly the General Practice Research Database]), with Charlton *et al*. (2015) also including data from SAIL (the Secure Anonymised Information Linkage Databank). Characteristics of THIN, CRPD and SAIL datasets have been described by Blak *et al*. (2011), Lewis *et al*. (2007), Wood & Martinez (2004), Ford *et al*. (2009) and Lyons *et al*. (2009), respectively. THIN is a large primary care database that (by 2016) included data from over 11 million patients registered with more than 560 general practices in the UK, while the comparable CPRD covers over five million patients registered with more than 630 general practices. Specific to Wales, SAIL similarly includes data from over two million patients, covering more than 40% of the Welsh population. These datasets are considered to be representative of the general British and Welsh populations. All studies pooled their results, averaging prescribing rates for the years covered, with Petersen *et al*. (2011) charting an increase in the rates of antidepressant prescribing in women both before and during pregnancy by year (Figure 2-2).

Table 2-2 summarises inclusion and exclusion criteria used by each study, while Table 2-3 presents their definitions of pregnancy and fetal exposure to SSRIs. Table 2-4 lists the period prevalence of putative maternal exposure to SSRIs before (T0) and after (T4) pregnancy, and maternal-fetal exposure during the three trimesters (T1, T2 and T3), as well as overall during pregnancy.

Figure 2-2 - Time trends of the prevalence of antidepressant prescribing (from Petersen *et al.*, 2011)

Figure 1. Time Trends of the Prevalence of Antidepressant Prescribing[a]



[a]For individuals at 0–6 months before pregnancy and during pregnancy. Includes individuals who received at least 2 prescriptions within 3 months (logarithmic scale shows consistent proportionate differences between time periods).

Irene Petersen, Ruth E Gilbert, Stephen J W Evans, Shuk-Li Man, Irwin Nazareth; Pregnancy as a Major Determinant for Discontinuation of Antidepressants: An Analysis of Data From The Health Improvement Network; The Journal of Clinical Psychiatry; 72(7); p979-985; 2011. Copyright 2011; Physicians Postgraduate Press. Reprinted by permission.

http://www.psychiatrist.com/jcp/article/Pages/2011/v72n07/v72n0715.aspx

Table 2-2 – Inclusion & exclusion criteria for each study

Study	Inclusion criteria	Exclusion criteria
1	Live births to different mothers, between 1992 and 2006, with data for mothers for at least 6 months before pregnancy until delivery	In mothers with more than 1 pregnancy, 1 was selected at random; mothers prescribed antidepressants at presumed subtherapeutic doses
2	All singleton pregnancies ending in live birth, stillbirth, miscarriage or TOP[1], in mothers aged 15-45, between 1990 and 2009	Pregnancies in mothers with psychotic/bipolar illness; pregnancies in women registered in Northern Ireland (due to different abortion legislation)
3	All singleton live births, to mothers aged 12-49, with linked mother-child data from 15 months before pregnancy, between 1 January 1996 and 30 November 2010	Mother-child dyads for whom dates were anomalous and/or could not be reconciled; mothers prescribed non-contraceptive FDA[2]-pregnancy category X drugs between 15 months preconception and delivery; infants with chromosomal abnormalities, sequences or single-gene inherited diseases
4	All singleton live births, to mothers aged 15-45, with linked mother-child data from 1 year before and throughout pregnancy available, between 1990 and 2009	Births to mothers with psychotic/bipolar illness or anti-manic/-psychotic drugs antenatally
5	All pregnancies resulting in live birth(s), between 1 January 1989 and 31 December 2010, with linked mother-child data from 6 months before pregnancy until 3 months after delivery	Nil in addition to inclusion criteria
6	All pregnancies resulting in live birth or stillbirth, beginning and ending between 1 January 2004 and 31 December 2010, with data available from 1 year before pregnancy until 1 year after delivery.	Nil in addition to inclusion criteria

[1]TOP = termination of pregnancy

[2]FDA = Food and Drug Administration

Table 2-3 – Definitions of pregnancy, & maternal & fetal exposure to SSRIs

Study	Definitions of pregnancy	Definitions of fetal exposure to SSRIs
1	Live birth; length of pregnancy estimated from gestation at birth, LMP and free text entries, or assumed to be 280 days if data missing (including for preterm births)	Prescription for SSRI during pregnancy
2	Singleton pregnancy ending in live birth, stillbirth, miscarriage or TOP; conception estimated from several variables (expected delivery date, maturity estimates, timing of routine monitoring events) – where data was missing, delivery assumed to be at 40 weeks, and miscarriage and TOP at 10 weeks	Prescription for SSRI in maternal records within first 90 days following conception
3	Singleton delivery; delivery dates estimated, as accurate birth dates not recorded, start of pregnancy estimated from LMP for term deliveries (pregnancy assumed to last 273 days if data missing), and from records if preterm (pregnancy assumed to last 258 days if data missing)	Prescription for SSRI issued during T1 or T2, or before pregnancy where the number of days supplied would overlap with T1
4	Singleton live birth	Prescription for SSRI in maternal records from 4 weeks before to 12 weeks after first day of LMP
5	Live birth, multifetal classified as one pregnancy; start of pregnancy estimated by LMP or codes for preterm delivery; length of pregnancy calculated from gestation at birth, and assumed to be 273 days for term deliveries and 258 days for preterm deliveries if data missing	Prescription for SSRI issued during gestational periods (3 months before pregnancy, T1, T2, T3, and 3 months after delivery)
6	Pregnancy resulting in live birth or stillbirth; “the best estimate of the start of pregnancy was calculated” (no details provided)	Prescription for SSRI issued during pregnancy

Table 2-4 – Period prevalence of perinatal exposure to SSRIs

Study	T0	T1	T2	T3	T4	Any stage during pregnancy
1	4.8%	1.9%	0.77%	0.75%	-	2.11%
2	-	2.77%	-	-	-	-
3	-	-	-	-	-	[2.15%][2]
4	-	2.28[1]	-	-	-	-
5	3.43%	2.06%	0.94%	0.99%	4.44%	-
6a (UK)	8.8%	-	-	-	12.9%	3.7
6b (Wales)	9.6%	-	-	-	15.0%	4.5%

[1](2.20% SSRIs only, 0.08% SSRI co-prescribed with non-SSRI AD)

[2]Prescriptions during T3 not included

Prevalence and timing of exposure to antenatal SSRIs

As summarised in Table 2-4, two studies either stated or described data sufficient to calculate overall exposure rates to SSRIs at any stage during pregnancy (Petersen *et al.*, 2011; Charlton *et al.*, 2015), with a third providing figures permitting a similar calculation but omitting prescriptions issued in T3 (a reasonable estimate of overall exposure, as studies indicated that few women were commenced on SSRIs *de novo* in the third trimester) (Margulis *et al.*, 2013). Ban *et al.* (2012) and Ban *et al.* (2014) gave exposure rates during T1 only. While neither detailing nor describing data to allow estimation of overall exposure during pregnancy, Margulis *et al.* (2014) did define SSRI exposure rates for each of the individual trimesters.

Petersen *et al.* (2011) based their study on UK data for 145,532 pregnancies in 114,999 women who had a live birth between 1992 and 2006, identified via THIN. The researchers identified all pregnant women issued with at least two consecutive prescriptions for an antidepressant, with at least one of these being

in the three months prior to the date of conception (calculated from baby's gestational age at the time of birth, and information on the last menstrual period). (Drugs classified as antidepressants, but prescribed at doses lower than what would be generally be considered the minimum effective dose were excluded from their analysis, mainly due to the assumption that these prescriptions were likely to be for indications other than depression, e.g. "low dose" Amitriptyline for pain.) They also identified women who received only one prescription for an antidepressant during pregnancy, to allow comparison with other studies employing this methodology. A comparison group of 22,677 non-pregnant women was employed to provide an estimate of baseline prescribing in the general population. Rates of antidepressant prescribing per year were plotted graphically (Figure 2-2, reproduced with permission), ranging from 0.8% in 1992 to 3.3% in 2006, mirroring the greater than four-fold increase in antidepressant use in non-pregnant women from 1.2% in 1992 to 5.3% in 2006.

Overall, from 1992 to 2006, 4.8% women were prescribed an antidepressant in the 6 months before conceiving, with almost half (2.3%) continuing into pregnancy. 78.5% of those on an antidepressant during pregnancy received an SSRI (although not necessarily SSRI monotherapy). The main focus of Petersen *et al*'s study was to establish rates of and reasons for antidepressant discontinuation during pregnancy, and they therefore looked at rates of antidepressants prescribed during different stages, rather than overall exposure (Table 2-4). Nevertheless, they concluded that, overall, around 2.7% of British women were prescribed an antidepressant at some point during pregnancy (2.1% SSRIs). It was not clear whether these data referred to women receiving only one prescription, or the stricter criteria for those receiving at least two prescriptions within three months.

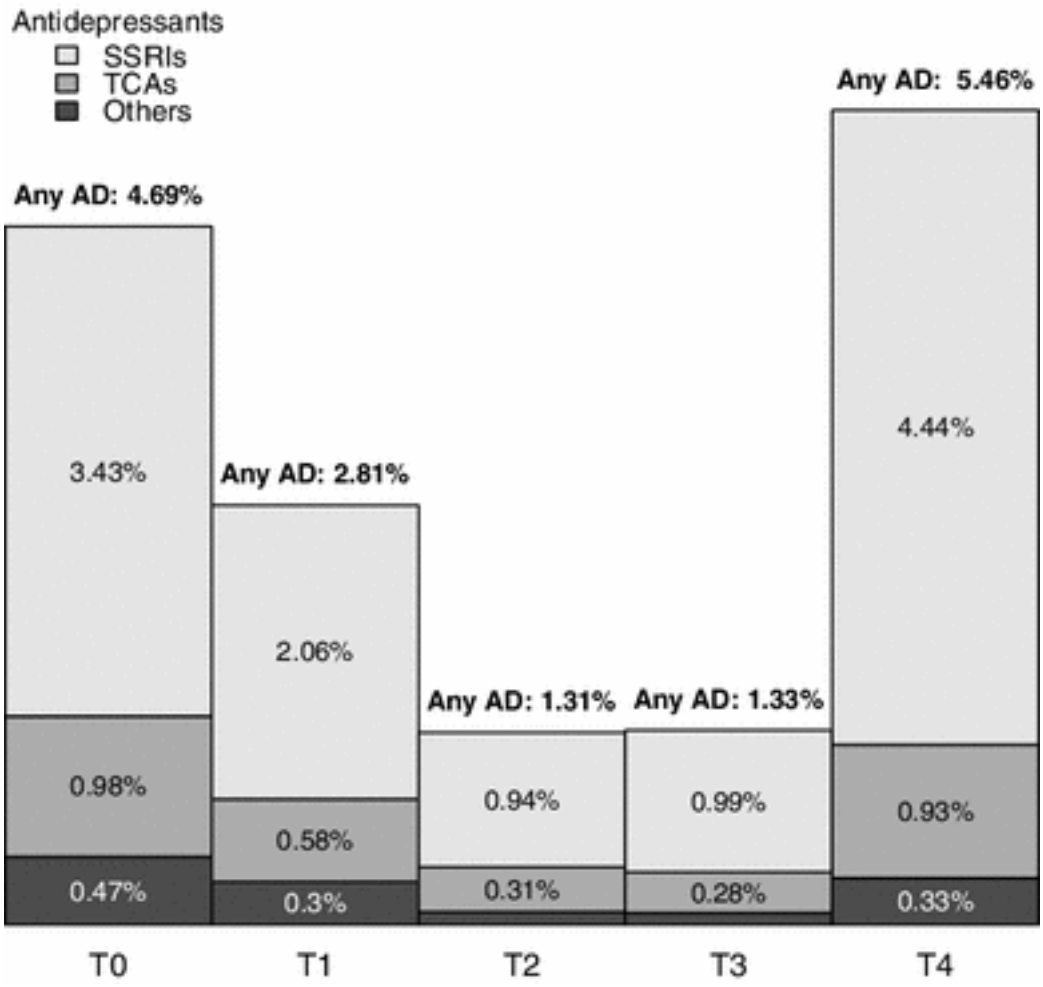
Margulis, Kang and Hammad (2014) used the CPRD's Mother-Baby Link to identify mothers with a live birth between 1 January 1989 and 31 December 2010 (inclusive), with the aim of delineating longitudinal patterns for perinatal psychotropic prescriptions. Women who were registered from six months before pregnancy through until three months postpartum were included, 421,645 out of 907,642 deliveries (46.5%). The researchers calculated the beginning of

pregnancy using gestational age at birth for the 22% for whom this was available, and estimated the rest depending on whether they were term or preterm births, for which they used 273 days and 258 days, respectively. Period prevalence for antidepressants (and antipsychotics) was calculated for five epochs: three months preconception (T0); trimesters one, two, and three (T1-3); and three months postpartum (T4) (Table 2-4). 21,363 subjects issued with a prescription in T0 and/or T3 were assigned to one of six discrete categories: (1) treatment discontinuation (all drugs discontinued); (2) treatment simplification (some drugs discontinued, or dose lowered); (3) no change in drugs or dose; (4) drug switch; (5) treatment intensification (drugs added to prior treatment, or dose increased); and (6) treatment start. The necessity of using so many categories when considering prescriptions for only one medication type illustrates the challenges in characterising perinatal psychotropic prescription patterns. Margulis, Kang and Hammad reported that of 19,774 women prescribed any antidepressant (i.e. not just SSRIs) in T0, 79.6% discontinued in T1, and 0.4% of those not prescribed an antidepressant in T0 had started by T3.

Charlton *et al*. (2015) compared perinatal rates of SSRI prescribing in six European populations between 2004 and 2010 (Denmark, two Italian regions, the Netherlands, the UK and Wales), utilising the CPRD (with Welsh data excluded) and SAIL. Rates of prescribing were highest in the UK, and especially in Wales - 4.5% of Welsh and 3.7% of other British women were prescribed an SSRI during pregnancy, while the average for the six regions reported to be 2.3%, with rates of 1.2-1.6% in Italy, and 2.3% in both Denmark and the Netherlands (Table 2-4). The relatively high rates of antenatal exposure in the UK were attributed to the higher pre-pregnancy prescribing rates (8.8-9.6% versus 3.3-4.4% in other areas), leading to increased first trimester exposure in particular. As per Margulis, Kang and Hammad (2014), the period prevalence of antidepressants followed a "J-shaped" curve, of prescribing rates reducing markedly from periconception through the first and second trimesters, before increasing postnatally, as summarised in Figures 2-3 and 2-4, similar to Petersen *et al*. (2011), as well as American and Danish findings reported by Reefhuis, Rasmussen and Friedman (2006) and Jimenez-Solem *et al*. (2013), respectively.

Characteristics of exposure to antenatal psychotropics are discussed in more detail in Chapter 5.

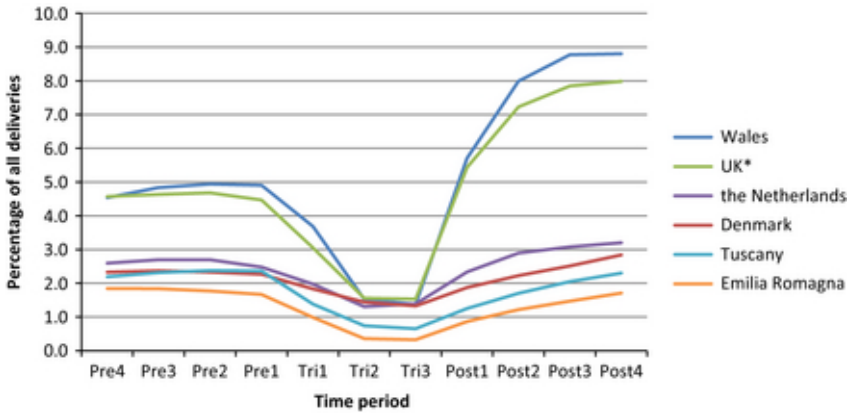
Figure 2-3 – Period prevalence of perinatal antidepressants 1989-2010 (from Margulis, Kang & Hammad, 2014)



'Because some women used more than one class of antidepressants, the prevalence of use of any antidepressant may be lower than the addition of SSRIs, TCAs and other antidepressants. AD antidepressant, CPRD Clinical Practice Research Datalink, SSRIs selective serotonin reuptake inhibitors, TCAs tricyclic antidepressants, T0 the 3 months before pregnancy, T1 first gestational trimester, T2 second gestational trimester, T3 third gestational trimester, T4 3 months after delivery.'

Reprinted by permission from Springer Customer Service Centre GmbH: Springer; Maternal and Child Health Journal; 18:1742-1752; Patterns of Prescription of Antidepressants and Antipsychotics Across and Within Pregnancies in a Population-Based UK Cohort; Andrea V Margulis, Elizabeth M Kang, Tarek A Hammad; Figure 1; Copyright 2014. https://link.springer.com/article/10.1007%2Fs10995-013-1419-2

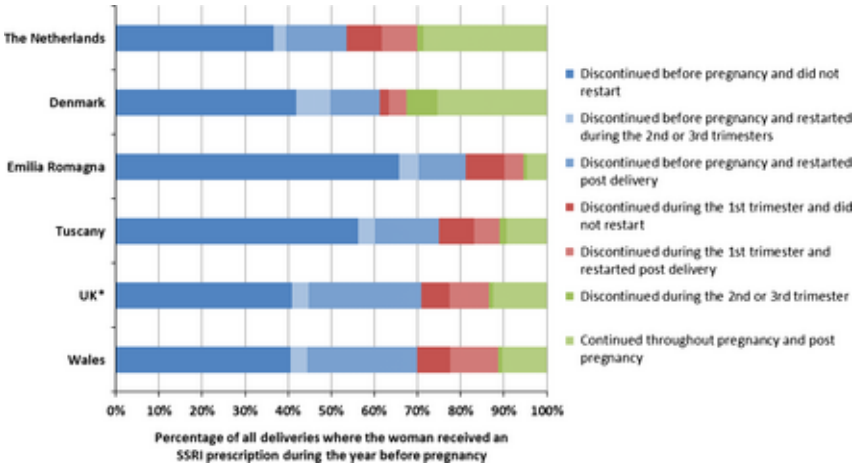
Figure 2-4 – Period prevalence of perinatal SSRIs 2004-2010 (from Charlton *et al.*, 2015)



* Excluding Wales

John Wiley and Sons, BJOG 2015;122:1010-1020, Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions, Rachel A Charlton et al., Figure 1, © John Wiley and Sons.
https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.13143

Figure 2-5 – Prescribing patterns during pregnancy (from Charlton *et al.*, 2015)



John Wiley and Sons, BJOG 2015;122:1010-1020, Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions, Rachel A Charlton et al., Figure 2, © John Wiley and Sons.
https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.13143

Types of SSRIs prescribed

Two studies (Petersen *et al.*, 2011; Charlton *et al.*, 2015) provided data on individual SSRIs prescribed during pregnancy as a whole (Figure 2-6), with Fluoxetine and Citalopram the most commonly used, and Sertraline, Paroxetine and Escitalopram vying for third place (Fluovoxamine was rarely prescribed). Ban *et al.* (2014) provided limited data on SSRIs prescribed in the first trimester, with Petersen *et al.* (2011) describing individual SSRI prescribing rates in each trimester (Table 2-5). Although Charlton *et al.* (2015) did not give exact numbers, presenting their data in chart form, Dr Charlton kindly provided the raw data on request (personal communication). Citalopram appeared more popular than Fluoxetine in Wales during the study period, although the CPRD dataset indicated that Fluoxetine use was more prevalent in England and Scotland.

Figure 2-6 – Prevalence of antenatal exposure to individual SSRIs (%)

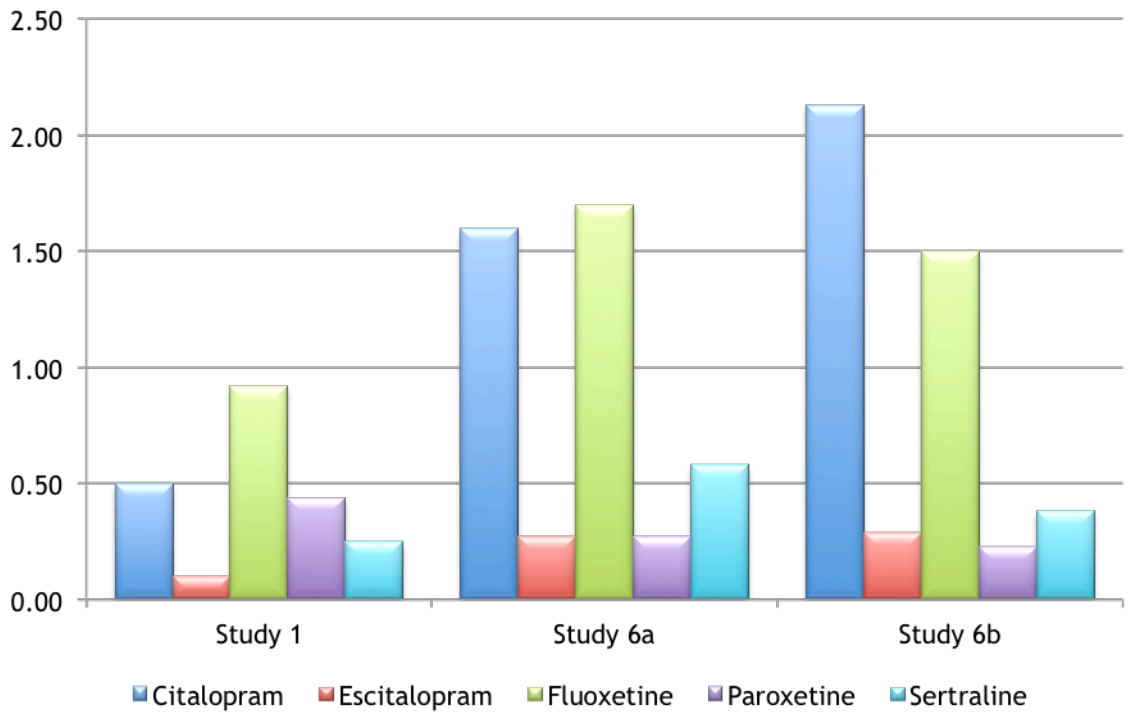


Table 2-5 – Prevalence of antenatal exposure to individual SSRIs by trimester

SSRI/study	T1	T2	T3	Any stage during pregnancy
Citalopram				
1	0.4%	0.16%	0.15%	0.50%
4	0.6%	-	-	-
6a (UK)	-	-	-	1.60%
6b (Wales)	-	-	-	2.13%
Escitalopram				
1	0.1%	0.01%	0.01%	0.10%
4	0.1%	-	-	-
6a (UK)	-	-	-	0.27%
6b (Wales)	-	-	-	0.29%
Fluoxetine				
1	0.8%	0.33%	0.33%	0.92%
4	0.9%	-	-	-
6a (UK)	-	-	-	1.70%
6b (Wales)	-	-	-	1.50%
Fluvoxamine				
1	<0.1%	0.00	0.00	<0.1%
4	-	-	-	-
6a (UK)	-	-	-	0.01%
6b (Wales)	-	-	-	0.004%
Paroxetine				
1	0.4%	0.2%	0.17%	0.44%
4	0.3%	-	-	-
6a (UK)	-	-	-	0.27%
6b (Wales)	-	-	-	0.23%
Sertraline				
1	0.2%	0.1%	0.09%	0.25%
4	0.2%	-	-	-
6a (UK)	-	-	-	0.58%
6b (Wales)	-	-	-	0.38%

Doses of SSRIs prescribed

None of the studies described doses in any detail, although Margulis *et al*. (2014) noted that 5.1% of women prescribed an antidepressant in the three months before pregnancy who continued medication during pregnancy "simplified" their treatment – this included 4.0% who switched to a lower dose (with an additional 0.01% "unclassified", having increased and/or decreased some doses during pregnancy).

Timing and duration of antenatal SSRIs (Tables 2-4 and 2-5)

Ban *et al*. (2012) reported that 50.8% of women potentially exposed to SSRIs in T1 discontinued them in T1. While not giving raw data, Charlton *et al*. (2015) again charted several different exposure patterns, with around 20% of those prescribed an SSRI in T0 discontinuing in T1, roughly 1% stopping in T2 or T3, and approximately 10% continuing throughout pregnancy (Figure 2-4). Petersen *et al*. (2011) described an overall reduction in exposure to SSRIs from 4.85% in T0, to 1.86% in T1, 0.77% in T2 and 0.75% in T3, while Margulis, Kang and Hammad (2014) reported a similar pattern of a decrease in exposure from 3.43% in T0, to 2.06% in T1, 0.94% in T2 and 0.99% in T3 (Figure 2-2). Margulis, Kang and Hammad (2014) and Charlton *et al*. (2015) also found significant increases in rates of SSRIS prescribed postnatally, to 4.4%, and 12.9% (UK) and 15.0% (Wales), respectively. Owing to varying methodologies, primary purposes and reporting formats, detailed comparisons and conclusions could not be realised.

It was striking that, despite historical awareness of perinatal mental health problems and contemporary concerns about fetal outcomes, a non-systematic review of the medical literature at the outset of this body of work in 2008 had not identified any publications with a primary focus on the characteristics of antenatal exposure to SSRIs in the UK. Apart from a few studies mentioning psychotropics in the context of antenatal exposure to medication in general (e.g. Headley *et al.*, 2004), it was not until 2009 that Durrani and Cantwell (2009) reported on the general characteristics of patients attending the Glasgow Perinatal Mental Health Service (PMHS), devoting a total of 160 words to describing and commenting briefly on issues relating to psychotropic medication. The first study specifically describing patterns of antidepressant prescribing during pregnancy in the UK did not appear until 2011 (Petersen *et al.*, 2011).

Data quality and methodological considerations

Together, the six studies that met criteria for our systematic review included more than 20 years of data on nearly two million pregnancies, although given that studies explored overlapping years and converged on the same databases, the extent to which subjects overlapped across the studies is likely to be high, and impossible to determine from the published reports. The studies were heterogeneous, varying in how they defined subjects for inclusion, with most but not all requiring singleton pregnancies, and some focusing on live births while others included stillbirths, miscarriages and terminations of pregnancy (TOPs). Maternal age ranges were not restrictive, and all studies required data for both mothers and offspring to be available throughout pregnancy, with several requiring data pre- and post-pregnancy, too. The datasets used had face validity, given that over 98% of the UK population are registered with a GP, and less than 0.01% of patients opt out of having their clinical details included. It appears likely that all scripts for SSRIs issued via the patients' GPs would have been captured (unless handwritten).

However, the possibility of bias and confounding cannot be excluded, as patients who were not registered with a GP, did not consent to being included in THIN, CPRD or SAIL, or had data missing (e.g. due to poor attendance at antenatal appointments, being removed from their practice for non-attendance, relocating during the study periods, or receiving prescriptions via specialist services not included in the primary care databases, such as those provided for homeless, abused, addicted or vulnerable women) would not be included in the data; characteristics potentially associated with significant depressive illness, as depressed women may be less likely to engage effectively with antenatal care (Bennett *et al.*, 2004b; Marcus & Heringhausen, 2009; Walsh, 2009; Ludermir *et al.*, 2010; Beydoun *et al.*, 2012; Grzeskowiak, Gilbert & Morrison, 2012a; Bassuk & Beardslee, 2014).

While the absolute number of patients in these categories is likely to have been low, nevertheless, they may have been overrepresented among those prescribed antenatal SSRIs, leading to underestimates of prevalence. Similarly, bias may be introduced through including only live births, if exposure to antenatal SSRIs is associated with early or late miscarriage, TOP or stillbirth; as may including multiple and/or serial pregnancies in the same women, given that multiparity is a potential confounding factor for both maternal and progenic outcomes (see Chapter 6) (Louis *et al.*, 2006; Ban *et al.*, 2012; Grzeskowiak, Gilbert & Morrison, 2012a; Redshaw & Henderson, 2013; Sockol & Battle, 2013; Lahti *et al.*, 2014).

Challenges in defining pregnancy, and antenatal exposure to SSRIs

The challenges in defining the start, duration and even end of pregnancy from retrospective data that were not collected primarily with this end in mind have been highlighted above, outlined in Table 2-3, and are explored further in Chapter 6. With regards to pregnancy, the gold standard would be to know both the child's date of birth and gestation at delivery (as estimated by antenatal ultrasound scan), thus allowing accurate calculation of the date of conception.

However, these data were not available for all subjects in the included studies, leading to the different researchers resorting to alternative methods to compensate, e.g. (in order of decreasing preference) estimating the start of pregnancy from the LMP or "free text entries", or simply assigning standard lengths of pregnancy to so-called "term" and "preterm" deliveries (Table 2-3). Overestimating length of pregnancy may lead to overestimating early exposure to drugs prescribed periconception, while underestimating length of pregnancy leads to the opposite error. While most studies gave details of their methodology, Charlton *et al*. (2015) stated simply that "the best estimate of the start of pregnancy was calculated" without giving further details.

Defining antenatal exposure to SSRIs is similarly fraught. Most studies used the date the prescription was issued to specify timing of exposure, but this does not necessarily indicate that this was the date the prescription was dispensed. Moreover, neither issuing nor dispensing proves when or even if the medication was actually taken and, given that most prescriptions usually cover at least a 28 day period, simply using the date of issue will tend to underestimate antenatal exposure in women who received a prescription less than 28 days before conception, which provided sufficient tablets from them to persist into the first trimester, only to stop when they discover they are pregnant. Similar issues affect estimations of exposure and timing across the trimesters, as well as contributing to potential overestimations of third trimester exposure, when prescriptions for medicines planned to start postnatally are issued before delivery.

Moreover, there is no agreed definition of the trimesters of pregnancy, hence references to exposure by trimester may not be identical across studies (Appendix 5). Notwithstanding, Petersen *et al*. (2011) did describe how they defined trimesters, "as the first day of the last menstrual period to 14 weeks and 6 days (first trimester); 15 weeks to 27 weeks and 6 days (second trimester); and 28 weeks to delivery (third trimester)".

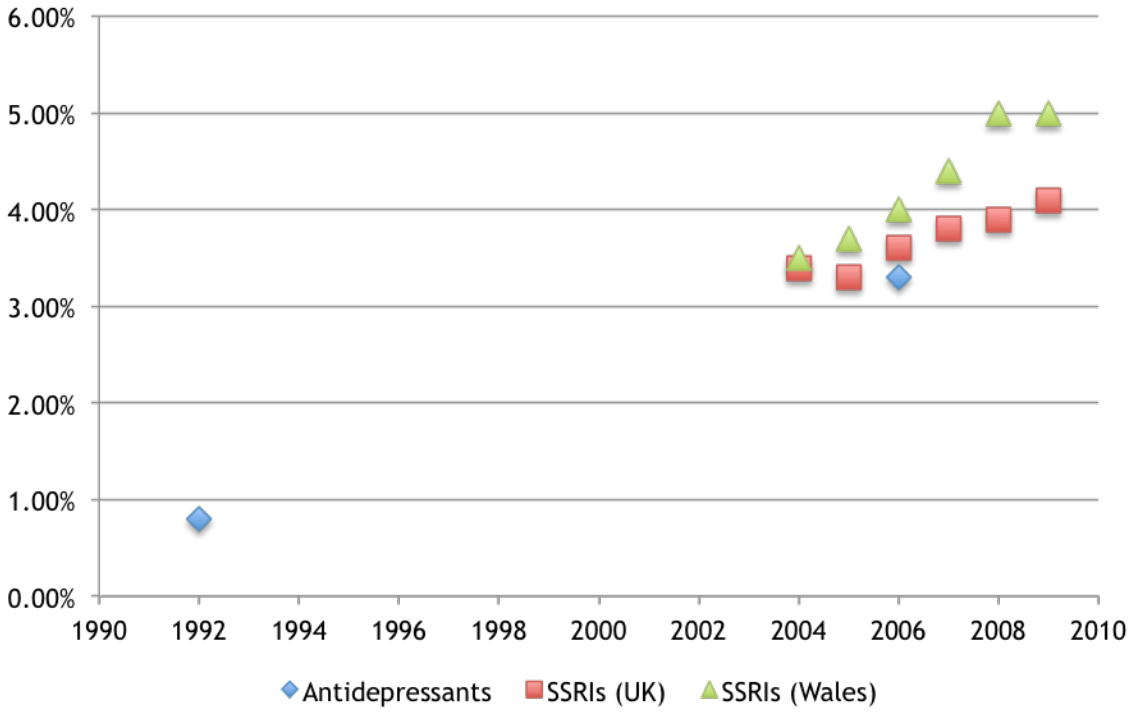
Furthermore, estimating actual fetal exposure to SSRIs is even more problematic, when one takes into account maternal adherence and dose taken,

in addition to issues such as maternal absorption, placental transfer, maternal and fetal genotypes, and epigenetic factors.

One significant issue is that all studies pooled data over the years of the study periods, meaning that the overall rates of antenatal exposure may be an underestimate. For example, while Petersen *et al*. (2011) reported that 2.69% of pregnancies between 1992 and 2006 were exposed to an antidepressant, the actual rates of antidepressant prescribing increased more than fourfold from 0.8% in 1992 to 3.3% in 2006. This suggests that averaging exposure rates over the years may be misleading, by more recent rates being artificially suppressed by those from a decade or more ago. Moreover, if the trend described by Petersen *et al*. (2011) continued, even at a slower pace, then current rates will be higher still – Charlton *et al*. (2015) indicated that rates of fetal exposure to SSRIs increased by more than 40% over a five year period (2004-9), from 3.5% to 5.0% in Wales, and from 3.4% to 4.1% in the rest of the UK (plotted together in Figure 2-7) (raw data kindly provided by Dr Charlton). Increasing rates are strongly correlated with years (Spearman's rank correlation coefficient rho=0.843, p=0.000582). This trend towards increasing antenatal exposure to SSRIs over time may be driven by various factors, including a general increase in prescriptions for antidepressants in general, and SSRIs in particular, in the population (including in women of childbearing age), and a shift towards continuing antidepressants into and throughout pregnancy rather than stopping. These developments were concurrent with phenomena such as campaigns to promote awareness, recognition and treatment of depression, with increased media coverage and reduced stigma surrounding depression and antidepressants; and changes in the delivery of antenatal mental health care, including increasing access to specialist perinatal services, more evidence on which to base guidelines and treatment decisions (e.g. relapse rates in those stopping antidepressants during pregnancy, and the relatively low risk of adverse consequences of fetal exposure in contrast to those of untreated maternal antenatal depression), and therefore more women continuing to be prescribed antidepressants (particularly SSRIs) throughout the perinatal period.

Notwithstanding the above, the included studies appeared complementary in their definitions of pregnancy and exposure, and their broad agreement on prevalence and types of SSRIs prescribed, and "J-shaped" patterns of exposure from T0 through T4 (Figures 2-3 and 2-4).

Figure 2-7 - Rates of exposure to antidepressants and SSRIs 1992-2008



Prevalence of antenatal SSRIs

Despite the methodological issues, and although varying by a factor of more than two, the studies from which the prevalence of exposure to SSRIs during pregnancy could be calculated were comparable in the range ~2.1& to 4.5%, with a clear trend towards prescribing rates increasing over time (Table 2-4; Figure 2-2; Figure 2-7). Indeed, NHS Digital recently reported that, for the fourth consecutive year, prescriptions for antidepressants in England alone increased more than other drugs, with an increase of 6.0% from 2015-6 alone, contributing to an overall doubling of antidepressant items dispensed since 2006

(from 31.0 million to 64.7 million) (NHS Digital, 2017). The situation in Scotland appears similar, with Lockhart and Guthrie (2011) describing a threefold increase in antidepressant prescribing between 1995-6 and 2006-7 (attributable to "a complex mixture of more patients being prescribed SSRI and 'other' antidepressants, the use of higher doses, and longer durations of treatment, with the balance changing over time"), consistent with news reports of a ~30% increase in antidepressant prescribing between 2009 and 2015, and a ~5% increase from 2014-5 alone (BBC, 2015).

However, these observations require cautious interpretation in light of McCrea *et al's* 2016 study using THIN, where new prescriptions for SSRIs doubled between 1995 and 2001, but remained stable thereafter through 2012. McCrea *et al*. (2016) did find, however, that the apparent duration of treatment rose from a median of 112 days for those commencing in 1995 to 169 days in 2010, suggesting that at least some of the increases reported by NHS Digital (2017) may be attributable to patients and/or prescribers continuing SSRIs for longer rather than more individuals starting them, as per Moore *et al*. (2009). However, other sources report rates of increase of more than 50% in the number of under 18s prescribed antidepressants between 2005 and 2012, with a proportionately greater fourfold increase in under 13s between 2009 and 2016 (Bachmann *et al.*, 2016; BBC, 2017). This inverse relationships between age and prescribing rates may explain in part why SSRI exposure appeared to be higher in Wales than in the rest of the UK, as Charlton *et al*. (2015) noted that the mean age of the Welsh mothers was statistically significantly lower than their English and Scottish counterparts. However, lower socioeconomic status in Wales is likely to have been an contributing factor.

Prescriptions for SSRIs (and antidepressants in general) reduced from 3.43%-9.6% in T0 to ~1.5%-2.77% in T1 (reductions of between ~40% and ~70%), representing significant rates of discontinuation, presumably when women found themselves to be pregnant and decided, or were advised, to stop (Petersen *et al.*, 2011). Rates of exposure reduced again in the second trimester (to between <1% and ~1.5%), but remained fairly constant into the third trimester, rising again significantly to exceed pre-pregnancy rates in the year following delivery (4.4%-

15.0%). While period prevalence for the whole of pregnancy was predictably higher than in T1 (due to a small number of women commencing SSRIs during pregnancy after the first trimester), nevertheless, T1 rates appeared comparable in the one study that reported data for both (Petersen *et al.*, 2011).

The rates of antenatal SSRIs of ~5% by 2009 are not out of kilter with the reported rates of antenatal major depression of ~2-10% (discussed in Chapter 1), particularly when taken in the context of GPs having been found to issue antidepressant prescriptions for around 50% of those who score as "probable depression" using the Hospital Anxiety and Depression Scale (HADS) (Cameron, Lawton & Reid, 2009).

The rates of exposure reported by Charlton *et al.* (2015) were significantly higher than those reported in other studies. A plausible explanation is that while all other papers pooled results from 1989-96 until 2006-11, Charlton *et al.* (2015) included only data from more recent years, 2004-10, reflecting the increase in prescribing rates over the years described above. It follows that fetal exposure to SSRIs in the UK may now be higher still, and vary by demographic, given that rates of increase appear to be inversely proportional to age.

Types and doses of SSRIs

As per Table 2-5 and Figure 2-6, Fluoxetine was the most common SSRI prescribed (except in Wales). Citalopram was the next most prevalent (the front runner in Wales), with Sertraline and Paroxetine alternating for third and fourth place, and Escitalopram and Fluvoxamine fifth and sixth, respectively. These findings mirror clinical experience in the UK, and reflect clinical guidelines – although historically tricyclic antidepressants were used during pregnancy due to experience and reasonably reassuring data and clinical experience regarding safety, in line with the general shift towards SSRIs (due to their comparable efficacy, but superior tolerability) GPs, NICE and other bodies came to recommend Fluoxetine as the antidepressant of choice in pregnancy during the

years included and, arguably, Citalopram remains the antidepressant most commonly prescribed by GPs (NICE CG45, 2007 [updated 2014]); Cipriani *et al.*, 2009; Taylor, Paton & Kapur, 2015; personal observation). Paroxetine was also frequently used by GPs and in secondary care, but following the US Food and Drug Administration's warning in 2005 about Paroxetine's potential for teratogenic effects (but not other SSRIs), prescribers moved away from using Paroxetine in pregnancy, and its prominence in the studies above is likely to represent a historical artifact of the years to which their data belong (Stone *et al.*, 2009). Sertraline gained popularity in the latter years of the included studies, likely due to its preferable safety, efficacy and tolerability profile, and prominence as perhaps the SSRI (and antidepressant) of choice in breastfeeding, hence promoting its suitability for antenatal use (SIGN, 2012). Escitalopram was relatively less commonly prescribed, presumably at least in part due to its greater cost under patent until 2014, and Fluovoxamine was rarely used in the UK. None of the studies included gave a detailed account or analysis

International context and comparisons

Our six included studies indicated that antenatal exposure to antidepressants in the UK was significantly less common than in some general maternity populations in America, where rates of up to 13.4% of pregnant women on antidepressants were reported (10.2% for SSRIs alone) (Cooper *et al.*, 2007). However, the exposure rates were not inconsistent with other international estimates, with rates of SSRI prescribing during pregnancy in North America, Europe and Australia between 1976 and 2010 between 0.44% and 10.2%, a 23-fold difference (Table 2-6). It should be noted, however, that sample sizes ranged from 805 to 848,786, and most studies reported rates averaged over years. These data are summarised in Table 2-6, alongside our findings discussed in Chapters 4 and 5 (Taylor, Cameron & Julyan, 2010; Wood, Cameron & Julyan, 2015). Papers which included longitudinal comparisons demonstrated increases in prescribing over time consistent with Petersen *et al.* (2011) and Charlton *et*

Table 2-6 – International rates of antenatal SSRIs

Study	Country	Pregnancies	Year(s)	SSRIs
Oberlander *et al.* (2006)	Canada	119547	1997-2002	5.0%
Reefhuis, Rasmussen & Friedman (2006)	USA	4,094	1997-8	1.5%
			1999-2000	2.8%
			2001-2	2.3%
Cooper *et al.* (2007)	USA	105,335	1999	2.9%
			2003	10.2%
Ramos *et al.* (2007)	Canada	97,680	1998-2002	3.7%
Andrade *et al.* (2008)	USA	118,935	1996	1.5%
			2005	6.2%
Bakker *et al.* (2008)	Netherlands	14,902	1995-2004	2.1%
Wichman *et al.* (2008)	USA	27,908	1993	0.44%
			2007	6.61%
Taylor, Cameron & Julyan (2010)	UK	805	2010	2.36%
Alwan *et al.* (2011)	USA	6,582	1998-2005	3.8%
Colvin *et al.* (2011)	Australia	123,405	2002-5	3.0%
Mitchell *et al.* (2011)	USA	25,313	1976-2008	5.8%
Petersen *et al.* (2011)	UK	114,999	1992-2006	2.11%
Jimenez-Solem *et al.* (2012)	Denmark	848,786	2004	1.4%
			2007	2.4%
Hanley & Mintzes (2014)	USA	343,299	2006-11	5.1%
Charlton *et al.* (2015)	Denmark	320,846	2004-10	2.3%
	Italy: Emilia Romagna	129.220		1.2%
	Italy: Tuscany	157,916		1.6%
	Netherlands	13.935		2.3%
	UK	182,920		3.7%
	Wales	58,106		4.5%
Wood, Cameron & Julyan (2015)	UK	875	2012	7.89%

al. (2015) (Reefhuis, Rasmussen & Friedman, 2006; Cooper *et al*., 2007; Andrade *et al*., 2008; Wichman *et al*., 2008; Jimenez-Solem *et al*., 2012)

Charlton *et al*. (2015) provided a direct comparison of six European regions, with the striking finding that SSRIs were significantly more commonly prescribed in the UK before, during and after pregnancy than in other regions, almost fourfold higher than some (Table 2-6). While the non-UK databases reporting prescriptions dispensed rather than prescriptions issued may have "magnified" differences, this appears unlikely to be a sufficient explanation, especially given the differences between Wales and the rest of the UK. Other possible explanations include that the UK's continental neighbours favour non-SSRI antidepressants or are more circumspect about prescribing, or that UK regions diagnose, prescribe for, or actually have more depressed residents.

Timing of antenatal psychotropics

The findings of Petersen *et al*. (2011), Margulis, Kang and Hammad (2014) and Charlton *et al*. (2015) are broadly consistent with other studies in Australia, Denmark, Finland, Germany, the Netherlands, Canada, Norway, and the USA reporting on rates of antidepressants (not just SSRIs) during T1, T2 and T3 (Malm *et al*., 2003; Egen-Lappe & Hasford, 2004; Reefhuis, Rasmussen & Friedman, 2006; Ververs *et al*., 2006; Ramos *et al*., 2007; Engeland *et al*., 2008; Hanley & Mintzes, 2014; Jimenez-Solem, 2014) (Table 2-7). Numerous studies report that many women prescribed antidepressants periconception discontinue during pregnancy, most commonly in the first trimester, although with ongoing reductions in the second and third trimesters. In fact, most reports (except for Ververs *et al*. [2006]) suggest that it is the minority of women who continue antidepressants throughout pregnancy.

Table 2-7 – International rates of antidepressants by stage of pregnancy

					Trimester		
Authors	**Country**	**Pregnancies**	**Year(s)**	**Overall**	**1**	**2**	**3**
Malm *et al.* (2003)	Finland	43,470	1999	1.0%	0.8%	0.3%	0.3%
Egen-Lappe & Hasford (2004)	Germany	41,293	2000-1	-	-	-	0.08%
Ververs *et al.* (2006)	Netherlands	29,005	2000-3	-	2.0%	1.8%	1.8%
Cooper *et al.* (2007)	USA	~20,000	2003	13.3%	10.0%	6.4%	5.9%
Ramos *et al.* (2007)	Canada	97,680	1998-2002	-	3.7%	1.6%	1.1%
Andrade *et al.* (2008)	USA	118,935	1996-2005	6.6%	5.1%	3.8%	4.1%
Engeland *et al.* (2008)	Norway	106,329	2004-6	2.6%	1.1%	0.5%	0.4%
Taylor, Cameron & Julyan (2010)	UK	805	2010	2.86%	2.48%	2.24%	2.48%
Alwan *et al.* (2011)	USA	6,582	1998-2005	4.5%	3.1%	2.2%	2.3%
Colvin *et al.* (2011)[1]	Australia	123,405	2002-5	3.0%[1]	1.7%[1]	1.5%[1]	1.5%[1]
Petersen *et al.* (2011)	UK	114,999	1992-2006	2.7%	2.4%	1.04%	0.99%
Hanley & Mintzes (2014)	USA	343,299	2006-11	6.5%	5.0%	3.6%	3.5%
Margulis, Kang & Hammad (2014)	UK	421,645	1989-2010	-	2.81%	1.31%	1.34%
Wood, Cameron & Julyan (2015)	UK	875	2012	9.83%	9.14%	4.69%	3.89%

[1]SSRIs only

Tables 2-6 and 2-7 imply that perinatal antidepressant prescribing rates vary from country to country - this is likely to be attributable to a number of factors. A full account would require a further systematic review (which is beyond the scope of this thesis), but in anticipation of the more detailed discussion of

methodological issues discussed in Chapter 6, it is worthwhile summarising them briefly here.

The studies in Tables 2-7 and 2-8 were conducted using different databases in each country, which ranged from those including the whole population to others based on subsets, defined by those with certain types of health insurance or benefits, whether private or state-funded. Moreover, some studies excluded those with missing data, over half of the initial number identified in some cases. These aspects had the potential to lead to biases relating to issues such as socioeconomic deprivation and funded access to specialist services or medication. Indeed, as noted by Andrade *et al.* (2008), rates varied between 5.5% and 9.1% in different health plans in 2005, while Hanley and Mintzes (2014) found that rates varied between 6% and 15% in different American states.

Some studies included all pregnancies, whereas other were based only on live births, i.e. they excluded women with pregnancies ending in spontaneous or elective termination, a stillbirth, or birth defects. If antidepressants or the conditions they were being used to treat were associated with increased fetal loss or teratogenicity, this could lead to under-estimates.

Studies varied in defining number of subjects, with some referring to individuals, others pregnancies, and still others live births. This meant that some women with multiple pregnancies during the study period (up to 22 years for Margulis, Kang and Hammad [2014]) were included more than once, leading to potential bias given the association between perinatal depression (and therefore antidepressant use) and multiparity (Redshaw & Henderson, 2013; Sockol & Battle, 2013; Lahti *et al.*, 2014).

Different epochs were used for analysis, with some studies reporting results for specific years, while others averaged their findings over several years. The longer the period over which figures were combined and averaged, the less contemporary relevance they have, given the significant increases in prescriptions for antidepressants (particularly SSRIs) in recent years.

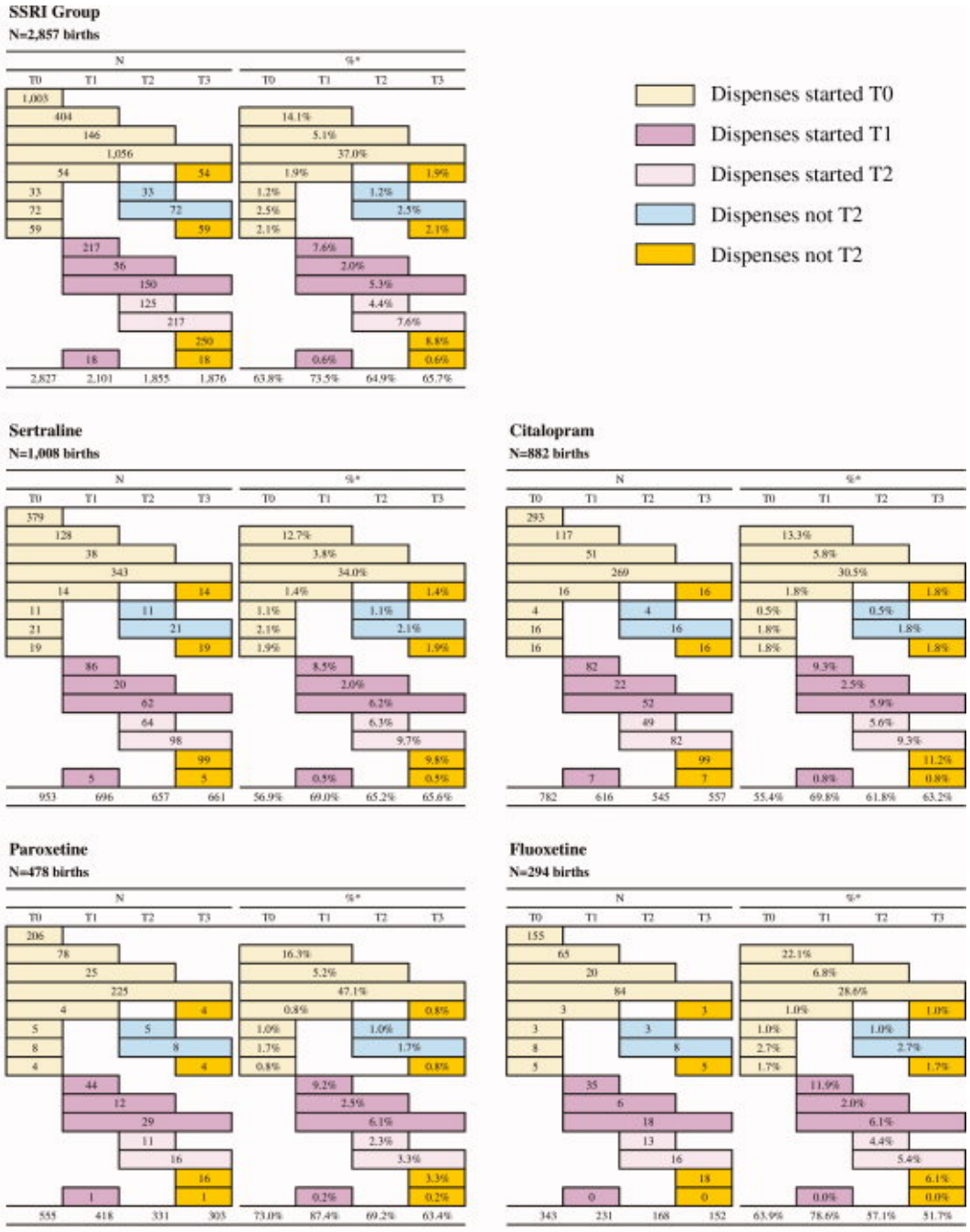
Some studies defined prescriptions as those issued, while others referred to drugs dispensed or reimbursed. It is entirely possible that some prescriptions may not have been captured, particularly those not issued electronically, or by the patients' registered doctor.

Few studies took account of the dynamic nature of antenatal prescriptions, which can include continuing, stopping, pausing/restarting, adding or switching drugs; or maintaining, increasing, or reducing doses; suggesting that using period prevalence alone to define fetal exposure to antidepressants may miss some importance variations in timing, duration, and continuity. The study by Colvin *et al*. (2011) serves to highlight some of the complexity of perinatal prescribing patterns, as illustrated in Figure 2-8. It is important to note that, as with depressive symptoms, prescriptions for antidepressants may come and go for many women during pregnancy (Colvin *et al.*, 2011; Parker *et al.*, 2015).

In addition to defining the start and end of pregnancy to allow an estimate of at what gestational stage(s) medication was taken as noted above, another issue critical to identifying clinically significant fetal exposure to SSRIs is the condition(s) for they were prescribed, and their severity, chronicity and response. It has already been acknowledged that the underlying illnesses for which antenatal psychotropics are prescribed share some sequelae with their pharmacological treatments and hence, for example, low dose tricyclics for pain are not directly comparable to higher dose SSRIs for major depression.

Notwithstanding, studies were broadly consistent in reporting a slight or significant reduction in antidepressant prescribing in T1 as compared to T0, with further reductions in T2 and T3 (Table 2-7). However, as per our findings, this was not a universal phenomenon, and some found either no change between T2 and T3, or a small but potentially significant increase. It has already been noted that many estimates were based on when prescriptions were either issued or dispensed, but this does not necessarily indicate if, when, or how consistently medication was taken, nor therefore define fetal exposure.

Figure 2-8 – Prescribing patterns during pregnancy (from Colvin *et al.*, 2011)



* Percentages are the proportion of all birth events dispensed the medicine within each three month period. If a medicine was dispensed in T0 only, the results are presented but not included in the number of birth events dispensed the medicine.

© 2011 Wiley-Liss, Inc. Birth Defects Research (Part A): Clinical and Molecular Teratology 91:142-152, Dispensing patterns and pregnancy outcomes for women dispensed selective serotonin reuptake inhibitors in pregnancy, Lyn Colvin et al., Figure 1.
https://onlinelibrary.wiley.com/doi/abs/10.1002/bdra.20773

Key points

- Three studies provided significant details of characteristics of antenatal exposure to SSRIs in the UK
- Findings were influenced by methodological heterogeneity
- Prescriptions for SSRIs before, during and after pregnancy have been increasing from 1992 through 2010
- By 2010 up to 1 in 20 British women were exposed to an SSRI at some point during pregnancy
- Prescriptions for SSRIs fell significantly during the first trimester, and again to a lesser degree through the second and third trimesters, before increasing again to postnatal levels higher than those prenatally
- Although most women discontinued SSRIs in the first trimester, some continued throughout pregnancy, some who discontinued restarted in the second or third trimester, and some started *de novo* during pregnancy
- The most common SSRIs prescribed were Fluoxetine and Citalopram, with Sertraline becoming more popular in recent years, and Paroxetine less
- These UK data are comparable to international reports
- Minimal data on the changing patterns, timing and duration of SSRI exposure through the perinatal period were reported, with no details on doses

Chapter 3 - Characteristics of antenatal exposure to SSRIs in a specialist perinatal mental health service

Specialist perinatal mental health services are appropriate settings in which to explore patterns of perinatal prescribing. We extended our analysis of the data from our existing review of the records of patients attending the Glasgow PMHS, to clarify issues surrounding local antenatal psychotropic prescribing, to address the gaps in the literature, and to provide a realistic basis for our proposed scanning study.

Research questions

(1) What proportion of women attending the PMHS was seen during pregnancy?

(2) At what stage of pregnancy were they seen?

(3) How many were prescribed psychotropic medication?

(4) What was prescribed, including at what doses, and when?

(5) With which diagnoses were psychotropics associated?

(6) How many had a primary diagnosis of depression?

(7) How many had a diagnosis of depression, were receiving SSRI monotherapy during pregnancy, and attended in the first or second trimesters, i.e. how many potential scanning participants could be recruited from the PMHS?

Setting and subjects

The Glasgow PMHS was formally established in October 2004 to provide specialist inpatient care for women and babies in the West of Scotland (~25,000 live births per annum) during pregnancy and up to 1 year postnatally, in addition to community/liaison input to the Greater Glasgow area (~10,000 live births per annum) (ISD Births in Scottish Hospitals, 2014). Annual referrals increased from around 250 initially to more than 1,100 by 2017, received from both Primary and Secondary Care, for a variety of reasons, from preconception advice through to tertiary inpatient care. Patients attending the service are from a range of socioeconomic backgrounds and, although several areas of Glasgow are among the most deprived in the UK, there are also patients demographically similar to those reported by the Centre for Maternal and Child Enquiries (CMACE) in the Confidential Enquiries (CMACE, 2011).

Data sources

Data collection forms are routinely completed by clinicians for all patients attending the PMHS – these collate clinically relevant details to facilitate audit, and to provide a basis for research (Appendix 2). Two researchers reviewed all data collection forms available between 2007 and 2009. Anonymised details were entered into a Microsoft® Excel® spreadsheet for descriptive analysis, including age, diagnosis, date/gestation seen, and psychotropic and other medication during pregnancy. A key was established to define how to interpret ambiguities, and agreement reached through discussion where necessary. We annotated each form after its contents had been transferred to the spreadsheet, and noted any uncertainties or missing data, to be verified later with PMHS staff and/or the clinical records. Each form was allocated a unique study number to

allow accurate identification of not only unique subjects, but also discrete episodes of care, as some patients attended the PMHS more than once during different pregnancies. The details harvested from the data collection sheets were not cross-checked with each patient's PMHS record, as our initial audit had not found this fruitful in terms of clarifying ambiguities nor influencing conclusions to any significant degree (Julyan, Cavanagh & Cantwell, 2009).

Psychotropics were defined as antidepressants, antipsychotics (oral or long-acting injectable), or mood stabilisers described in the British National Formulary (BNF) Sections 4.3, 4.2 and 4.2.3 (excluding Benzodiazepines, but including Lamotrigine [Section 4.8.1]), with prescribed Methadone being recorded separately from psychotropics and non-psychotropics, to allow discrete analysis (Appendix 3) (BNF 60, September 2010). Co-prescribing of psychotropics with other psychotropics, non-psychotropics and Methadone was identified. Psychotropic prescribing patterns were categorised according to drug type and timing of exposure to allow analysis via descriptive statistics, including early and late exposure to psychotropics in general, and antidepressants and SSRIs in particular, as per Chambers *et al*. (1996) and Oberlander *et al*. (2008), i.e. any exposure in the first and second trimesters that ended before the third trimester was defined as "early", and any exposure in the third trimester was designated "late". Excel's® inbuilt functions were utilised to calculate median ages at the time of delivery, and filter/sort and analyse data by category.

Contributors

RC (PMHS consultant psychiatrist) arranged access to the data, and helped to refine EJ's research questions. After completing the audit on the first 206 patients, EJ processed a further ~200 data collection sheets; transferred the relevant data to Excel®; trained, supervised and supported RC (medical student) to process an additional ~200 sheets, and transfer to Excel®; and completed descriptive statistical analysis.

Summary sheets were available for 627 women seen between 28 October 2002 and 24 September 2009. Most forms had missing, incomplete, inconsistent, or illegible entries in a variety of data fields (see below). Notwithstanding, we analysed the available information carefully, to answer our research questions as far as the records allowed.

Age at estimated date of delivery

The median age at estimated date of delivery (EDD) in our sample was 31 (range 16-45). We were unable to calculate the age for 34.0% (213/627) women, due to data being unrecorded or unspecified, incomplete or illegible, or self-evidently incorrect (Table 3-1).

Table 3-1 – Missing data

Data	Recorded (%)	(N)	Not recorded/ Specified (%)	(N)	Incomplete/ Illegible (%)	(N)	Incorrect	(N)
DOB	96.3	(604)	3.7	(23)	0	(0)	0	(0)
EDD	68.4	(429)	29.7	(186)	1.6	(10)	0.3	(2)
Date seen	97.8	(613)	1.3	(8)	1.0	(6)	0	(0)

Dates of birth (DOBs) were missing in 3.7% (23/627), of which five also had EDD missing (three were described as “Delivered”, one as “Planning”, and one blank). Of the 31.6% (198/627) EDDs that were unavailable or erroneous, 4.6% (29/627) had no entry, 22.0% (138/627) were recorded as “Delivered”, 2.7% (17/627) as “Planning”, 0.2% (1/627) as “Miscarriage”, and 0.2% (1/627) as TOP (termination of pregnancy); 1.6% (10/627) had one or more digits missing or illegible (e.g. ??/03/05); and two were mistakes (“00/01/08” and “16/07/20098”), presumably typographical errors made when entering data into Excel® (Table 3-1).

Calculating age when first seen at the PMHS reduced the number of missing values to 4.5% (28/627), and yielded identical median age and age range.

Stage seen

“Date seen” was completed for 97.8% (429/627), with 1.3% (8/627) having no entry, and 1.0% (6/627) being incomplete/illegible, e.g. one digit being ambiguous (Table 3-1). In addition to the stages indicated by entries under “EDD”, comparison of the “Date seen” with “EDD” yielded the breakdown summarised in Table 3-2. Stage seen was accurately identified under “EDD” in 85.0% (17/20) as preconception, and in 78.9% (138/175) as postnatal. However, stage seen remained unknown and incalculable in 6.2% (39/627), due to a mixture of missing/incomplete “Date seen” and/or “EDD”. Overall, 62.4% (391/627) were pregnant at the time of initial contact, with the majority being seen later in pregnancy.

Table 3-2 - Stage first seen at the PMHS

Stage first seen	%	(N)
Preconception	3.2	(20)
Pregnant	62.4	(391)
First trimester	3.7	(23)
Second trimester	25.5	(160)
Third trimester	33.2	(208)
Postnatal	27.9	(175)
Post-miscarriage[1]	0.2	(1)
Post-TOP[2]	0.2	(1)
Unknown	6.2	(39)

[1] Miscarriage at 11 weeks, seen at the PMHS 3 weeks later

[2] Termination of pregnancy due to Trisomy 21 (Down's syndrome)

(Neither were documented as taking psychotropic medication during pregnancy)

Diagnoses

The primary diagnoses are shown in Table 3-3, alongside those reported by Durrani and Cantwell (2009), confirming that 49.1% (308/627) were diagnosed with an affective disorder, 41.3% (259/627) with a depressive episode or recurrent unipolar depression (15.9% [100/627], and 25.4% [159/627], respectively), or bipolar affective disorder (6.1%, 38/627).

Types and rates of antenatal psychotropics

Prescribing data for all 627 women are summarised in Table 3-4, showing that 42.1% (264/627) of the women were documented as taking a psychotropic at some point during pregnancy, with 35.2% (93/264) of these co-prescribed non-

psychotropic drugs. Overall, 51.8% (325/627) were documented as having been prescribed at least one drug antenatally, whether a psychotropic or a non-psychotropic. Methadone prescriptions were documented for 4.0% (25/627), and co-prescribed with psychotropics in 3.0% (19/627), representing 7.2% of those on psychotropics (19/264), 6.8% of those prescribed antidepressants (16/235), and 5.7% of those exposed to SSRIs (10/175). Generally speaking, drugs were specified, with only one described as an "antidepressant". Doses were less consistently documented.

Table 3-3 - Primary psychiatric diagnoses

ICD-10	Description	%	(N)	Durrani & Cantwell (2009) (%)
F0x	**Organic, including symptomatic, mental disorders**	**0.2**	**(1)**	**0.4**
F1x	**Mental & behavioural disorders due to psychoactive substance use**	**1.6**	**(10)**	**2.5**
F2x	**Schizophrenia, schizotypal and delusional disorders**	**3.0**	**(19)**	**4.7**
F20	Schizophrenia	1.1	(7)	1.4
F21	Schizotypal disorder	0.2	(1)	0.4
F22	Persistent delusional disorders	0.3	(2)	0.4
F23	Acute and transient psychotic disorders	1.0	(6)	1.4
F25	Schizoaffective disorder	0.3	(2)	1.1
F29	Unspecified non-organic psychosis	0.2	(1)	-
F3x	**Mood (affective) disorders**	**49.1**	**(308)**	**33.6**
F30	Manic episode	0.2	(1)	-
F31	Bipolar affective disorder	6.1	(38)	5.1
F32	Depressive episode	15.9	(100)	14.8
F33	Recurrent depressive disorder	25.4	(159)	11.9
F34	Persistent mood [affective] disorders	1.8	(11)	1.8
F4x	**Neurotic, stress-related & somatoform disorders**	**18.8**	**(118)**	**16.2**
F40	Phobic anxiety disorders	1.3	(8)	1.1
F41	Other anxiety disorders	6.9	(43)	6.5
F42	Obsessive-compulsive disorder	1.4	(9)	2.9
F43	Reaction to severe stress, and adjustment disorders	9.1	(57)	5.4
F45	Somatoform disorders	0.2	(1)	0.4
F5x	**Behavioural syndromes associated with physiological disturbances and physical factors**	**0.6**	**(4)**	**0.4**
F50	Eating disorders	0.3	(2)	-
F51.0	Non-organic insomnia	0.2	(1)	-
F53	Mental and behavioural disorders associated with the puerperium, not elsewhere classified	0.2	(1)	-
F6x	**Disorders of adult personality & behaviour**	**2.4**	**(15)**	**3.6**
F60	Specific personality disorder (unspecified)	0.2	(1)	-
F60.3	Emotionally unstable personality disorder	2.1	(13)	3.2
F68.1	Intentional production or feigning of symptoms or disabilities, either physical or psychological [factitious disorder]	0.2	(1)	-
F7x	**Mental retardation**	**0.6**	**(4)**	**0.4**
N94.3	**Premenstrual tension syndrome**	**0.2**	**(1)**	**-**
Zx	**Factors influencing health status and contact with health services**	**3.7**	**(23)**	**-**
Unknown	**Diagnosis not recorded**	**19.6**	**(123)**	**-**

Table 3-4 – Proportion of women prescribed antenatal medication[1]

	Antenatal medication		+ non-psychotropics		+ Methadone	
	%	(N)	%	(N)	%	(N)
No psychotropics	57.9	(363)	9.4	(59)	1.0	(6)
Psychotropics	42.1	(264)	14.8	(93)	3.0	(19)
Any antidepressant	37.5	(235)	13.2	(83)	2.6	(16)
Antidepressants only	33.5	(210)	11.5	(72)	2.2	(14)
Any SSRI	27.9	(175)	9.4	(59)	1.6	(10)
SSRIs only	23.0	(144)	15.9	(100)	1.0	(6)
SSRI monotherapy	20.9	(131)	6.2	(39)	0.3	(2)
Citalopram	5.7	(36)	1.8	(11)	0	(0)
Escitalopram	0.5	(3)	0.2	(1)	0	(0)
Fluoxetine	8.8	(55)	2.2	(14)	0.3	(2)
Paroxetine	2.1	(13)	0.8	(5)	0	(0)
Sertraline	3.8	(24)	1.3	(8)	0	(0)
Any TCA	6.7	(42)	3.2	(20)	0.6	(4)
Any SNRI	3.5	(22)	1.0	(6)	0.3	(2)
Other ADs	3.2	(20)	1.8	(11)	0.5	(3)
>1 AD	5.1	(32)	2.2	(14)	0.5	(3)
Any mood stabiliser	3.3	(21)	1.0	(6)	0.3	(2)
Mood stabilisers only	1.3	(8)	0.3	(2)	0	(0)
Any antipsychotic	6.4	(40)	2.6	(16)	0.3	(2)
Antipsychotics only	2.7	(17)	1.1	(7)	0.3	(2)

AD = antidepressant, TCA = tricyclic, SNRI = serotonin noradrenaline reuptake inhibitor

[1] Rows and categories do not always add up consistently, due to some patients being co-prescribed non-psychotropics and/or Methadone, and those on mood stabilisers and/or antipsychotics being omitted from the "only" and "monotherapy" categories.

Table 3-4 illustrates the complexity of the prescribing, with the 264 women on psychotropics receiving a mixture of concurrent and consecutive psychotropics and non-psychotropics in patterns defying simple categorisation. Notwithstanding, in essence (and ignoring co-prescriptions for non-psychotropics, mood stabilisers, antipsychotics, and Methadone) 37.5% (235/627) were prescribed at least one antenatal antidepressant, 27.9% (175/627) at least one SSRI, and 20.6% (129/627) SSRI monotherapy only. A further 1.4% (9/627)

women were exposed to two consecutive SSRIs, and no other drugs, but they were not classed as receiving strict SSRI monotherapy – the type of antenatal psychotropic prescribing desirable for our proposed scanning project.

Table 3-5 shows the numbers prescribed each type of psychotropic, whether receiving co-prescriptions for non-psychotropics or not (omitting patients also taking non-psychotropics would have excluded more than one third of the sample). Each row includes any exposure to a psychotropic within that category, regardless of co-prescriptions, unless already counted in a row above. For example, a patient exposed to an SSRI and a TCA would appear in the "Any SSRI" row under the "TCAs" column, but then not in the "Any TCA" row below – the shaded boxes have been left blank to minimize repetition and redundancy.

Of the 32 women exposed to more than one antidepressant, 1.4% (9/627) were exposed to two consecutive SSRIs; 1.3% (8/627) an SSRI and an TCA consecutively; 0.2% (1/627) to two consecutive SSRIs and then a TCA; 0.5% (3/627) an SSRI and an SNRI consecutively; 0.5% (3/627) an SSRI and Trazodone concurrently; 0.2% (1/627) an SSRI following Mirtazapine; 0.2% (1/627) an SSRI and Bupropion concurrently; 0.5% (3/627) a TCA and Mirtazapine, or Reboxetine, or an unspecified antidepressant (respectively); 0.2% (1/627) a TCA and an SNRI consecutively; and 0.2% (1/627) a TCA following concurrent exposure to an SNRI and Reboxetine.

The TCAs consisted of Lofepramine (23/627), Amitriptyline (10/627), Clomipramine (5/627), Dosulepin (2/627), Imipramine (1/627), and Trimipramine (1/672); SNRIs Venlafaxine (20/627) and Duloxetine (2/627); and other antidepressants Mirtazapine (9/627), Trazodone (4/627), Reboxetine (3/627), Bupropion (1/627), and Moclobemide (1/627).

Table 3-5 – Psychotropic co-prescribing[1]

Psychotropic	(N)	SSRIs	TCAs	SNRIs	Other	>1 AD	MS	Lithium	Carbamazepine	Lamotrigine	Valproate	AP	"Typical" Aps	"Atypical" Aps	Methadone
Any AD	(235)	175	42	22	20	32	9	2	4	**1**	2	19	8	13	**16**
Any SSRI[2]	(175)		12	3	3	27	6	2	3	**0**	1	12	7	7	**10**
Any TCA	(42)			2	4	17	4	0	2	**1**	1	5	1	4	**4**
Any SNRI	(22)				1	5	1	0	1	**0**	0	2	0	1	**2**
Other	(20)					11	1	0	1	**0**	0	2	1	2	**3**
>1 AD	(32)						2	0	2	**0**	0	2	1	2	**3**
Any MS	(21)							6	7	**2**	7	7	3	5	**2**
Lithium	(6)								0	**0**	0	3	1	3	**0**
Carbamazepine	(7)									**0**	0	0	0	0	**0**
Lamotrigine	(2)										1	0	0	0	**0**
Valproate	(7)											4	2	2	**2**
Any AP	(40)												21	23	**4**
"Typicals"	(21)													3	**4**
"Atypicals"	(23)														**0**

AD = antidepressant, TCA = tricyclic, SNRI = serotonin noradrenaline reuptake inhibitor, MS = mood stabiliser, AP = antipsychotic.

[1] Figures indicate co-prescribing of the two drugs/classes intersecting, and include patients prescribed other drugs. For example, if a patient was prescribed an SSRI, a TCA, and a mood stabiliser, they would be included in SSRI-TCA, SSRI-MS and TCA-MS. Hence, given the complexity of some of the prescribing patterns, some subjects are represented multiple times in several different places. For simplicity, numbers do not take into account concurrent non-psychotropics.

[2] Includes 10 patients exposed to two different SSRIs (consecutively), with one of these also prescribed a TCA.

Timing of antenatal psychotropics

Again, the data fields defining timing of exposure were frequently incomplete. Reasons for this were not specified, although at least some of the time it appeared to be because patients were seen only once during pregnancy, hence subsequent details were not available. Where drugs were documented in the first trimester, but there was no entry for the second or third trimesters, it was taken that they were stopped in the first trimester. Of the 57 women to whom this applied, 94.7% (54/57) either had a separate entry confirming that the medication was discontinued in the first trimester, or they were seen in the second trimester or later. Conversely, when drugs were commenced in the second or third trimesters, but not mentioned thereafter, we assumed that they were continued until delivery, unless otherwise specified. This was the case for 49 women, 29 of which received SSRI monotherapy (of whom 10 also took non-psychotropics).

Rather than using *a priori* categories into which the data was made to fit, we employed a mixture of stage started, stage stopped, and stage restarted to describe the prescribing patterns (Table 3-6). Thus, P was used to refer to medicines commenced preconception, and 1, 2, or 3, if commenced in the first, second, or third trimesters, respectively. A small "s" was used to identify when medication stopped, with 1, 2, 3 to indicate in which trimester, and "r" to indicate when restarted. For example, Ps1 indicated that a drug taken preconception was stopped in the first trimester, while P signified that the drug was taken throughout pregnancy.

Of the 264 women on antenatal psychotropics, 78.4% (207/264) were taking medication before conception, with 31.0% (82/264) continuing throughout pregnancy, and 36.7% (97/264) stopping in the first trimester (Table 3-6). A number of patients stopped and restarted drugs during pregnancy, several more than once, with 20.5% (54/264) commencing in the second and third trimesters (11.0% [29/264], and 9.5% [25/264], respectively). This pattern was similar for antidepressants in general, and SSRI monotherapy in particular, including the

13.1% (82/627) depressed women receiving only one SSRI. Thus the majority of women taking psychotropics during pregnancy commenced before conceiving.

Table 3-7 presents the same data from a different perspective, indicating the actual numbers of those exposed to psychotropics before and during the three trimesters of pregnancy. Overall, the pattern for SSRI monotherapy was comparable to that of psychotropics in general. Exposure to one SSRI only, i.e. no mood stabilisers, no antipsychotics, and no Methadone (although prescriptions for other non-psychotropics, including benzodiazepines were not excluded) was characterised as follows.

35.2% (94/627) of the total cohort were prescribed SSRI monotherapy before pregnancy, with the majority receiving Fluoxetine (43.6%, 41/94), Citalopram (34.0%, 32/94), or Sertraline (11.7%, 11/94). Overall, 64.9% (61/94) of those exposed to SSRI monotherapy preconception stopped during the first trimester, while 35.1% (33/94) continued. Of those who stopped, two restarted in trimester one, one restarted in trimester two, and two restarted in trimester three. Another woman started and subsequently stopped in the first trimester. Two others started in trimester one, and continued thereafter until delivery. There was variation between individual SSRIs, in that 73.2% (30/41), 63.6% (7/11), and 62.5% (20/32) of those on Fluoxetine, Sertraline, and Citalopram (respectively) stopped, while 37.5% (12/32), 36.4% (4/11), and 26.8% (11/41) of those on Citalopram, Sertraline, and Fluoxetine (respectively) continued.

The overall numbers exposed to psychotropics obscure some of the detail as depicted in Tables 3-6 and 3-7, in that while the majority (67.4%, 87/129) of those exposed to SSRI monotherapy at any point during pregnancy fell into the categories of either commencing preconception and continuing throughout pregnancy (P), or stopping in the first trimester (Ps1), almost one third followed a different, frequently complicated pattern. The first trimester represented the stage during which women were most likely to stop and least likely to start an SSRI; the converse was true for the second and third trimesters.

Table 3-6 – Timing of exposure to antenatal psychotropics

		Timing															Exposure			
	(N)	P	Ps1	Ps1r1	Ps1r2	Ps1r2s2	Ps1r3	Ps2	Ps2r2	Ps3	1	1s1	2	2s2	2s3	3	Early	Late	+ non-psychotropics	+ Methadone
Any psychotropic	(264)	82	97	3	13	1	6	2	1	2	2	1	24	3	2	25	104	160	93	19
Any AD	(235)	68	88	3	12	1	6	1	1	2	2	1	23	3	2	22	94	141	83	16
ADs only	(196)	55	72	3	10	1	5	1	1	2	2	1	20	3	1	19	78	118	63	-
Any SSRI	(175)	47	66	3	9	0	4	0	1	2	2	1	17	2	2	19	69	106	59	10
SSRIs only	(138)	35	56	2	5	0	3	0	0	2	2	1	13	2	1	16	59	79	40	-
SSRI monotherapy	(129)	31	56	2	1	0	2	0	0	2	2	1	14	2	1	15	59	70	38	-
Citalopram	(36)	11	19	1	0	0	0	0	0	1	0	1	2	0	0	3	20	18	11	-
Escitalopram	(3)	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	3	-
Fluoxetine	(53)	9	26	1	1	0	2	0	0	1	1	0	5	1	0	5	27	25	53	-
Paroxetine	(13)	5	3	0	0	0	0	0	0	0	1	0	1	0	0	3	3	10	13	-
Sertraline	(24)	4	7	0	0	0	0	0	0	0	0	0	6	1	1	5	8	16	24	-
Depressed + any SSRI	(82)	20	30	1	1	0	1	0	0	2	2	1	10	1	0	13	32	50	19	-

In the second trimester, 28.7% (37/129) continued their SSRI, 13.2% (17/129) started, and 0.8% (1/129) restarted, while 1.6% (2/129) stopped, with a similar pattern in the third trimester; 38.8% (50/129) continued, 11.6% (15/129) started and 1.6% (2/129) restarted, while 2.3% (3/129) stopped. These observations were complemented by the overall proportion of women exposed to any SSRI monotherapy during pregnancy, 15.5% (97/627) in the first trimester, 8.6% (54/627) in the second trimester, and 11.2% (70/627) in the third. Thus, while most discontinued in the first trimester, this was also when most were exposed, with the reduced rate of exposure in the second trimester gradually increasing into the third trimester.

Table 3-7 – Stage of exposure to antenatal psychotropics

		Any psychotropic	Any AD	Any SSRI	SSRIs only	SSRI monotherapy	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline
	(N)	(264)	(235)	(175)	(138)	(129)	(36)	(3)	(53)	(13)	(24)
Before pregnancy		207	182	132	103	94	32	2	41	8	11
Trimester 1	**Continued**[1]	87	72	50	35	33	12	1	11	5	4
	Started	3	3	3	3	3	1	0	1	1	0
	Stopped	121	111	83	69	62	21	1	30	3	7
	Restarted	3	3	3	3	2	1	0	1	0	0
	Total	210	190	135	106	97	33	2	42	9	11
Trimester 2	**Continued**	89	75	54	40	37	13	1	13	6	4
	Started	29	28	21	17	17	2	0	5	1	8
	Stopped	7	6	3	2	2	0	0	1	0	1
	Restarted	15	14	10	6	1	0	0	1	0	0
	Total	135	118	85	63	55	15	1	20	7	12
Trimester 3	**Continued**	125	109	79	58	50	14	1	18	7	10
	Started	25	22	19	15	15	1	1	5	3	5
	Stopped	4	4	4	3	3	1	0	1	0	1
	Restarted	6	6	4	3	2	0	0	2	0	0
	Total	160	141	106	79	70	16	2	26	10	16

[1] "Continued" refers to those already on the relevant drug at the start of the trimester, and who remained on it throughout that trimester without stopping.

Early and late exposure to antenatal psychotropics

Of those who received a psychotropic during pregnancy, 39.4% (104/264) were exposed in the first and second trimesters only, with 60.6% (160/264) exposed in the third trimester (Table 3-6). With regards to the 129 women receiving SSRI monotherapy, 45.7% (59/129) were exposed in early pregnancy, and 54.3% (70/129) in late pregnancy. Due to lack of precise dates and gestation for starting and stopping each medication, the exact durations of exposure could not be determined.

Timing of exposure to SSRI monotherapy, and stage first seen at the PMHS

With regards to women exposed to SSRI monotherapy, their stage first seen at the PMHS is shown in Table 3-8. Most were seen after the first trimester, i.e. after the majority of prescribing decisions. However, most of those commencing an SSRI in the second or third trimesters were first seen via the PMHS at that stage.

Table 3-8 – Timing of exposure to SSRI monotherapy by stage seen

		Stage of pregnancy first seen at the PMHS			
		Trimester 1	Trimester 2	Trimester 3	Other
	(N)	(1)	(51)	(48)	(29)
P	(31)	0	11	12	8
Ps1	(56)	1	19	19	17
Ps1r1	(2)	0	1	1	0
Ps1r2	(1)	0	1	0	0
Ps1r3	(2)	0	1	0	1
Ps3	(2)	0	1	1	0
1	(2)	0	1	0	1
1s1	(1)	0	0	1	0
2	(13)	0	10	2	1
2s2	(2)	0	2	0	0
2s3	(1)	0	1	0	0
3	(16)	0	3	12	1
Early	(59)	1	21	20	17
Late	(70)	0	30	28	12

Type of exposure by diagnosis

Type of exposure to antenatal psychotropics for all diagnoses is shown in Table 3-9. As per antidepressants only, almost two thirds of those exposed to SSRI monotherapy had a primary diagnosis of depression, and around one fifth a primary diagnosis of a neurotic, stress-related, or somatoform disorder.

Table 3-9 – Antenatal psychotropic exposure by diagnosis[1]

		Psychoses	Bipolar	Depression	Neuroses	Other
	(N)	(19)	(38)	(259)	(118)	(193)
No psychotropics	(363)	2.8	5.2	33.6	20.7	37.7
Any psychotropic	(264)	3.4	7.2	51.9	16.3	21.2
Any AD	(235)	1.3	3.8	56.6	17.9	20.4
ADs only	(196)	0	2.6	61.2	18.9	17.3
Any SSRI	(175)	1.1	4.0	58.9	19.4	16.6
SSRIs only	(138)	0	2.2	63.8	20.3	13.8
SSRI monotherapy	(129)	0	2.3	63.6	19.4	14.7
Citalopram	(36)	0	5.6	63.9	19.4	11.1
Escitalopram	(3)	0	0	66.7	33.3	0
Fluoxetine	(53)	0	1.9	62.3	15.1	20.8
Paroxetine	(13)	0	0	61.5	23.1	15.4
Sertraline	(24)	0	0	66.7	25.0	8.3

[1] expressed as a percentage of those exposed to each type of drug, i.e. each row totals 100%

Of the 259 women with a primary diagnosis of depression, 31.7% (82/259) were exposed to SSRI monotherapy (Table 3-10), with 78.0% (64/82) of these seen during pregnancy, 48.4% (31/64) in trimester two, and 51.6% (33/64) in trimester 3 (Table 3-11).

Table 3-10 - Proportion of women receiving SSRI monotherapy with a primary diagnosis of depression

Diagnosis	%	(N)
F32	18.6	(24)
F33	45.0	(58)

Table 3-11 – Stage first seen for all women receiving SSRI monotherapy, for all diagnosis, and those with a primary diagnosis of depression

	All diagnoses		Depression	
Stage first seen	**%**	**(N)**	**%**	**(N)**
Preconception	1.6	(2)	-	(0)
Pregnant	77.5	(100)	-	(0)
First trimester	0.8	(1)	-	(0)
Second trimester	39.5	(51)	24.0	(31)
Third trimester	37.2	(48)	25.6	(33)
Postnatal	16.3	(21)	10.9	(14)
Unknown	4.7	(6)	3.1	(4)

Table 3-11 reveals that 10.2% (64/627) of the total PMHS sample who received SSRI monotherapy for depression were seen during pregnancy. Of these, more than half attended in the third trimester, possibly too late to be recruited to the scanning study, leaving 31 women seen in the second trimester. 1.8% (11/6.27) were exposed in early pregnancy, and 3.2% (20/627) in late pregnancy. Table 3-12 summarises the prescribing patterns for the 31 women who would have been potential participants in our scanning study.

Table 3-12 – Timing and duration of exposure to SSRI monotherapy for woman with a primary diagnosis of depression attending the PMHS during pregnancy

		Timing (%)									Exposure (%)	
	(N)	P	Ps1	Ps1r1	Ps1r2	Ps3	1	2	2s2	3	Early	Late
Any SSRI[1]	(31)	5.4	7.8	0.8	0.8	0.8	0.8	4.7	0.8	2.3	41.9	58.1
Citalopram	(5)	0.8	1.6	0.8	0.0	0.8	0	0	0	0	40.0	60.0
Escitalopram	(0)	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	(15)	3.1	3.9	0	0.8	0	0	2.3	0.8	2.3	40.0	60.0
Paroxetine	(3)	0.8	0.0	0	0	0	0.8	0	0	2.3	33.3	66.7
Sertraline	(8)	0.8	2.3	0	0	0	0	2.3	0	0.8	50.0	50.0

[1] SSRI monotherapy, i.e. no other antidepressants, mood stabilisers, antipsychotics, or Methadone

Results summary

(1) 62.4% (391/627) of women attending the PMHS were seen during pregnancy, the majority in the second and third trimesters (Table 3-4).

(2) 3.7% (23/627) were seen in the first trimester, 25.5% (160/627) in the second trimester, and 33.2% (208/627) in the third trimester (Table 3-2).

(3) 42.1% (264/627) were exposed to a psychotropic medication during pregnancy (Table 3-4).

(4) Of those exposed to a psychotropic, 89.0% (235/264) were exposed to an antidepressant, 74.2% (196/264) to antidepressants only, 66.3% (175/264) to an SSRI, 52.3% (138/264) to SSRIs only, and 48.9% (129/264) to SSRI monotherapy. Of those exposed to SSRI monotherapy, 42.6% (55/129) took Fluoxetine, 27.9% (36/129) Citalopram, 18.6% (24/129) Sertraline, 10.1% (13/129) Paroxetine 13/129, and 2.3% (3/129) Escitalopram. Doses were neither clearly nor consistently specified. Co-prescribing was common, 35.2% (93/264) with non-psychotropics, and 7.2% (19/264) with Methadone. Of those prescribed an antidepressant, 13.6% (32/235) were exposed to more than one antidepressant, and 10.6% (25/235) were exposed to at least one mood stabiliser and/or an antipsychotic. With regards to those taking SSRI monotherapy, 72.9% (94/129) were exposed at conception, of whom 33.0% (31/94) continued throughout pregnancy, and 67.0% (63/94) stopped during pregnancy; 64.9% (61/94) in the first trimester, and 2.1% (2/94) in the third. A few women who stopped in the first trimester subsequently restarted, 2.1% (2/94) in the first trimester, 1.1% (1/94) in the second, and 2.1% (2/94) in the third. Of those on SSRI monotherapy, 45.7% (59/129) were exposed "early" in pregnancy, and 54.3% (70/129) "late". There were a range of prescribing patterns, with 2.3% (3/129) starting in the first trimester (one stopped almost immediately, and returned to Duloxetine), 13.2% (17/129) starting in the second (with three subsequently stopping), and 11.6% (15/129) starting in the third and continuing until delivery. The SSRIs most commonly started during pregnancy were Fluoxetine and

Sertraline, in 9.3% (12/129) and 10.1% (13/129), respectively (Tables 3-4, 3-5, and 3-6).

(5) The majority of those exposed to psychotropics had a primary diagnosis of depression, and more than 60% of those prescribed antidepressants only (Table 3-9).

(6) 41.3% (259/627) had a primary diagnosis of depression (Table 3-3).

(7) Over the seven years under scrutiny, 4.9% (31/627) women had a primary diagnosis of depression, were exposed to SSRI monotherapy during pregnancy, and attended the PMHS in the first or second trimesters, i.e. were seen early enough to be invited to participate in scanning.

Discussion

These findings represent a detailed analysis of antenatal psychotropic prescribing patterns in a sizeable cohort of patients attending a specialist perinatal mental health service over several years. We have been unable to find comparable published data from the UK. Several findings of both general importance and specific relevance to the scanning study emerged.

Data integrity

There were significant challenges posed by the partial and ambiguous nature of much of the data. Consistent with the findings of Durrani and Cantwell (2009) (who reported that 79% of forms had some sections incomplete), the majority of the data collection forms analysed had one or more blank fields. Despite the intended content of the information fields in the PMHS data collection forms

appearing self-evident, many were completed (or not) in ways that did not provide the kind of detail necessary for accurate and comprehensive analysis.

Although the PMHS did not formally open until 2004, we were able to access forms from 2002 onwards. This was because the lead Consultant Psychiatrist had been providing specialist perinatal care and advice via general psychiatry services in a consultation-liaison model, and had established the practice of collecting and organising clinically relevant data via his bespoke forms alongside the clinical records, to facilitate informed audit, and to provide a basis for research even before the PMHS opened (Appendix 2). These forms were partially mined, to answer some basic questions about the PMHS's clinical activity and practice, as subsequently reported by Durrani and Cantwell (2009). However, when we started processing the forms in 2007 this data had not yet been fully analysed, reported nor published, hence our pre-study assumptions were largely based on anecdotal evidence – that most referrals were from maternity services; that most patients were pregnant when seen; that affective disorders were the most common diagnostic category; that around half received prescribed medication; and that SSRIs were the single most common type of drugs prescribed.

The forms did provide data in a more organised, concise, efficient and relevant way than the clinical records. However, as they had not been designed specifically to answer the questions we were asking, they posed challenges to forensic analysis, particularly with regards to exact timing and amount of exposure to prescribed and other medication, and confounding factors such as alcohol, smoking, and illicit drugs. This appeared partly related to how the forms were laid out, and the amount of space provided to update details of drugs before, during and after pregnancy.

In addition, the forms did not facilitate a longitudinal perspective, with multiple contacts being documented in an easily identifiable way, but rather a snapshot of (mainly) the initial clinical encounter. It was not always clear whether the patients had attended only once, or had been seen multiple times, nor if the forms had been updated by clinical staff at each subsequent attendance, hence

uncertainties over exactly when drugs were started and stopped, and therefore exactly when and for how long fetuses had been exposed. Moreover, patients were seen and forms completed by a variety of clinicians, some of whom were less experienced and only working with the PMHS for short periods, e.g. core psychiatry trainees. It is plausible that their completion of the forms was less detailed and/or relevant than that of the more experienced permanent PMHS staff, and the Consultant Psychiatrist who had initiated the forms.

Furthermore, the data collection forms were simply a summary of the clinical encounter, i.e. information affected by a mixture of patients' recall bias, availability and accuracy of records, the clinician's interpretation, and the time available for documentation (staff were expected to complete forms in addition to the standard clinical entries). We verified the first 206 forms with the clinical records, which clarified some, but not all, of the issues. Overall, cross-checking added little to the details contained in the forms, and did not result in subjects changing categories for analysis, hence was not deemed necessary for the remainder.

Issues of interpretation were seen most clearly in the sections dedicated to smoking, alcohol, and drug use. For example, as alcohol use was documented by stating the number of units consumed each week, it is plausible that figures represented an over- or under-estimate by either patients or clinicians, whether by intention or error. It has been established that women may significantly under-report alcohol use within pregnancy, and that doctors and nurses in general, and psychiatric staff in particular, do not display universally accurate knowledge of units (Ernhart *et al.*, 1988; Anderson, Flanigan & Jauhar, 1999; Webster-Harrison *et al.*, 2001; Das *et al.*, 2009; Das *et al.*, 2014).

Another unexpected challenge was the dynamic nature of the data. Early in the project we were puzzled by the weekly appearance of new forms amongst those already competed, and the disappearance of forms already processed. Forms were stored alphabetically by surname in a folder, and it emerged that the administrative system involved new forms being added as new patients were seen, and old forms belonging to patients discharged from the PMHS being

removed and archived in a separate folder. Moreover, forms for patients who were returning to clinic for review were (sometimes, but not always) removed temporarily to allow them to be updated, then returned to the folder. Furthermore, as forms accrued it became impossible to file them all in one folder, necessitating transfer to further folders, by year seen. This made it difficult to ensure that our cohort was composed of consecutive attendees, and included all patients, to avoid confounding via non-random sampling, e.g. missing those attending for frequent review.

Although the overall impact of data quality issues was difficult to estimate, we found that even minor parameters such as calculating age at EDD or stage seen at the PMHS were affected by missing information. However, we discerned no reason to suspect that the available details were biased, nor unrepresentative of the true facts.

Stage first seen at the PMHS, diagnoses, and the extent of antenatal psychotropics

Perhaps unsurprisingly due to the period prevalence of perinatal mental health problems, more than one third (37.6%, 236/627) of women attending the PMHS for whom data collection forms were available were seen outwith pregnancy, with most of these receiving postnatal care (74.2%, 175/236). This contrasts somewhat with the proportion reported by Battle *et al.* (2006), who found that 63.7% (318/500) of women attending specialist perinatal mental health services in Rhode Island, USA, attended outwith pregnancy, all postpartum. This suggests different emphases between Battle *et al's* services (encompassing both outpatients and day hospital attendees) and the Glasgow PMHS, and may simply reflect the increasing awareness of psychiatric disorders during pregnancy and the development of specialist perinatal mental health services over time, as Battle *et al's* sample were seen between 1999 and 2002.

Similarly, while Battle *et al*. established that 80.6% (403/500) of their cohort had a primary diagnosis of depression (55.9% (57) of the 102 outpatients, and 86.9% (346) of the 398 day hospital attendees), the PMHS had a rate of only half that. As Battle *et al*. did not give a comprehensive breakdown of all diagnoses, it is difficult to comment further, although the smaller proportion of depressed patients in our sample may be attributable to a variety of factors, including demographic and diagnostic issues, service progression, or more patients being seen during pregnancy – Battle *et al's* rates for bipolar affective disorder and neurotic, stress-related and somatoform disorders were substantially lower at 2.0%, and ~11.6%, respectively (although these combined figures mask some differences between their outpatients and day hospital attendees).

Despite the specialist nature of the PMHS, more than half of those attending were not documented as having been prescribed a psychotropic during pregnancy (58.0%, 363/627), including those seen during pregnancy (53.5%, 209/391). While both Durrani and Cantwell (2009) and Julyan, Cavanagh and Cantwell (2009) reported that around 60% of the PMHS attendees were exposed to a psychotropic at some point during pregnancy, this analysis of a larger sample refined this figure down to around 40%. The explanation for this is unclear, although may be due to our sample including women seen later in the development of the PMHS, from 28 October 2002 to 24 September 2009, while Julyan, Cavanagh and Cantwell's sample spanned 30 June 1999 to 27 August 2003, and Durrani and Cantwell covered 1 April 2005 to 31 April 2006.

It could be assumed that most women attending a specialist PMHS would be moderately to severely ill, and therefore require psychotropics. Referrals for milder, uncomplicated cases (in which medication is less likely to be indicated) are generally redirected to the patient's General Practitioner (GP) or sector Community Mental Health Team (CMHT), while those seen via the PMHS tend to be more severely unwell, or have complicated diagnostic or management needs (Dr Cantwell, personal communication). There are several possible explanations why less than half of those attending the PMHS were prescribed a psychotropic, discussed below.

Notwithstanding, we took our findings as being broadly credible and as having face validity, given the experience of the clinicians involved, and the published literature – a significant proportion of pregnant women attending the PMHS, and thus their fetuses, are exposed to psychotropic drugs at some point, and the most common antenatal drugs are antidepressants, especially SSRIs. It followed that our enquiries should be extended to pregnant women in the general population, and that attempts should be made to address the inaccuracies inherent in the data.

Types of antenatal psychotropics

We found examples of women prescribed psychiatric drugs from every available class, including antidepressants, mood stabilisers, and (oral and long-acting injectable) antipsychotics. It proved difficult to know how best to categorise drugs such as Methadone, benzodiazepines, and anticonvulsants as, although they are psychoactive and associated with adverse outcomes for mothers and babies, they are not strictly speaking psychiatric drugs prescribed only for psychiatric illnesses. We chose to classify only antidepressants, mood stabilisers (including Lamotrigine), and antipsychotics as psychotropics, with benzodiazepines being categorised as non-psychotropics, and Methadone being analysed separately. The lack of comparable studies in other specialist perinatal populations has already been noted, although the rates of psychotropic prescribing in the PMHS differed somewhat from those of Battle *et al*. (2006), who reported that 25.4% (127/500) from their sample took a psychotropic, with 83.5% (106/127) of these prescribed an antidepressant. It should be noted, however, that Battle *et al*. reported only "medications at intake", i.e. point prevalence, mainly postpartum, and our figures referred to total prevalence, hence could reasonably be expected to be higher.

Consistent with the published literature, SSRIs were the single most commonly prescribed psychotropics, with patients on SSRI monotherapy comprising 48.9% (129/264) of all patients exposed to a psychotropic, 55.0% (129/235) of those

prescribed an antidepressant and 65.8% (129/196) of those receiving antidepressants only (Margulis, Kang & Hammad, 2014). This is in keeping with current guidelines on the pharmacological management of depressive illness in the non-pregnant population, where SSRIs are recommended as first line agents due to their safety, efficacy and tolerability (NICE CG90, 2009). Largely due to the amount of available data, Fluoxetine has been recommended as the antidepressant of choice during pregnancy, and Sertraline postnatally, due to its relatively low excretion in breast milk – these two SSRIs made up 60.0% (77/129) of SSRI monotherapy, with Citalopram and Paroxetine being the next most commonly used SSRIs (27.9% [36/129] and 10.1% [13/129], respectively). It was noteworthy that when an SSRI was commenced during pregnancy, the most commonly used were Fluoxetine and Sertraline, each comprising 35.5% (11/31) of those starting SSRI monotherapy (Table 3-13).

Timing of antenatal psychotropics

Given the myriad of psychotropics, prescribed at different doses and for different indications, alongside other drugs (including non-psychotropics and Methadone), at different times and for different durations, it proved challenging to know how to categorise prescribing patterns. For the purposes of this study we elected simply to describe each patient's prescribing details, for exposure to all psychotropics combined, as well as their classes (antidepressants, mood stabilisers, and antipsychotics), antidepressants only, and SSRIs monotherapy, including for each specific SSRI (Tables 3-6 and Table 3-12). This allowed us to identify any patterns without pre-specification, to avoid imposition of biases or suppositions.

Antenatal psychotropic prescribing patterns appeared to fall into six main categories, shown in Table 3-13.

Table 3-13 – Categories of antenatal psychotropic prescribing

		Timing					
	(N)	P	Ps1	1	2	3	Other
Any psychotropic	(264)	82	97	2	24	25	34
Any AD	(235)	68	88	2	23	22	32
ADs only	(196)	55	72	2	20	19	28
Any SSRI	(175)	47	66	2	17	19	24
SSRIs only	(138)	35	56	2	14	16	16
SSRI monotherapy	(129)	31	56	2	14	15	11
Citalopram	(36)	11	19	0	2	3	3
Escitalopram	(3)	1	1	0	0	1	0
Fluoxetine	(53)	9	26	1	5	5	6
Paroxetine	(13)	5	3	1	1	3	0
Sertraline	(24)	4	7	0	6	5	2
Depressed + any SSRI	(82)	20	30	2	10	13	7

In order of frequency, the most common patterns of prescribing for SSRI monotherapy were 43.4% (56/129) exposed periconception and stopping in the first trimester, 24.0% (31/129) exposed periconception and continuing throughout pregnancy, 11.6% (15/129) commencing in the third trimester, 10.9% (14/129) commencing in the second trimester, 8.5% (11/129) following various "stop-start" sequences, and 1.6% (2/129) commencing in the first trimester. Five of those who were exposed periconception and stopped in the first trimester subsequently restarted and continued until delivery; two in the first trimester

(one Fluoxetine, one Citalopram), one in the second (Fluoxetine), and two in the third (both Fluoxetine).

Of the women prescribed psychotropics before conception, less than one third were documented as continuing these medicines throughout pregnancy (31.1%, 82/264), and less than one quarter of those exposed to SSRI monotherapy (24.0%, 31/129). This is consistent with other studies in non-specialist populations, which have reported that more than half of those taking an antidepressant before pregnancy stop in the first trimester, with others discontinuing in the second or third (Ververs *et al.*, 2006; Ramos *et al.*, 2007; Petersen *et al.*, 2011; Jimenez-Solem, 2014; Margulis, Kang & Hammad, 2014; Charlton *et al.*, 2015). The relatively low rates of prescribing in the PMHS appeared counterintuitive, in that one might have expected women seen via the specialist PMHS, who are presumably more unwell or have more complex needs, to be more likely to require psychiatric medication throughout pregnancy, with the opposite being true for women who can be managed in primary care, or by their general psychiatry team. There are several possible explanations, including that pregnant women are more likely to stop psychotropic medication if referred to a specialist perinatal mental health service. Conversely, it may be that pregnant women on psychotropics who wish to stop are more likely to be referred for specialist assessment and advice. However, as Cohen *et al.* (2006) found that around two thirds of remitted depressed women who discontinued antidepressants perinconception subsequently relapsed during pregnancy, this may explain why those who stopped medication in the first trimester required specialist psychiatric follow-up.

Women receiving care via the PMHS are not representative of the general population, but are an asymmetrically skewed cohort. For example, pregnant women prescribed SSRI monotherapy for “mild” “uncomplicated” depression are generally not seen by the PMHS, nor those with stable severe mental illnesses already in contact with mental health services. Thus the PMHS sample is more likely to be comprised of “atypical” or “complicated” patients with diagnoses other than unipolar depression, including those with severe current and/or historical perinatal psychiatric disorders. In this regard, it may be expected that

psychotropic prescribing, including polypharmacy, would be common. However, there may be differences in the clinical management of patients attending the PMHS, compared to that provided by CMHTs. Several factors are of potential explanatory relevance, including those specifically relating to patients, referrers, the PMHS clinicians and interventions, and the data itself.

Firstly, patient factors. It may be that women referred to PMHS are more motivated to seek help, and therefore more open to considering alternatives to medication, even if driven mainly by anxiety over possible teratogenicity (Koren, 2014). Indeed, some may seek referral specifically in an attempt to identify non-pharmacological options for their symptoms. It is certainly not the case that everyone referred to or seen via the PMHS is severely or acutely unwell, and only a small proportion of pregnant women on psychotropics from the referable population are referred to or attend the PMHS (Dr Cantwell, personal communication).

Secondly, referrer factors. As most referrals to the PMHS originate from maternity services, it is plausible that some may be motivated to link with the PMHS when they suspect that antenatal psychotropics are not necessary, and could be safely discontinued (Durrani & Cantwell, 2009). (The corollary is that mums-to-be with more severe mental health problems, who are stable on long term psychotropics, and who are receiving care from a general psychiatry service or CMHT, may be less likely to be referred, due to the perception that this would not change management.) Moreover, as the PMHS became known over time, and midwives and others became more aware of and screened for perinatal mental health problems, it is also possible that the increasing number of referrals included women who did not require medical treatment. For example, while 48.3% (232/480) of those with an ICD-10 “F” code (indicating a mental, behavioural, or neurodevelopmental diagnosis) received a psychotropic during pregnancy, only 21.8% (32/147) with other/no diagnosis were exposed. (These 147 women comprised 24 with an ICD-10 “N” or “Z” code, of whom 12.5% [3/24] were on a psychotropic, and 123 with no diagnosis recorded, of whom 23.6% [29/123] were exposed to psychiatric medication.) In other words, around 50% of those with a psychiatric diagnosis were prescribed a psychotropic,

although this included conditions for which psychiatric medication is not necessarily indicated nor routinely prescribed.

Thirdly, PMHS factors. The PMHS clinicians have special experience in managing perinatal mental health problems, and hence might have different thresholds for starting and stopping psychiatric drugs during pregnancy. Furthermore, the availability of non-pharmacological interventions offered by the specialist PMHS may have the potential to enable women to stop medication due to the psychosocial support available, in contrast to the more limited therapies available via GPs or CMHTs. It is also conceivable that expectant mothers may be more willing to try stopping their medication if they are confident that they will be closely followed-up, and monitored for relapse.

Fourthly, data quality. The apparent low rates of prescribing may be explained simply by the data being inaccurate. As intimated above, in the early stages of data collection we crosschecked the contents of the first 206 data collection forms with each patient's PMHS records, as most sheets had sections that had not been completed, and some of the information was ambiguous. Even then not all queries could be addressed, and several issues emerged. Firstly, the data collection forms were not specifically designed to collect information in a way that allowed us to answer the specific questions we posed, particularly with regards to timing of exposure to medication throughout pregnancy. Secondly, while the forms were generally populated to some extent at patients' first contact, they were not necessarily completed nor updated at subsequent appointments. Thus the data was incomplete, leading to a potential under- or over-estimate of prescribing rates, e.g. if a patient commenced a psychotropic after being seen by or discharged from the PMHS, this would not have been captured by our methods, and vice versa. Thirdly, the data were ultimately based on patients' self-reporting of what medication they were taking, introducing potential recall bias, and inaccuracies relating to patients' knowledge and adherence to treatment as prescribed, i.e. what drug, at which dose, for how long, and at what stage(s) of pregnancy. However, we did not attempt to harmonise the data from the following 421 sheets with the clinical records, as the anticipated inaccuracies appeared unlikely to influence our

overall conclusions and subsequent actions at this stage, in addition to medicolegal, ethical and information governance considerations related to accessing the PMHS patients' clinical records.

Notwithstanding, we noted that despite the apparent reduction in ongoing exposure to SSRI monotherapy in this sample from 15.0% (94/627) periconception to 8.8% (55/627) by the second trimester due to patients discontinuing in the first trimester, there was an increase back to 11.2% (70/627) by the third trimester, mainly due to patients starting an antidepressant for the first time during pregnancy (Table 3-7). This trend was reflected in the rates for other antidepressants and psychotropics, and is consistent with the twin observations that women attending the PMHS are seen later in pregnancy, and are more likely to be unwell, thus requiring medical treatment. This is a finding that contrasts somewhat with those reported in general (non-specialist) perinatal populations as outlined in Chapter 2, and appears related both to the different samples, and the different methodologies employed to estimate exposure, discussed further in Chapters 6 and 8 (see Figures 2-3, 2-4, 2-5 and 8-5).

Categories of exposure to antenatal psychotropics

The ultimate aim of characterising antenatal exposure to psychotropic medication is to identify which types of exposure are associated with which sequelae, and to establish valid predictor variables for specific outcomes. Studies exploring the progenic consequences of antenatal antidepressants have frequently dichotomised the exposure type into fetuses exposed during the first trimester, and those exposed later in pregnancy, with the former generally being evaluated with regards to miscarriage and/or congenital malformations, and the latter for neonatal and longer term neurobehavioural outcomes (e.g. Maschi *et al.*, 2007; Ramos *et al.*, 2008; Nakhai-Pour, Broy & Bérard, 2010; Ban *et al.*, 2012; Ban *et al.*, 2014). Some researchers have investigated length/duration of exposure as a related but distinct variable, concluding that this may be a better predictor of adverse birth outcomes than timing of

exposure (e.g. Oberlander *et al.*, 2008; Casper *et al.*, 2011), discussed further in Chapters 5 and 6.

We were unable to calculate the length of exposure accurately from the data available. This was not critical for our conclusions above, as we were not exploring consequences of exposure at this stage of our enquiries. Nevertheless, as exploring outcomes of exposure was a planned future step, we used the definition of "early" and "late" exposure used by Chambers *et al.* (1996) to estimate how many neonates may be at increased risk of short term sequelae (Table 3-6).

Whether considering all antenatal psychotropics together, antidepressants only, or SSRI monotherapy, (with the exception of Fluoxetine) we found that at least half of the women prescribed drugs were exposed later in pregnancy. In other words, given that fetal exposure to SSRIs longer and later in pregnancy may convey a higher risk of early complications, it is possible that a sizeable proportion of women seen at the PMHS will deliver babies with neonatal complications that may or may not require specialist intervention, or be at longer term risk of adverse outcomes.

However, duration of exposure is related to several other factors, including timing and severity of illness, access to medical advice and care, maternal preferences and adherence to prescribed drugs, and intertwined issues such as medication efficacy and tolerability. Decisions on when to start, stop and continue medication are made personally and clinically, taking into account each individual patient's presentation and preferences, in addition to their doctor's experience, with a joint weighing of the potential advantages and disadvantages. Furthermore, while it is likely that patients with more severe illness will persist with prescribed medication for longer, illness severity and duration itself may contribute to at least some of the risks associated with duration of exposure (Oberlander *et al.*, 2008).

Prescribing decisions

It was noteworthy that while the majority of prescribing decisions were made in the first trimester (including whether to stop or continue medication), most women were not seen in the PMHS until the second or third trimester (Tables 3-2 and 3-8). This is in keeping with Durrani and Cantwell's finding that the majority of referrals originated from maternity services, where women are usually seen for "booking" towards the end of the first trimester. This does indicate, however, that potentially significant specialist input with regards to the risks and benefits of stopping, continuing or commencing medication may not be accessed by most women either before, or early enough within, pregnancy.

Notwithstanding, many of those who stopped or started medication during pregnancy were seen before or during the trimester of change; it appeared that around 20-25% of prescription changes may have been made alongside PMHS involvement.

Identifying potential participants for scanning

One aim of our analysis was to estimate how many depressed women on SSRI monotherapy we would be able to recruit for our proposed scanning study. Only 4.9% (31/627) of the sample would have been potential participants, although a further 5.3% (33/627) may have been suitable, save for attending the PMHS in the third trimester, possibly too late to take part. This suggested that 5-10% of the >200 women who attend the PMHS each year may be eligible, perhaps up to 20 women each year, 1-2 per month. However, as we also sought depressed unmedicated women as well as healthy unmedicated controls, we agreed that we may need to look outwith the PMHS to recruit, and consider seeking subjects from general maternity services, as well as from GPs and CMHTs.

Challenges to analysis

The above account of different antenatal psychotropic drugs - alone and in combination with other psychotropics, non-psychotropics, and Methadone; at different stages of pregnancy; for varying lengths of time; and in heterogeneous maternal clinical states - illustrates the complexity of this area of enquiry (see also Figure 2-8). Yet for a full understanding of the consequences, a detailed and nuanced awareness of antenatal exposure to psychotropics is necessary, in conjunction with other parameters influencing offspring's neurodevelopment, including paternal factors (e.g. genotype; age at conception; mental health), maternal factors (e.g. genotype; mental illness type, timing, severity, and functional impact; adherence to medication; drug metabolism/serum levels; substance misuse; personality; lifestyle), obstetric factors (e.g. placental transfer; complications) and fetal factors (e.g. genotype; birthweight).

Future work

Given that the above findings were specific to a specialist perinatal population, we progressed to undertake a pilot study into establishing the characteristics of antenatal exposure to psychotropic medication in a general maternity sample.

Key points

- ~2 in 3 women attending the PMHS were seen during pregnancy, mainly in the second and third trimesters.
- ~2 in 5 took psychotropic medication at some point during pregnancy, with ~1 in 4 exposed to SSRI monotherapy.
- ~2 in 5 attending the PMHS had a primary diagnosis of unipolar depression.
- ~1 in 2 with depression were exposed to a psychotropic (virtually all antidepressants), and ~1 in 3 to SSRI monotherapy.
- ~2 in 3 exposed to SSRI monotherapy had a primary diagnosis of unipolar depression.
- Attending the PMHS was associated with an increased rate of exposure to psychotropics in general, and SSRIs in particular, as pregnancy progresses, presumably because those seen are referred due to significant mental health problems.
- PMHS data collection forms were not necessarily complete or accurate.
- Our findings are not likely to be fully representative of the general population.

Chapter 4 - Characteristics of antenatal exposure to SSRIs in a general maternity sample

Phase 1 Antenatal psychotropics in a general maternity sample

Given that our findings in the Glasgow PMHS were unlikely to be representative of the non-specialist population, we set out to establish the characteristics of psychotropic prescribing during pregnancy in women attending a general maternity service. It was agreed to repeat the methodology employed within the PMHS, as far as the general maternity data would allow, to address our research questions (below). We also aimed to establish what relevant data could be extracted from routine clinical records.

Research questions

(1) What proportion of women was prescribed psychotropic medication during pregnancy?

(2) What was prescribed, at what doses, and when?

(3) With which diagnoses were psychotropics associated?

Methods

Subjects and setting

Ayrshire Maternity Unit (AMU) was selected as a suitable site for this pilot study. Established in 2006, AMU serves the whole of Ayrshire (a relatively stable

population of around 370,000), oversees ~3,800 live births annually, and collects electronic data on all patients, that can be linked to their mental health records and other databases, including the Information Services Division (ISD) of the National Health Service in Scotland. AMU is located within University Hospital Crosshouse, and is served by a psychiatric Maternity Liaison Service (MLS), also established in 2006. Effective working relationships between AMU and the MLS clinical staff have been developed, with the MLS raising awareness of perinatal mental health issues, providing education on perinatal mental health to the midwives, and supporting obstetric staff in identifying women with current and historical psychiatric disorders, and those at increased risk of new onset illness, e.g. those with a family history or bipolar affective disorder or puerperal psychosis (NICE CG45, 2007). The MLS has access to Eclipse, the electronic patient record and database used by AMU (see below). We interrogated Eclipse using its built-in reporting tools, to identify all postnatal women discharged from AMU within a three month period (24 May to 23 August 2010, inclusive), reviewing details of frequency, type and timing of antenatal psychotropics (defined as per Chakrabarti, Julyan & Cantwell, 2010; Appendix 3), in addition to any referrals to the MLS. These data were exported to a Microsoft® Excel® worksheet, anonymised, and descriptive statistical analysis, using Excel's® inbuilt functions. We registered the project via Healthcare Quality, who confirmed that formal R&D/ethical approval was not required.

Eclipse

Eclipse, the System C Medway Maternity Information System www.systemc.com/our-solutions/medway-maternity/, is used to register and store information on all women receiving obstetric care in AMU, and has fields specifically dedicated to historical and current mental health problems, and medication, explicitly including psychotropics, in addition to sections for standard comprehensive obstetric assessment and management. A new Eclipse record is generated for every woman who registers ('books') to receive

antenatal care and/or deliver at AMU, and clinical details are entered and updated following outpatient and inpatient contact.

Contributors

EJ generated the research questions; planned the methodology; arranged access to Eclipse via MC (MLS consultant psychiatrist); trained, supervised and supported RT (elective medical student) in transferring relevant data to Excel®; and completed descriptive statistical analysis.

Results

A total of 805 postnatal women discharged from AMU during the study period were identified, but similar to the PMHS data collection forms, not all relevant data fields in Eclipse were consistently populated. Furthermore, it was not clear that Eclipse had been updated following each clinical contact. Due to these uncertainties over the accuracy of the data, it was not possible to establish full details, and we were unable to verify details with the patients' clinical records *post hoc*, as the information had been anonymised as it was entered. In particular, it was not possible to determine maternal diagnoses, details for all psychotropics, nor particulars of non-psychotropics prescribed. Notwithstanding, several findings emerged.

Type of drug

Table 4-1 summarises prescribing data for all 805 women, showing that 3.0% (24/805) of the women were documented as having been prescribed a psychotropic medication during pregnancy. All but one received an antidepressant (95.8%, 23/24), and 87.5% (21/24) of those on psychotropics were

exposed to antidepressant monotherapy, with 75.0% (18/24) prescribed one SSRI only. In other words, 2.2% (18/805) of the whole cohort were exposed to SSRI monotherapy at some point during pregnancy. Of the other three women on non-SSRI antidepressant monotherapy, one was prescribed a tricyclic, and two received another class of antidepressant (one Duloxetine, one unspecified), as detailed in Table 4-2. The three women not on antidepressant monotherapy (0.4% of the total sample) received 'atypical' antipsychotics – one received Aripiprazole monotherapy, and two were co-prescribed Olanzapine alongside an antidepressant (one Amitriptyline, and one Sertraline). None were documented as having received a mood stabiliser. The most common drugs prescribed were the SSRIs Fluoxetine, Citalopram, and Sertraline, taken by 41.7%, 16.7%, and 12.5% (10/24, 4/24, and 3/24), respectively.

Table 4-1 – Proportion of women prescribed antenatal medication

	Antenatal medication	
	%	(N)
No psychotropics	97.0	(781)
Psychotropics	3.0	(24)
Any antidepressant	2.9	(23)
Antidepressants only	2.6	(21)
Any SSRI	2.4	(19)
SSRIs only	2.4	(19)
SSRI monotherapy	2.2	(18)
Citalopram	0.5	(4)
Escitalopram	0.1	(1)
Fluoxetine	1.2	(10)
Paroxetine	0.0	(0)
Sertraline	0.4	(3)
Any TCA	0.2	(2)
Any SNRI	0.1	(1)
Other ADs	0.1	(1)
>1 AD	0	(0)
Any mood stabiliser	0	(0)
Mood stabilisers only	0	(0)
Any antipsychotic	0.4	(3)
Antipsychotics only	0.1	(1)

Table 4-2 - Type, dose, timing and duration of antenatal psychotropics, and referrals to MLS

Subject	Type	Dose	Timing	Exposure	Referred to MLS
14	Fluoxetine	60mg	P	Late	Yes
23	Fluoxetine	?	Ps1	Early	No
96	Aripiprazole	20mg	3	Late	No
108	Escitalopram	20mg	P	Late	No
131	Fluoxetine	20mg	Ps1r1	Late	No
135	Fluoxetine	20mg	P	Late	No
153	Sertraline	50mg	1	Late	Yes
185	Amitriptyline	20mg	P	Late	No
240	Duloxetine	60mg	P	Late	No
251	Citalopram	20mg	P	Late	No
262	Fluoxetine	20mg	P	Late	Yes
263	Antidepressant (unspecified)	?	Ps1	Early	Yes
266	Sertraline	50mg	P	Late	Yes
329	Amitriptyline Olanzapine	50mg 5mg	P	Late	Yes
361	Sertraline Olanzapine	? 10mg	P	Late	No
376	Sertraline	25mg	P	Late	No
404	Fluoxetine	20mg	P	Late	No
413	Fluoxetine	20mg	P	Late	No
419	Fluoxetine	20mg	P	Late	No
433	Citalopram	20mg	3	Late	No
597	Fluoxetine	20mg	P	Late	No
680	Fluoxetine	20mg	P	Late	No
787	Citalopram	?	?	?	No
789	Citalopram	20mg	3	Late	Yes

Timing of drug

Eclipse indicated that 79.2% (19/24) of the women exposed to a psychotropic during pregnancy started prior to conception, with 66.7% (16/24) continuing throughout pregnancy, and 12.5% (3/24) stopping in the first trimester (Table 4-3). One of the latter restarted in the first trimester (4.2%, 1/24), with another woman starting in the first trimester (4.2%, 1/24), and three in the third trimester (12.5%, 3/24). Details of dose and timing were unclear for one subject on SSRI monotherapy (Citalopram). Overall 16.7% (4/24) commenced medication during pregnancy, 4.2% (1/24) in the first trimester and 12.5% (3/24) in the third trimester, and all continued until term. In keeping with the PMHS findings, the timing of exposure to SSRIs was similar to that of psychotropics overall (Table 4-3).

Table 4-4 summarises the actual numbers of those exposed to psychotropics before and during the three trimesters of pregnancy, showing little variation throughout pregnancy, as although three women stopped medication in the first trimester, one restarted shortly thereafter, and three additional patients commenced a psychotropic in the third trimester - two patients commenced SSRI monotherapy (Citalopram), and one started antipsychotic monotherapy (Aripiprazole). 2.2% (18/805) of the sample were prescribed SSRI monotherapy before pregnancy, with the majority receiving Fluoxetine (55.6%, 10/18), Citalopram (22.2%, 4/18), or Sertraline (16.7%, 3/18). Overall, 16.7% (3/18) of those exposed to SSRI monotherapy preconception stopped during the first trimester, while 80.0% (8/10), 66.7% (2/3), and 25.0% (1/4) of those on Fluoxetine, Sertraline, and Citalopram (respectively) continued. 54.2% (13/24) of those on SSRI monotherapy commenced preconception and either continued throughout pregnancy, or stopped in the first trimester. Of the others, one was exposed preconception, stopped in the first trimester, and then restarted, continuing thereafter until delivery; one commenced in the first trimester; two commenced in the third trimester; and details were not available for the fourth.

Table 4-3 – Timing of exposure, and referrals to MLS, by type of psychotropic[1]

		Timing					Exposure		Referred to MLS
	(N)	P	Ps1	Ps1r1	1	3	Early	Late	
Any psychotropic	(24)	16	2	1	1	3	2	21	7
Any AD	(23)	16	2	1	1	2	2	20	7
ADs only	(21)	14	2	1	1	2	2	18	6
Any SSRI	(19)	13	1	1	1	2	1	17	5
SSRIs only	(19)	12	1	1	1	2	1	16	5
SSRI monotherapy	(18)	12	1	1	1	2	1	16	5
Citalopram	(4)	1	0	0	0	2	0	3	1
Escitalopram	(1)	1	0	0	0	0	0	1	0
Fluoxetine	(10)	8	1	1	0	0	1	9	2
Paroxetine	(0)	0	0	0	0	0	0	0	0
Sertraline	(3)	2	0	0	1	0	0	3	1

[1] Details for one patient taking Citalopram were not specified, and one antidepressant type was unknown.

Table 4-4 – Stage of exposure to antenatal psychotropics[1]

			Any psychotropic	Any AD	Any SSRI	SSRIs only	SSRI monotherapy	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline
		(N)	(24)	(23)	(19)	(19)	(18)	(4)	(1)	(10)	(0)	(3)
Before pregnancy			19	19	15	15	14	1	1	10	0	2
Trimester 1	**Continued[2]**		16	16	13	13	12	1	1	8	0	2
	Started		1	1	1	1	1	0	0	0	0	1
	Stopped		3	3	2	2	2	0	0	2	0	0
	Restarted		1	1	1	1	1	0	0	1	0	0
	Total		20	20	16	16	15	1	1	10	0	3
Trimester 2	**Continued**		18	18	15	15	14	1	1	9	0	3
	Started		0	0	0	0	0	0	0	0	0	0
	Stopped		0	0	0	0	0	0	0	0	0	0
	Restarted		0	0	0	0	0	0	0	0	0	0
	Total		18	18	15	15	14	1	1	9	0	3
Trimester 3	**Continued**		18	18	15	15	14	1	1	9	0	3
	Started		3	2	2	2	2	2	0	0	0	0
	Stopped		0	0	0	0	0	0	0	0	0	0
	Restarted		0	0	0	0	0	0	0	0	0	0
	Total		21	20	17	17	16	3	1	9	0	3

[1] Details for one patient taking Citalopram were not specified, and one antidepressant type was unknown.

[2] 'Continued' refers to those already on the relevant drug at the start of the trimester, and who remained on it throughout that trimester without stopping.

Early and late exposure to antenatal psychotropics

As per Tables 4-3 and 4-4, Eclipse implied that of those who were prescribed a psychotropic during pregnancy, 8.3% (2/24) were exposed in the first and second trimesters only, while 87.5% (21/24) were exposed in the third trimester. A similar pattern emerged for those on SSRI monotherapy, with 5.6% (1/18) exposed in early pregnancy, and 88.9% (16/18) in late pregnancy. The exact durations of exposure in days could not be determined from the Eclipse data.

Referrals to the MLS

According to Eclipse, 1.6% (13/805) of the total sample were referred to the MLS (Table 4-5). Although 53.8% (7/13) of these were prescribed psychotropic medication during pregnancy, 70.8% (17/24) of those on psychotropics were not referred to the MLS, i.e. 2.1% (17/805) of the total sample, including two taking antipsychotics, one of whom commenced their antipsychotic in the third trimester. In other words, the majority of pregnant women documented by their midwives as receiving psychiatric medication were not referred for specialist mental health review, and around half of those referred to the MLS were not receiving psychotropics. Of the three patients commencing psychotropic monotherapy in the third trimester (one Aripiprazole, and two Citalopram), one of those started on Citalopram was documented as having been referred to the MLS.

Table 4-5 - Referrals to the MLS

	Referred to the MLS	Not referred to the MLS	Total (%)
Exposed to psychotropics	7	17	24
Not exposed to psychotropics	6	775	781
Total	13	792	805

Results summary

(1) 3.0% (24/805) of women who delivered at AMU were documented as being exposed to a psychotropic medication during pregnancy, and 2.4% (19/805) to an SSRI (Table 4-1).

(2) Of those exposed to a psychotropic, 95.8% (23/24) were exposed to an antidepressant, 87.5% (21/24) to antidepressants only, 79.2% (19/24) to an SSRI, 79.2% (19/24) to SSRIs only, and 75.0% (18/24) to SSRI monotherapy. Of those exposed to SSRI monotherapy, 55.6% (10/18) took Fluoxetine, 22.2% (4/18) Citalopram, 16.7% (3/18) Sertraline, 5.6% (1/18) Escitalopram, and none Paroxetine. Type and dose were not specified for one antidepressant, and details of dose and timing were not documented for one woman on SSRI monotherapy (Citalopram). Doses were specified for all but four antidepressants (three SSRIs, and one unknown, Table 4-2), and both women exposed to a tricyclic received low dose Amitriptyline (50mg, and 20mg), suggesting an indication other than depression. Co-prescribing was less common than in the PMHS, with (2/24) receiving an antidepressant and an antipsychotic. None were exposed to more than one antidepressant during pregnancy. Of those prescribed SSRI monotherapy, 77.8% (14/18) were exposed at conception, of whom 85.7% (12/14) continued throughout pregnancy. 14.3% (2/14) stopped during pregnancy, both in the first trimester, one of whom restarted in the first trimester. Of those on SSRI monotherapy, 5.6% (1/18) were exposed "early" in pregnancy, and 88.9% (16/18) "late" (Table 4-3). Prescribing patterns were less varied than in the PMHS, with 5.6% (1/18) starting in the first trimester, none in the second, and 11.1% (2/18) in the third – all who commenced during pregnancy continued until delivery. The SSRIs started during pregnancy were Citalopram and Sertraline, in 11.1% (2/18) and 5.6% (1/18), respectively (Tables 4-2 and 4-3). Exposure rates to antidepressants [SSRIs] in trimesters one, two, three, and pregnancy as a whole were 2.5% (20/805) [2.0%, 16/805], 2.2% (18/805) [1.9%, 15/805], 2.5% (20/805) [2.1%, 17/805], and 2.9% (23/805) [2.4%, 19/805], respectively.

(3) Diagnoses were not available.

Discussion

These data provide a retrospective estimate of antenatal psychotropic prescribing patterns in a sample of women representative of the general population. As expected, rates of prescribing were significantly less than those found in the Glasgow PMHS, and prescribing patterns less varied.

Data integrity

However, as with the PMHS data collection forms, numerous fields in Eclipse were unpopulated, and it was not clear that information was updated following each clinical contact. Therefore, the details may be incomplete and hence inaccurate. As discussed in Chapter 6, this could lead to an under- or over-estimate of antenatal prescribing, due to failure to identify medication started or stopped after booking, respectively. Moreover, anonymising the data as it was processed had the unintended consequence of rendering us unable to clarify any ambiguities or omissions from the clinical records, or indeed, even calculate ages. As before, issues such as patients forgetting, misremembering, or not disclosing information about psychotropics may also have influenced our findings, in addition to the quality of assessment and documentation by AMU staff. Furthermore, given the number of different fields used to record details in Eclipse, it is possible that we missed some references to antenatal psychotropics, despite the care taken.

Nevertheless, our findings of 2.9% and 2.4% exposed to antenatal antidepressants and SSRIs (respectively) were not inconsistent with other UK and international reports, as discussed in Chapter 2 (our figures included as Taylor, Cameron & Julyan [2010] to two decimal places for comparison in Tables 2-6 and 2-7).

Our prevalence rates were broadly comparable for T1, but appeared proportionately significantly higher in T2 and T3 than those reported by Petersen *et al*. (2011) and Margulis, Kang and Hammad (2014) (Table 2-7). The latter study in particular is worthy of discussion in this context. As per our findings that 84.2% (16/19) of those taking antidepressants periconception continued throughout pregnancy and only 15.8% (3/19) stopped in T1, and in contrast to Margulis, Kang and Hammad's (2014) report that 79.6% stopped in T1, Eclipse indicated that antenatal exposure reduced slightly from T1 to T2, but returned to (and slightly exceeded) T0 levels by T3 (Table 4-4).

This difference may be attributable to various factors influencing both our and Margulis, Kang and Hammad's methodologies. As noted in relation to the PMHS in Chapter 3, we may have under- or over-estimated prevalence, due to patients' reports, clinicians' assessments and documentation, and inadequate updating of data at follow-up. As Margulis, Kang and Hammad interrogated a high quality inclusive electronic database, it could be assumed that their findings were more accurate. However, a number of factors may also have influenced their conclusions, some (but not all) of which they acknowledge and discuss.

Firstly, their sample may not be truly representative of the general population, as their inclusion criteria effectively excluded over half of the relevant sample. This was considered necessary for the sake of data quality, and ensuring that details of patients' prescriptions for all time periods studied were available. However, it was not clear whether the requirement to be registered from six months before pregnancy until three months postpartum referred to registration with any participating practice, or the CPRD itself. This may have systematically excluded certain subsets of the population, e.g. those who moved frequently, or

who were removed from practices for non-attendance, leading to an underestimate of prevalence, as depressed women may be less likely to attend antenatal appointments (Walsh, 2009; Grzeskowiak, Gilbert & Morrison, 2012a). The AMU sample was representative, albeit small in size.

Secondly, the prescribing data was based on prescriptions issued, as recorded in the CPRD. This is one step removed from prescriptions actually being dispensed, and yet further from medication actually being taken as prescribed. Estimates suggest that around 90% of prescriptions issued are dispensed (Jick, Jick & Derby, 1991). Skurtveit *et al.* (2014) compared self-reported use of prescribed medication during pregnancy (established from MoBa, a large population-based prospective pregnancy cohort study of >90,000 mothers) with the national Norwegian Prescription Database (NorPD) (which includes all drugs dispensed to outpatients). They found that while there was good agreement between the MoBa and NorPD, in that both yielded a figure of 1.0% for antidepressants taken during pregnancy, the NorPD figure increased to 1.3%, then 1.5%, when 30 days and 60 days before pregnancy, respectively, were also taken into account. This indicates that issues surrounding estimating exactly when pregnancy begin, and thus defining the exact stage at which perinatal prescriptions are issued, dispensed, and actually taken, are critical in estimating exposure rates. (The difficulties in identifying the date of conception and hence stage of gestation from databases are well-recognised, and are discussed further in Chapter 6 (Margulis *et al.*, 2013; Margulis *et al.*, 2015). One important matter is how definitions of exposure such as that used by Margulis, Kang and Hammad can influence estimates of exposure rates – if a one or two month supply of medication is issued in T0 but not thereafter, the early fetus may be exposed in T1, even though no prescription was issued in that epoch (Grzeskowiak, Gilbert & Morrison, 2012b; Grzeskowiak, Gilbert & Morrison, 2013). Conversely, and as they acknowledge, prescriptions issued in T3 may be intended for T4 use, and hence artificially inflate T3 prevalence. The AMU data were prone to other limitations, including that they were based on what midwives established from patients, encompassing issues such as the adequacy and detail of history taking, and patients' knowledge and recall.

Thirdly, a related issue is the difficulty in interpreting exactly what prescriptions represent. In an ideal world, patients would pick up monthly prescriptions for unambiguous quantities of medication. However, this is frequently not the reality. Timing, dose, and quantity can affect interpretation, as can potential duplicates. For example, if a patient is prescribed 84 Fluoxetine 20mg tablets, this could represent a three month supply of Fluoxetine 20mg daily, or a one month supply of Fluoxetine 60mg daily, or even a two month supply of Fluoxetine 20mg daily for one month, followed by titration to 40mg daily thereafter. Prescriptions issued or dispensed earlier or later than anticipated may either indicate lost scripts, dose changes, or inconsistent adherence. Moreover, they do not necessarily reveal when the drugs were actually taken. In the absence of other data, interpreting exactly what was taken, at what dose, and when, can be largely a matter of guesswork, no matter how intelligent or informed. On this basis Margulis, Kang and Hammad (2014) excluded all prescriptions that were not for tablets or capsules with clearly defined doses, representing 7.4% of the sample, and a further 0.8% that appeared to be duplicate scripts. Again, the AMU data were dependent on clinical assessment, interpretation and documentation.

Fourthly, as the CPRD included only electronic prescriptions issued in primary care, any medicines prescribed via handwritten scripts or provided by secondary care specialists would be missed. These would be most likely to include new episodes of treatment, or medicines such as long-acting antipsychotic injections, Lithium or Clozapine. Of particular concern is that prescriptions for antidepressants (or antipsychotics) provided via specialist perinatal mental health services may have been excluded, thus resulting in an underestimate of prevalence. The AMU data were not affected by this.

Fifthly, as only pregnancies resulting in one or more live births were included, any pregnancies resulting in miscarriage, elective termination, or stillbirth would not be counted. Given that antidepressants have been linked with an increased risk of spontaneous and therapeutic abortion, this factor may also have contributed to an underestimate of perinatal antidepressant prevalence (Nakhai-Pour, Broy & Bérard, 2010; Kieler *et al.*, 2014). (It should be noted,

however, that antidepressants are not independently associated with miscarriage in women with a diagnosis of depression [Kjaersgaard *et al.*, 2013].) The AMU data were similarly derived from live births only.

Sixthly, Margulis, Kang and Hammad basing their longitudinal analysis on those who received a prescription in either T0 or T3 meant that any who started in T1 or T2, and stopped before T3 would be missed. Although this is likely to be a low absolute number (there were none in our AMU sample, and only 3 [0.5%] in the PMHS population), nevertheless, to provide a truly comprehensive account of the longitudinal course of antidepressants in pregnancy, one should take account of all patients and prescriptions. The corresponding AMU limitation was that we were unable to confirm if the data were updated timeously, fully, accurately or at all – they were likely to represent a "snapshot" at the time of the clinical encounter, rather than a comprehensive dynamic account of exposure throughout pregnancy.

Seventhly, Margulis, Kang and Hammad (2014) discuss the challenges they encountered in interpreting medication changes, and thus allocating subjects to their categories. They acknowledged that changes in drug type or dose may signify altered illness severity or pharmacokinetic changes due to pregnancy, thus confounding attempts to attribute outcomes to prescriptions rather than pathology.

Timing of antenatal psychotropics

As per Table 2-7, the majority of women prescribed antidepressants periconception discontinue during pregnancy, most commonly in the first trimester, with only a minority continuing throughout pregnancy, similar to our findings in the PMHS. This raises significant questions about our AMU data, derived from Eclipse. If details about timing were incorrect, even if simply due to records not being updated to reflect antidepressants being discontinued after booking, it follows that our findings may not be accurate.

However, our main findings were not inconsistent with the literature, and within the estimated international ranges, with the majority of pregnant women on antidepressants being exposed to SSRI monotherapy. The types and proportions of psychotropics were also broadly comparable with the PMHS sample.

Early and late exposure to antenatal psychotropics, and access to specialist care

We found a relatively low rate of antenatal psychotropics prescribed locally. While this was somewhat reassuring in terms of concerns over safety, it nevertheless suggests that of the approximately 750,000 babies born each year in the UK, >20,000 may have been exposed antenatally to psychotropic drugs, with more than 100 fetuses exposed to antidepressants in Ayrshire annually (Office for National Statistics, 2015; National Records of Scotland, 2015). Moreover, it appears that women receiving antenatal care in Ayrshire may be more likely to continue antidepressants throughout pregnancy than women in some other countries and settings, and the relative proportion of fetuses exposed to antidepressants late in pregnancy was higher than that found in the PMHS (87.0% [20/23] versus 60.0% [141/235]), as was the percentage exposed throughout pregnancy (69.6% [16/23] versus 28.9% [68/235]). Late fetal exposure has been linked with increased risks for early adverse outcomes in a number of studies (Chambers *et al.*, 1996; McElhattan *et al.*, 1996; Cohen *et al.*, 2000; Simon, Cunningham & Davis, 2002; Kallen, 2004; Moses-Kolko *et al.*, 2005; Boucher, Bairam & Beaulac-Baillargeon, 2008; Grigoriadis *et al.*, 2014; Huybrechts *et al.*, 2015). However, other studies have challenged these findings, e.g. Jimenez-Solem *et al.* (2013), Furu *et al.* (2015), and Grzeskowiak *et al.*, (2015), and the seminal study published by Oberlander *et al.* (2008) implicated duration of exposure more than timing.

Also concerning, and possibly linked to how long women receiving antenatal care in Ayrshire appear to take antidepressants during pregnancy, is the prospect that many pregnant women on psychotropics may not access specialist psychiatric

input – less than one third of those on psychotropics during pregnancy were documented as being referred to the MLS (7/24, 29.2%). It is possible that these women were already being seen in general adult psychiatry, especially those on antipsychotics (it seems unlikely that a non-psychiatrist would prescribed antipsychotics during pregnancy, or that midwives would not refer such patients if not being seen by a specialist). It is also plausible if not likely that referrals from AMU to the MLS may not have been documented in Eclipse, as discussed below – in any given three month period MLS would expect to see ~25 expectant mums, with the bulk of these being referred from AMU; significantly more than the 13 women suggested by the sample. Unfortunately, as our data were anonymised we were unable to identify individuals *post hoc* to allow verification with their psychiatric case-records, and therefore could not investigate further.

While the contrast between AMU and the PMHS re: proportions of women taking antidepressants throughout pregnancy (less than one third of those attending the PMHS, but more than two thirds of those attending AMU) could suggest that access to specialist perinatal psychiatric care reduces antenatal medication usage, the finding that only 14.3% (1/7) of the women on psychotropics referred to the MLS stopped medication during pregnancy (in the first trimester) casts doubt on this. Of the others, 57.1% (4/7) took psychotropics preconception and continued throughout pregnancy, while 28.6% (2/7) started medication during pregnancy, one in the first trimester, and one in the third. In other words, 80.0% (4/5) of those prescribed medication before conceiving who were referred to the MLS continued throughout pregnancy. Similarly, 92.3% (12/13) of those receiving a psychotropic but not referred to the MLS continued throughout pregnancy (Table 4-6). Attendance at the MLS appeared to have little effect on whether psychotropics stopped or started, with similar patterns being seen whether referred or not. Again, however, because our data was anonymised, it was not sufficiently detailed to allow in-depth analysis of individual cases - further work is indicated to establish more details via analysis of a larger sample. Furthermore, as we did not have details about the stage(s) of pregnancy when women were seen at the MLS, we were unable to identify when prescriptions for antenatal psychotropics were stopped or started, i.e. what difference(s) attendance at the MLS made.

Closer scrutiny of the PMHS data showed that although it was the minority of attendees who continued antidepressants throughout pregnancy, those who stopped did so before being seen in the specialist service, and 12.9% (81/627) started or restarted during pregnancy, compared with 15.4% (2/13) of the MLS mothers (Table 4-6). In other words, women who received care from the PMHS were more likely to have stopped medication before being seen than those referred to the MLS, suggesting that there were factors that resulted in referral rather than attendance resulting in medication being stopped. It would be useful to clarify what proportion of those who stopped or started psychotropics did so as a consequence of their attendance at the PMHS and the MLS, but we were unable to establish this from our data.

Table 4-6 – Psychotropic timing, and referrals to the MLS

	Referred to MLS	Not referred to MLS	Total
Continued psychotropics throughout pregnancy	4 (0.5%)	12 (1.5%)	16 (2.0%)
Stopped psychotropics during pregnancy	1 (0.1%)	1 (0.1%)	2 (0.2%)
Started psychotropics during pregnancy	2 (0.2%)	2 (0.2%)	4 (0.5%)
Total	7 (0.9%)	15 (1.9%)	22[1]

[1] the total is 22 rather than 24, as one subject stopped medication in the first trimester, but restarted, and the details for another subject were unspecified

As previously intimated, differences may simply be due to the incompleteness and hence inaccuracy of the data from either or both the PMHS and AMU. However, they may also be explained by reference to patient-, referrer-, clinician- or service-specific factors, and these differences between the MLS and the PMHS require confirmation and explanation. It should be noted that the MLS and the PMHS are not identical services, and absolute numbers attending the

MLS are low than the PMHS, but an intriguing possibility is that receiving specialist care via a dedicated and well-resourced perinatal mental health service enables more women to stop psychotropic medication during pregnancy. This is not supported by our findings, given that most stopped before attending the PMHS. However, as discontinuation of antidepressants during pregnancy is associated with younger maternal age, commencing an antidepressant shortly before pregnancy, and being prescribed only one antidepressant, the PMHS and the MLS data could be analysed further to detect any systematic differences in their attendees with regards to these factors (Petersen *et al.*, 2011; Margulis, Kang & Hammad, 2014). It is possible, of course, that these factors are simply proxy markers for chronicity, severity, or treatment-resistance of underlying illness.

Nevertheless, it seems like uncontroversial common sense for GPs, obstetricians and midwives to be encouraged to consider referring all pregnant women on psychotropics for psychiatric review, at the very least by a general adult psychiatrist. Indeed, this is now recommended by the updated NICE guidelines on antenatal and postnatal mental health (NICE CG192, 2014). However, the issues raised by the AMU and the PMHS data indicated that further work was needed, both to check the accuracy of our findings thus far, and to explore what sequelae of antenatal psychotropics could be identified, so that women of childbearing potential prescribed psychotropic medication can make more informed choices. We therefore agreed to repeat and extend our methodology, this time without anonymisation, and with the addition of external validation via reference to other “gold standard” datasets.

Key points

- ~1 in 30 women attending AMU were documented as being prescribed a psychotropic medication during pregnancy, the majority SSRI monotherapy.
- ~2 in 3 of those on psychotropics at conception, and ~1 in 2 of those on SSRI monotherapy, continued throughout pregnancy.
- ~9 in 10 women on psychotropics, and 15 in 16 on SSRI monotherapy, were exposed late in pregnancy.
- Not all women receiving antenatal psychotropics were referred to the MLS, but referral was not associated with significant differences in prescribing.
- The AMU data were not necessarily complete or accurate.

The questions re: data quality raised by our findings in the PMHS and AMU indicated that further work in this area was necessary. In light of the incompleteness of both the PMHS data collection forms and Eclipse fields, it was agreed to repeat the AMU study, but this time Eclipse data would be verified with accurate external sources, while establishing what information would be available to explore select neonatal outcomes of exposure to antenatal psychotropics.

The first step was to agree how best to verify Eclipse data. As Eclipse also specifies each patient's GP surgery we considered contacting individual practices to request all prescribing data for their patients, whose names and Community Health Index numbers (CHIs) we would be able to provide. (CHIs are unique identifiers allocated to all individuals born or receiving planned healthcare in Scotland, and are 10 digit numbers usually made up by the first 6 digits representing date of birth, with four additional numbers, e.g. DDMMYY1234). However, these primary care data are not necessarily straightforward to extract, and we suspected that at least some of our GP colleagues might not participate. Moreover, this would not necessarily capture all prescribing data, as drugs such as Methadone and some psychotropics (including Clozapine and long-acting injectable antipsychotics [depots]) are not prescribed by Primary Care – this effectively excluded utilising the regional Primary Care Prescribing Database, too, in addition to its data not always being straightforward to interpret or analyse (Mario Hair, personal communication). Prescriptions issued by psychiatrists would not be included, either. Hence, after consultation with local colleagues we decided to access prescribing data held by the Information Services Division of the NHS in Scotland (ISD).

As we planned a more detailed project on antenatal psychotropics, taking into account select neonatal outcomes, we considered which other psychoactive prescription medicines to include. As opiate dependence is associated with significant psychiatric comorbidity, and maintenance prescribing is overseen by the NHS addictions service in Ayrshire, we therefore agreed to include

Methadone in this phase. Methadone is a mainstay of the pharmacological management of opiate dependence, and is a potentially significant (albeit heavily confounded) risk factor for poor neonatal outcomes, being associated with a well known postnatal abstinence syndrome (Jones *et al.*, 2010; Desai *et al.*, 2015). We therefore elected to establish accurate information on Methadone prescriptions during pregnancy via the NHS Ayrshire & Arran Shared Addiction Management System database (SAMS). Simultaneously, the MLS records and the NHS Ayrshire & Arran Mental Health Services electronic patient records and database (FACE), would be interrogated to corroborate Eclipse entries (and omissions) on past and current mental health problems and care. The Mental Health Services Pharmacy was unable to identify prescriptions for Clozapine and depots retrospectively.

Research questions

(1) How accurate was Eclipse, in comparison with ISD, SAMS, and FACE?

(2) What proportion of women was prescribed psychotropic medication during pregnancy?

(3) What was prescribed, at what doses, and when?

Methods

We accessed Eclipse to identify all women who delivered in AMU within a three month period (1 January to 31 March 2012, inclusive), in addition to information on psychotropics prescribed during pregnancy, those referred to MLS, and those screened for historical and current mental health problems, use of illicit substances, and substitute prescribing (Methadone). Psychotropics were defined as per Chakrabarti, Julyan and Cantwell (2010) (Appendix 3). These data were entered into a Microsoft® Excel® worksheet for descriptive statistical analysis,

using Excel's® inbuilt functions. Excel's® "Advanced filter" function was employed to identify and remove any duplicate records. As we planned to use CHI numbers to integrate data from various sources, subjects were sorted in order of their CHIs (thus allowing complementary datasets to be sorted in the same order). Once sorted, we allocated an ID number to each subject in CHI order, to allow anonymisation after matching and harmonising the various data sources. As some CHIs start with "0", and Excel® processes data defined as numbers by removing initial zeros, we ensured that CHIs were formatted as text. Excel's® "VLOOKUP" function was used to indicate where CHIs from different sources matched, and outcomes were dichotomised where possible into "0" or "1" to facilitate descriptive statistical analysis. All sources were interrogated for the 12 months prior to and during the three month study period, to ensure that all psychotropic prescriptions and psychiatric/addictions input both periconception and antenatally were identified. The project was registered with Healthcare Quality, who confirmed that formal R&D/ethical approval was not required. However, as ISD required approval from an appropriate sponsor within NHS Ayrshire & Arran, and SAMS also required approval, this was sought and obtained from the NHS Ayrshire & Arran Caldicott Guardian via Information Governance.

Data sources

ISD

As part of NHS National Services Scotland, ISD was set up to support the various parts of the NHS in Scotland, through providing statistical information to facilitate research, and ultimately improve patient care (www.isdscotland.org). ISD collects and retains information on diverse Scottish NHS data, and produces reports on a range of issues, available via their website. Details for all community NHS prescriptions dispensed ('filled') are available, traceable to each patient by their CHI number and date issued. ISD holds details of all drugs actually dispensed via the NHS in Scotland, not just prescribed, i.e. one step

closer to actually being taken – this data includes type, dose, amount and date of medication dispensed.

ISD agreed to provide prescribing data for psychotropics for the specified period free of charge, subject to approval from the NHS Ayrshire & Arran Caldicott Guardian. We emailed CHIs for the patients in our sample securely to ISD via NHS email (www.nhs.net), and received the relevant data in Excel® format, with CHIs anonymised via alphanumerical substitution (the key was emailed separately). A script was devised to convert the ISD codes back to CHIs, in addition to being verified manually.

SAMS

Colleagues in the local NHS addictions service confirmed that the information we sought was available via SAMS, an electronic database containing details of all Methadone scripts issued in Ayrshire, again coded by reference to CHI. We submitted all CHIs to the SAMS database manager, who provided dates and quantities of Methadone prescribed to any relevant patients. Supervised dispensing ensured that prescriptions issued equated to Methadone consumed.

MLS

Given that screening for past and present mental health issues by obstetric staff is recommended by national guidelines, and that Phase 1 had included referrals to the MLS from AMU, we elected to compare Eclipse entries about mental health with both the MLS and general psychiatry data sources. The MLS keeps a record of all patients referred via those offered an appointment, including details on name, date of birth, and date and source of referral, but not CHI. This information is stored in a Microsoft® Word® document in tabular format, which we imported to Excel®. MLS clinicians also complete data collection forms similar to those used in the Glasgow PMHS, but with some modifications, to

allow more accurate recording of medication by date/gestation started and stopped, via update at each clinical encounter (Appendix 4).

FACE

FACE has been used by Mental Health Services in NHS Ayrshire & Arran since 2004, and has become the primary clinical record for all disciplines (with the exception of medical staff, who still use paper for making contemporaneous notes, although all their official correspondence is uploaded and copied to a FACE record). FACE is a software solution to support clinical staff in managing information pertinent to the assessment and management of patients, with extensive options to produce reports, if data are appropriately tagged during entry. The FACE graphical user interface interrogates a SQL database.

Confirming Eclipse with FACE initially appeared to be a straightforward but laborious and time-consuming process, requiring that we access FACE manually for each subject's CHI, to ascertain firstly if they had a record, and secondly where and when they were seen. However, assuming an average of 5 minutes to check each record, this alone would have taken almost 70 hours, even before the ethical issues involved in accessing patient records were taken into account. We therefore discussed our requirements re: data extraction with the local FACE team, who arranged for appropriate scripts to be provided by FACE Europe, and run on Ayrshire data. FACE Europe provided two scripts to identify all women with a FACE entry for Adult Mental Health and Addictions (1) during the study period, i.e. perinatally, and (2) before the study period, to allow accurate identification of current and historical contact, although this could not distinguish between attendance for mental health or addictions.

Contributors

EJ generated the research questions; planned the methodology; arranged access to Eclipse (via MC), FACE, SAMS and ISD; trained, supervised and supported CW

(a medical student with a background in Information Technology) in processing relevant data in Excel®; and completed descriptive statistical analysis.

Results

The data fields included are shown in Table 4-7, alongside the percentage of records with an entry in that field.

Eclipse data

875 women who delivered during the study period were identified, with a median age of 28 (range 16 to 46), and a median of one previous pregnancy (range 0 to 13). It proved challenging to locate all details sought, as there were numerous different data fields associated with medication, with undefined purpose and scope, and the majority were left blank (Table 4-7). Therefore, rather than examining only the "Medication" and "Medication history" fields, we scanned all sections for each of the 875 records individually, in addition to using Excel's® search function to find "antidepressant", and the generic and brand names of individual SSRIs ("cipralex", "cipramil", "citalopram", "escitalopram", "faverin", "fluoxetine", "fluvoxamine", "lustral", "paroxetine", "prozac", "seroxat", and "sertraline"). This permitted a degree of confidence that all women recorded as having taken a psychotropic antenatally were identified, although it is possible that some entries were missed, especially as there were numerous spelling mistakes in the records, e.g. "cirtalopram" and "Mwthodone". 1.0% (9/875) of the women were documented as being prescribed a psychotropic medication during pregnancy, all SSRI monotherapy (six Fluoxetine, two Citalopram, and one Sertraline), with 0.3% (3/875) prescribed Methadone. 0.8% (6/875) appeared to have been referred or already known to the MLS, although some documentation was ambiguous. "Dr Cameron" (the MLS Consultant Liaison Psychiatrist) was mentioned specifically for six women.

Table 4-7 – Eclipse data fields and completion rates

Eclipse data field	Completed (%)	Affirmative (%)
Last name	100	-
First name	100	-
CHI number	100	-
Date of birth	100	-
Pregnancy number	67.2	-
Date and time of delivery	100	-
Medication	4.7	-
Medication Category	4.6	-
Medication Dose	4.5	-
Medication Form	3.2	-
Medication Frequency	4.6	-
Medication Instructions	0.8	-
Medication history	5	-
Medication history Category	4	-
Medication history Comments	1.1	-
Problem or health issue	83.3	-
Problem or health issue Category	39	-
Problem or health issue Comments	33.4	-
Feeling down depressed or hopeless	17.6	3.2
Feeling down depressed or hopeless Comments	0.5	-
Feeling little interest / pleasure in doing things	17.5	2.6
Feeling little interest / pleasure in doing things Comments	0.3	-
Feels she needs or wants help with low mood	2.5	22.7
Involvement with mental health services	17.6	17.5
Involvement with mental health services Comments	1.8	-
Perinatal mental health lead	0.3	-
Perinatal mental health lead Contact telephone number	0	-
Perinatal mental health lead Role	0.1	-
Plans and referrals	70.6	-
Plans and referrals Assigned to	1.7	-
Plans and referrals Comments	23.2	-
Plans and referrals Due on	37.1	-
Plans and referrals Priority	17.7	-
History of substance misuse	12.8	6.2
History of substance misuse Comments	0.7	-
History of substance misuse Last taken	0.7	-
Chemist for prescribed controlled drugs	0.2	-
Feel she needs or wants help with substance misuse	1	22.2
Involvement with substance misuse services	13.3	3.4
Involvement with substance misuse services Comments	0.2	-
Comments for perinatal mental health referral	0	-
Perinatal Mental health services referral sent to	0.2	-
Consent to perinatal mental health referral	0	-
Consent to perinatal mental health referral Comments	0	-
Comments for substance misuse referral	0	-

A seventh patient had “To see Dr” recorded in the “Plans and referrals” data field - she had a history of postnatal depression, and had stopped medication “two months” prior to booking, i.e. in the first trimester – the context suggested that the Dr was the MLS consultant, but may simply have indicated the obstetric consultant – there was no subsequent record of her being seen via the MLS.

It was unclear how many were screened for current or past mental health problems, as only 17.6% (154/875) had relevant fields completed – 17.0% (149/875) had “No” entered, while one of the remaining five was feeling sad due to bereavement, and four were identified as potentially having a current mental health problem (Table 4-7). Three of these four had an action clearly documented, with two being referred to the MLS (although this was described specifically as a referral for cognitive-behavioural therapy for one, and a referral to “Dr Cameron” for the other), and one being advised to see her GP in six weeks. Similarly, 13.1% (115/875) had screening for substance misuse documented – 105 had “No history of substance misuse” and seven had details of various substances recorded in the “History of substance misuse” field, with three having “None” recorded in the “Involvement with substance misuse services” field. In one case, prescribed Methadone in the absence of illicit drug use was recorded via the “History of substance misuse” section. 0.3% (3/875) were identified as being prescribed Methadone.

With regards to “Involvement with mental health services”, 1.0% (9/875) were documented as being currently involved, all of whom were asked about current symptoms of depression – two screened positive for “Feeling down depressed or hopeless”, and both were to be referred to the MLS. 1.8% (16/875) were recorded as having previous involvement with mental health services, and again all were asked about current depression – one screened positive, but did not think that any additional input was required (they had recently defaulted from psychiatry clinic). 0.2% (2/875) were “Not asked at this time”, with no reason given, but screening negative for current depression, 14.5% (127/875) were documented as having no mental health input, and 82.4% (721/875) had no entry. Of the nine women receiving a psychotropic, two were documented as to be referred to the MLS, entered in the “Plans and referrals” field, three were

recorded as having ongoing current input from a Community Psychiatric Nurse (CPN), one was attending a Consultant Psychiatrist, two were noted as having had previous involvement with mental health services, and one was "Not asked at this time".

It proved challenging to find and interpret the data due to the variety of overlapping fields, and the rather fragmented and haphazard manner in which entries appeared to have been made. There were several duplications, entries made in fields that did not always appear particularly clear as to their scope and purpose, and some entries consisted of apparently random characters (e.g. "#'), presumably typographical errors. Nevertheless, Eclipse data was compared with other sources to the best of our abilities, as described below, and summarised in Table 4-8.

Table 4-8 - Eclipse compared to other data sources

	Eclipse	ISD	MLS	FACE	SAMS
Number of relevant records	875	141	26	105	10
Antenatal psychotropics	9	89	-	-	-
Methadone	3	-	-	-	10
Referred/known to MLS	6	-	26	-	-
Potential mental health problem	5	-	-	-	-
Current psychiatry contact	9	-	-	105	-
Historical psychiatry contact	16	-	-	58	-
Substance misuse	3	-	-	-	-

Eclipse compared with ISD

In contrast to Eclipse, ISD data indicated that 16.1% (141/875) had had a prescription for a psychotropic (so defined) dispensed between 1 January 2011 and 31 March 2012 (inclusive) (Table 4-9). Of these, 3.1% (27/875) appeared to have finished the medication before conceiving, and 2.9% (25/875) to have started postnatally (see discussion). Of the 10.2% (89/875) who were exposed during pregnancy, 0.3% (3/875) received anticonvulsant monotherapy only (two Lamotrigine, and one Carbamazepine), and 1.3% (11/875) were prescribed Amitriptyline at a dose of less than 75mg daily, suggesting non-psychiatric indications, e.g. epilepsy and neuropathic pain, respectively. Although Petersen *et al*. (2011) excluded those on "low dose" Amitriptyline from their analyses, in the absence of access to the diagnostic justification, we included all as psychotropics for the purpose of our investigation. Therefore, 10.2% (89/875) women were exposed to an antenatal psychotropic, although at most 8.6% (75/875) appeared to have been prescribed medication for a psychiatric indication, all of whom received antidepressants (Table 4-9). 7.0% (61/875) were on SSRI monotherapy, 0.1% (1/875) was prescribed 2 different consecutive SSRIs (i.e. not simultaneously) in addition to a tricyclic, 0.1% (1/875) received SNRI monotherapy, 1.0% (9/875) took tricyclic monotherapy, 0.6% (5/875) were given Mirtazapine monotherapy, and 1.4% (12/875) were prescribed a combination of different concurrent and consecutive antidepressants, antipsychotics and/or mood stabilisers.

Table 4-9 - Eclipse compared with ISD

	Eclipse	ISD
Number of relevant records	875	141
Antenatal psychotropics	9	89
SSRI monotherapy	9	61

Eclipse compared with MLS

The MLS records proved difficult to interrogate for a number of reasons. CHIs had not been used to identify individual patients, and this, combined with missing or incorrect DOBs, forenames and surnames being stored in the same field, and several individuals having their names spelled in up to three different ways, meant that it was challenging to compare entries with Eclipse and ISD. To resolve this we reviewed each MLS record by hand, matching patients with their CHIs on Eclipse by means of their name and DOB. According to the MLS records, 190 patients were offered appointments between 1 January 2011 and 31 March 2012 (inclusive), although details for October 2011 were unavailable. Again, as the MLS records included both new and review appointments, with multiple different appointments for several patients (up to eight for one woman) during the study period, it took time to establish who attended when, and if this was before, during or after the index pregnancy. 13.7% (26/190) corresponded to our Eclipse sample, of whom 23 attended MLS at least once. Four of the six identified by ECLIPSE as being referred to the MLS were offered an appointment, and of the nine identified by ECLIPSE as being on a psychotropic, three were offered and attended an appointment with MLS, although only one had a data collection form completed.

Eclipse compared with FACE

FACE revealed that 12.0% (105/875) of the women had had contact with Adult Mental Health & Addictions (including the MLS) during the study period, with an additional 6.6% (58/875) having had previous (but not ongoing) contact. We were unable to reconcile these figures with Eclipse. Of the 721 women not documented as being screened for mental health issues, 9.6% (69/721) were found to be prescribed a psychotropic during pregnancy, 11.1% (80/721) were in current contact with psychiatric services, and 17.6% (127/721) were known to have previous contact. Moreover, of the 89 prescribed a psychotropic during pregnancy according to ISD, only 21.3% (19/89) were referred to the MLS, and

36.8% (7/19) of these did not have antenatal psychotropic medication documented by the MLS (including the two who did not attend).

Eclipse compared with SAMS

The Addictions' database confirmed that 1.1% (10/875) were prescribed Methadone antenatally, including all three correctly identified on ECLIPSE.

MLS compared with ISD, FACE and SAMS

ISD data showed that of the 23 women seen by the MLS, 1.8% (17/875) were prescribed a psychotropic during pregnancy. (19 of the 26 offered an appointment were exposed to antenatal psychotropics, i.e. two of the three who did not attend their MLS appointment were also on medication.) Of those who attended, 4.3% (1/23) were seen in the first trimester, 43.5% (10/23) in the second, and 52.2% (12/23) in the third. None of those who attended the MLS were prescribed Methadone, and contemporary FACE records existed for 14 of the 15 MLS patients.

Types and rates of antenatal psychotropics from ISD and SAMS

ISD data yielded comprehensive information about type, dose, timing and co-prescribing of psychotropics dispensed. Table 4-10 shows the breakdown of different psychotropics, and as drugs were prescribed alone and in combination, both concurrently and consecutively, simple categorisation proved impossible, even in this relatively small sample. Nevertheless, it can be see that 0.8% (86/875) were prescribed at least one antenatal antidepressant, 7.9% (69/875) at least one SSRI, and 7.0% (61/875) SSRI monotherapy only. The only woman exposed to more than SSRI was also exposed to a tricyclic (Citalopram 20mg

daily and Amitriptyline 20mg daily periconception, stopping in the first trimester, then Fluoxetine 20mg daily commenced towards the end of the first trimester, but apparently only dispensed once – this patient was not identified on Eclipse as having mental health problems, nor as having been on psychotropic medication, and was not seen by the MLS).

Table 4-10 - Proportion of women prescribed antenatal medication

	Antenatal medication		Methadone[1]	
	%	(N)	%	(N)
No psychotropics	89.8	(786)	0.9	(8)
Psychotropics	10.2	(89)	0.2	(2)
Any antidepressant	9.8	(86)	0.2	(2)
Antidepressants only	9.5	(83)	0.2	(2)
Any SSRI	7.9	(69)	-	-
SSRIs only	7.0	(61)	-	-
SSRI monotherapy	7.0	(61)	-	-
Citalopram	2.7	(24)	-	-
Escitalopram	0.2	(2)	-	-
Fluoxetine	3.2	(28)	-	-
Paroxetine	0.1	(1)	-	-
Sertraline	0.7	(6)	-	-
Any TCA	1.5	(13)	0.1	(1)
Any SNRI	0.3	(3)	-	-
Other ADs	1.0	(9)	0.1	(1)
>1 AD	0.9	(8)	-	-
Any mood stabiliser	0.5	(4)	-	-
Mood stabilisers only	0.3	(3)	-	-
Any antipsychotic	0.2	(2)	-	-
Antipsychotics only	0	(0)	-	-

[1] According to SAMS

Table 4-11 outlines the actual number of women prescribed each type of psychotropic, in addition to details of co-prescribing. (All women on SSRIs only were exposed to SSRI monotherapy, but the two categories continue to be shown to allow comparison with results from the PMHS and AMU.) Of the eight women exposed to more than one antidepressant, 0.1% (1/875) was exposed to two consecutive SSRIs with a concurrent TCA (described above), 0.1% (1/875) an SSRI and a TCA concurrently, 0.1% (1/875) a TCA then an SSRI consecutively, 0.1% (1/875) an SNRI then an SSRI consecutively, 0.1% (1/875) an SSRI then Trazodone consecutively, 0.1% (1/875) an SSRI then Mirtazapine consecutively (with concurrent Quetiapine), 0.1% (1/875) Trazodone followed by Mirtazapine then an SSRI consecutively (with an SNRI prescribed ~10 weeks before conceiving, hence take to have finished before pregnancy), and 0.1% (1/875) an SNRI then Trazodone consecutively.

The TCAs consisted of Amitriptyline (12/875 – in 11 cases the dose appeared to be less than 75mg daily, although two of these were also exposed to SSRIs), and Clomipramine (1/875 – although 84 25mg tablets were dispensed monthly at the start of pregnancy suggesting a daily dose of 75mg, the dose appeared to reduce to 50mg and then 25mg daily during the second trimester); the SNRIs of Venlafaxine (2/875) and Duloxetine (1/875); and other antidepressants Mirtazapine (7/875), and Trazodone (3/875). The single biggest category of psychotropic was SSRIs, comprising 77.5% (69/89) of those exposed to any psychotropic, and 92.0% (69/75) of those exposed to an antidepressant at a therapeutic dose.

Table 4-11 – Psychotropic co-prescribing

Psychotropic	N	SSRIs	TCAs	SNRIs	Other	>1 AD	MS	Carbamazepine	Lamotrigine	Valproate	AP	'Typical' Aps	'Atypical' Aps	Methadone
Any AD	**(86)**	**69**	13	3	9	8	1	0	0	**1**	2	1	1	3
Any SSRI	**(69)**		3	1	3	7	1	0	0	**1**	1	0	1	0
Any TCA	**(13)**			0	0	3	0	0	0	**0**	1	1	0	1
Any SNRI	**(3)**				1	2	0	0	0	**0**	0	0	0	0
Other	**(9)**					4	0	0	0	**0**	1	0	1	2
>1 AD	**(8)**						0	0	0	**0**	1	0	1	0
Any MS	**(4)**							1	2	**1**	0	0	0	0
Carbamazepine	**(1)**								0	**0**	0	0	0	0
Lamotrigine	**(2)**									**0**	0	0	0	0
Valproate	**(1)**										0	0	0	0
Any AP	**(2)**											1	1	0
'Typicals'	**(1)**												0	0
'Atypicals'	**(1)**													0

Timing of antenatal psychotropics from ISD and SAMS

ISD gave clear details of each prescription for the psychotropics under study, linked to CHI numbers. Data fields included the "Approved" and "Prescribable item name" for each drug, along with "Date prescription was prescribed", "Date prescription was dispensed", "Date prescription was paid", "BNF Section Code", "Drug Strength", "Drug Formulation", "Drug Description", "Number of Dispensed items", "Dispensed Quantity", and "Gross ingredient cost (£)".

However, a degree of interpretation was still required for two reasons. Firstly, it was not always clear exactly what dose was being taken by each patient, as only the strength and quantity of the tablets were defined. Using the example of the patient prescribed Clomipramine (described briefly above), her details were as summarised in Table 4-12 (her baby was born on 9 January 2012, indicating that pregnancy started *circa* 4 April 2011, assuming a term delivery, i.e. 280 days gestation). As can be seen, neither the prescribing nor the dispensing occurred in a regular pattern, and although it appears that the first two repeat prescriptions were picked up one month after the preceding prescriptions and thus were for 75mg daily, this changes to a two month gap, and then a three month gap for the next two prescriptions, suggesting a reduction in daily dose to 50mg daily, and then 25mg daily as the second trimester progressed. These conclusions are predicated on the assumption that the patient actually took Clomipramine on a daily basis. This illustrates the difficulty in interpreting quantities of tablets in multiples of 28 according to frequency of dispensing, and several patients had much more irregular gaps between prescriptions being dispensed than this particular individual.

Table 4-12 – Sample ISD prescribing data

Date prescribed	Date dispensed	Drug Strength	Dispensed Quantity
25 May 2011	30 June 2011	25mg	84
31 May 2011	31 May 2011	25mg	84
11 July 2011	31 July 2011	25mg	84
5 September 2011	30 September 2011	25mg	84
19 December 2011	31 December 2011	25mg	84

Secondly, and even more critically than knowing daily dose, establishing if antenatal exposure had taken place also required accurate gestational age at birth, in the absence of knowing either the estimated delivery date (EDD) by ultrasound scan, or the last menstrual period (LMP), both of which would allow gestation to be calculated, if date of delivery was known. Gestational age at birth was necessary to determine length of pregnancy, and hence whether drugs prescribed/dispensed had ended before conception (in the same way that date of delivery showed if drugs were taken until delivery, or not commenced until afterwards).

In contrast, it proved straightforward to characterise the timing of exposure to Methadone – all patients were prescribed Methadone before conceiving, and continued into the postnatal period. Notwithstanding the challenges in interpreting the ISD data, our interpretation of the timing details by drug type are summarised in Table 4-13. Of the 89 women exposed to antenatal psychotropics, 66.3% (59/89) were taking medication before conception, with 16.9% (15/89) continuing throughout pregnancy, and 31.5% (28/89) stopping for good in the first trimester. 1.1% (1/89) started in the first trimester, 2.2% (2/89) in the second, and 1.1% (1/89) in the third, who all continued until delivery, leaving 47.2% (42/89) who followed a different stop-start pattern – 18.0% (16/89) who commenced preconception, 25.8% (23/89) in the first trimester, and 3.4% (3/89) in the second trimester, who subsequently stopped +/- restarted. Again, the pattern was similar for antidepressants in general, and SSRIs in particular.

Table 4-13 - Timing of exposure to antenatal psychotropics

		Timing																									Exposure		
	(N)	P	Ps1	Ps1r1s2	Ps1r1s2r3	Ps1r1s3r3	Ps1r3	Ps1r3s3	Ps2	Ps2r3	Ps2r3s3	Ps3	Ps3r3	1	1s1	1s1r2s2	1s1r2s2r3	1s1r3	1s2	1s2r2s3r3	1s2r3	1s2r3s3	1s3	2	2s2	2s2r3	3	Early	Late	+ Methadone
Any psychotropic	(89)	15	28	3	1	1	2	1	4	1	1	1	1	1	14	1	1	1	2	1	1	1	1	2	2	1	1	54	35	2
Any AD	(86)	14	28	3	1	1	2	1	4	1	1	1	1	1	12	1	1	1	2	1	1	1	1	2	2	1	1	52	34	2
ADs only	(83)	13	27	3	1	1	2	1	4	1	1	1	1	1	12	1	1	1	2	0	1	1	1	2	2	1	1	51	32	2
Any SSRI	(69)	11	21	3	1	1	2	1	3	1	1	1	1	1	9	1	1	1	2	0	1	1	1	2	0	1	1	39	30	-
SSRIs only	(61)	9	19	2	1	1	2	1	3	1	1	0	0	1	8	1	1	1	2	0	1	1	1	2	0	1	1	35	26	-
SSRI monotherapy	(61)	9	19	2	1	1	2	1	3	1	1	0	0	1	8	1	1	1	2	0	1	1	1	2	0	1	1	35	26	-
Citalopram	(24)	4	10	2	0	1	0	0	0	0	0	0	0	0	2	0	0	0	2	0	0	0	1	2	0	0	0	16	8	-
Escitalopam	(2)	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	-
Fluoxetine	(28)	4	6	0	0	0	2	0	3	1	1	0	0	1	5	1	1	1	0	0	0	1	0	0	0	1	0	15	13	-
Paroxetine	(1)	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-
Sertraline	(6)	1	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	2	4	-

Table 4-14 presents the numbers exposed to psychotropics before and during the three trimesters of pregnancy, showing a trend towards an increase in period prevalence of around 50% in the first trimester, followed by a reduction of around 50% in the second trimester, and a further slight reduction in the third trimester. There was significant stopping and starting, and focusing on SSRI monotherapy revealed the following observations.

The most common patterns were exposure preconception and stopping finally in the first trimester, exposure preconception and continuing until delivery, or commencing in the first trimester and continuing until delivery, in 31.1% (19/61), 14.8% (9/61), and 13.1% (8/61), respectively. 5.0% (40/805) of the total cohort were exposed to SSRI monotherapy at conception, with the majority (55.7%, 34/61) receiving either Citalopram or Fluoxetine (both 27.9%, 17/61), 4.9% (3/61) Sertraline, 3.3% (2/61) Escitalopram, and 1.6% (1/61) Paroxetine.

With regards to the first trimester, 65.0% (26/40) of those exposed to SSRI monotherapy at conception stopped, while 35.0% (14/40) continued, 22.5% (9/40) until delivery, and 12.5% (5/40) into the second trimester. There was variation between individual SSRIs, with 54.2% (13/24) on Citalopram, 100.0% (2/2) on Escitalopram, 28.6% (8/28) on Fluoxetine, 100.0% (1/1) on Paroxetine, and 33.3% (2/6) on Sertraline stopping in the first trimester. The most common SSRI monotherapies commenced during pregnancy were Fluoxetine (1.4%, 11/805), Citalopram (0.9%, 7/805), and Sertraline (0.4%, 3/805).

Table 4-14 – Stages of exposure to antenatal psychotropics

		Any psychotropic	Any AD	Any SSRI	SSRIs only	SSRI monotherapy	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline
	(N)	(89)	(86)	(69)	(61)	(61)	(24)	(2)	(28)	(1)	(6)
Before pregnancy		59	58	47	40	40	17	2	17	1	3
Trimester 1	**Continued***	23	22	18	14	14	4	0	9	0	1
	Started	24	22	18	17	17	5	0	10	0	2
	Stopped	53	51	41	37	37	15	2	16	1	3
	Restarted	5	5	5	4	4	3	0	0	1	0
	Total	83	80	65	57	57	22	2	27	1	5
Trimester 2	**Continued**	19	19	13	11	11	6	0	5	0	1
	Started	5	5	3	3	3	2	0	1	0	0
	Stopped	20	20	16	15	15	4	0	9	1	1
	Restarted	3	3	2	2	2	0	0	2	0	0
	Total	42	41	34	29	29	11	0	14	1	2
Trimester 3	**Continued**	18	17	14	12	12	6	0	5	0	1
	Started	1	1	1	1	1	0	0	0	0	1
	Stopped	8	8	7	5	5	2	0	2	0	1
	Restarted	14	14	13	12	12	1	0	8	1	2
	Total	35	34	30	24	24	8	0	13	1	4

Early and late exposure to antenatal psychotropics

Of those prescribed a psychotropic during pregnancy, 60.7% (54/89) were exposed in the first and second trimesters only, while 39.3% (35/89) were exposed in the third trimester (Table 4-13). A similar pattern emerged for those on SSRI monotherapy, with 57.4% (35/61) exposed in early pregnancy, and 42.6%% (26/61) in late pregnancy. Again, the exact durations of exposure in days could not be determined from the ISD data, due to the difficulties in interpretation highlighted above.

Detailed comparison of MLS data collection forms with ISD

The MLS records indicated that 26 women from our cohort were offered an appointment, and 23 attended (Table 4-15). 66.7% (2/3) of those who did not attend were prescribed an SSRI during pregnancy according to ISD; one woman commenced Citalopram in the second trimester, and the other started Sertraline in the third, with both continuing until delivery. 43.5% (10/23) of those who attended the MLS did not have a data collection form completed. Conclusions based on the MLS data collection forms regarding antidepressant type and timing matched with those based on the ISD data for 61.5% (8/13) subjects. In the other five cases, there were examples of each source offering more detail than the other (IDs “55”, “283”, “296”, “574”, and “669” in Table 3-18). For example, the timing for subject “55” was ambiguous in the ISD data, but the clinician assessing the patient clearly documented that she stopped Fluoxetine in the first trimester, and restarted in the second. It appeared that while the ISD data were correct with regards to dispensing, details of timing could be more accurately derived from the MLS forms, due to assumptions about gestation (see Chapter 6). Overall, those attending the MLS did differ from those who did not: 73.9% (17/23) were exposed to a psychotropic during pregnancy; none exposed at conception stopped in the first trimester, and 82.4% (14/17) were exposed late in pregnancy.

Table 4-15 – MLS data collection forms compared with ISD

ID	MLS				ISD	
	Seen	Form	Type	Timing	Type	Timing
9[1]	No	No	?[2]	?	Sert	3
29	Yes	Yes	Cit	P	Cit	P
55	Yes	Yes	Flu	Ps1r2	Flu	P?
59	Yes	Yes	Flu	P	Flu	P
116	Yes	No	?	?	Sert	Ps1r3s3
117	Yes	Yes	Flu	Ps1r3	Flu	Ps1r3
128	Yes	No	?	?	0	0
140	Yes	Yes	Flu	P	Flu	P
169	Yes	No	?	?	0	0
282	Yes	No	?	?	Cit, AMT	1s1
283	Yes	Yes	Mtz	P	Sert, Mtz, Quet	P
296	Yes	Yes	Cit	?	Cit	2
418	No	No	?	?	0	0
429	Yes	No	?	?	Flu	1s1
460	Yes	Yes	0	0	0	0
517	Yes	Yes	Cit	P	Cit	P
522	Yes	No	?	?	Dul	P
574	Yes	Yes	Flu	2	Flu	2s2r3
597	No	No	?	?	Cit	2
618	Yes	No	?	?	Flu	Ps2
650	Yes	No	?	?	Cit	P
669	Yes	Yes	Clom, Flup	Ps3, P	Clom	1s2r2s3r3
727	Yes	Yes	0	0	0	0
733	Yes	No	?	?	0	0
803	Yes	No	?	?	0	0
860	Yes	Yes	Ven	P	Ven	P

[1] Subjects who did not attend, or for whom a data collection form was not available, are shaded in grey

[2] Missing or ambiguous data are represented by '?'

Cit = Citalopram; Clom = Clomipramine; Dul = Duloxetine; Flu = Fluoxetine; Flup = Flupentixol; Mtz = Mirtazapine; Quet = Quetiapine MR; Sert = Sertraline; Ven = Venlafaxine

Results summary

(1) Eclipse data was incomplete, identifying only 10.1% (9/89) of those actually prescribed a psychotropic according to ISD, and 30.0% (3/10) of those taking Methadone according to SAMS. Eclipse could not be reconciled with FACE.

(2) 10.2% (89/875) of women who delivered at AMU were recorded as having been dispensed a psychotropic likely taken during pregnancy (Table 4-10).

(3) Of those exposed to a psychotropic, 96.6% (86/89) were exposed to an antidepressant, 93.3% (83/89) to antidepressants only, 77.5% (69/89) to an SSRI, and 68.5% (61/89) to SSRIs only (all monotherapy). Of those exposed to SSRI monotherapy, 45.9% (28/61) took Fluoxetine, 39.3% (24/61) Citalopram, 9.8% (6/61) Sertraline, 3.3% (2/61) Escitalopram, and 1.6% (1/61) Paroxetine. 84.6% (11/13) exposed to a tricyclic received low dose Amitriptyline (<20mg), suggesting an indication other than depression, with the others taking Amitriptyline 200mg daily, and Clomipramine 75mg daily. Co-prescribing was less common than in the PMHS, with (3/86) receiving an antidepressant and a mood stabiliser or an antipsychotic. 9.3% (8/86) were exposed to more than one antidepressant during pregnancy. Of those prescribed SSRI monotherapy, 65.6% (40/61) were exposed at conception, of whom 22.5% (9/40) continued throughout pregnancy, and 47.5% (19/40) stopped for good in the first trimester. Of the others exposed periconception, 7.5% (3/40) stopped in the second trimester, and 22.5% (9/40) stopped and restarted at least once at different stages during pregnancy. Of those on SSRI monotherapy, 57.4% (35/61) were exposed 'early' in pregnancy, and 42.6% (26/61) 'late' (Table 4-13). Prescribing patterns appeared more varied than in the PMHS, with 27.9% (17/61) starting in the first trimester, 4.9% (3/61) in the second, and 1.6% (1/61) in the third – 19.0% (4/21) who commenced during pregnancy continued until delivery. The SSRIs started during pregnancy were Fluoxetine, Citalopram and Sertraline, in 18.0% (11/61), 11.5% (7/61) and 4.9% (3/61), respectively (Tables 4-13 and 4-14). Exposure rates to antidepressants [SSRIs] in

trimesters one, two, three, and pregnancy as a whole were 9.1% (80/875) [7.4%, 65/875], 4.7% (41/875) [3.9%, 34/875], 3.9% (34/875) [3.4%, 30/875], and 9.8% (86/875) [7.9%, 69/875], respectively.

Discussion

This pilot allowed not only data integrity to be compared between local clinical and central administrative sources, but also an estimate of recent rates of antenatal psychotropic prescribing in a sample likely to be representative of the general Scottish population.

Data integrity – Eclipse, ISD, SAMS, FACE and MLS

There was evidence of good local clinical practice, in that the AMU Eclipse record includes fields for documenting psychotropic medication, substance misuse and Methadone, as well as screening for ongoing and past contact with psychiatric services, and current evidence of potential mental health problems. There was also an active and accessible MLS, and evidence of shared awareness of the importance of identifying and managing women at increased risk of perinatal mental illness.

However, Eclipse documentation was patchy, with many fields left blank, and data regarding findings and action(s) taken (e.g. referral to MLS) entered inconsistently across unrelated and overlapping fields. Moreover, there were numerous examples of requests made by MLS for an alert to be put on Eclipse to trigger a request for postnatal review being missed. The vast majority of pregnant women who were prescribed a psychotropic or Methadone were not identified accurately via AMU records, nor was there evidence of adequate screening for mental health issues. This may represent incomplete documentation at the time of initial booking and/or lack of updating of records throughout the remainder of pregnancy. Midwives may also be unaware of the

consequences of both perinatal mental illness and its treatment on mothers and babies.

It was clear that while Eclipse was a reliable and accurate means of identifying pregnant women delivering in AMU, it was not a complete clinical record that could be used to establish either the extent or characteristics of exposure to antenatal psychotropics. The 10-fold discrepancy between the nine women documented as having taken a psychotropic (all SSRI monotherapy) and the 89 revealed by ISD to have been dispensed psychotropics likely to have been taken during pregnancy (a range of different antidepressants, mood stabilisers, and antipsychotics, both singly, consecutively and concurrently) was striking, and cause for clinical concern. However, discussion with AMU staff revealed that Eclipse is not used as the primary record of antenatal care, including booking, and paper notes remain the mainstay of documentation informing care. The exceptions to this are labour and delivery, with a range of data on peripartum interventions and outcomes being entered on Eclipse.

The non-universal utilisation of Eclipse essentially invalidates it as a source of data for detailed exploration of perinatal exposures and outcomes. However, it does explain the marked difference between the estimates of antenatal psychotropic exposure based on the AMU data in comparison to ISD. In particular, our findings should not be interpreted as implying that pregnant women are not being screened for mental health problems, and not being referred appropriately; at least, not on the basis of Eclipse alone.

(It follows that while Eclipse is a trustworthy way to identify those delivering in AMU, whether live or stillbirths, it cannot be used to identify those who experience spontaneous or induced abortion, or ectopic pregnancy, with the attendant issues of possible biases in basing epidemiological analyses on its contents. One further issue of note is that Eclipse therefore cannot be used to explore any influences of psychotropics on fecundity, either.)

Although the ISD data had significant face validity, nevertheless some issues emerged. In contrast to the SAMS database, where prescriptions for specified

daily doses of Methadone were dispensed at regular intervals for (generally) supervised ingestion, a significant degree of interpretation was required with regards to exactly when dispensed tablets started, what daily doses were taken, for how long medication was taken, and any gaps. Furthermore, it was not possible to time prescriptions with the exact gestation medication was taken, as although dates of birth were known, using an average pregnancy length of 280 days to determine fetal exposure retrospectively may have resulted in an under- or overestimate. For example, as deliveries from 37 weeks gestation onwards are taken as "term", a neonate born after 37 completed weeks (with a gestational age of 260 days, Appendix 5) would not have been exposed to medication that finished 265 days before birth, but would have been classified as such via our methodology. Moreover, as reduced gestational age (including preterm delivery) is associated with exposure to antenatal antidepressants, there remains the potential for significant misinterpretation of outcomes, via those with preterm deliveries being excluded from relevant studies (Oberlander *et al.*, 2008; Ross *et al.*, 2013).

Nevertheless, our findings regarding the extent of perinatal psychotropic prescribing (as well as type and timing of drugs) are broadly comparable with the current literature, summarised for SSRIs in Table 4-16 alongside the recent figures relevant to the UK (see Chapter 2). Again, there was a significant trend towards reduced rates as pregnancies progressed. It should be noted that although we identified psychotropics dispensed within at least the three months before conception, we did not specifically calculate the total prevalence pre-pregnancy and, in comparison with Margulis, Kang and Hammad (2014), our methodology had the potential to allow more accurate estimation of exposure by trimester, by using date and quantity of tablets dispensed to project actual gestation taken, rather than just when prescriptions were issued. This may explain our higher figures for T1 prevalence: as many women discontinue medication in the first trimester after realising they are pregnant, Margulis, Kang and Hammad (2014) reported a lower prevalence due to fewer prescriptions being issued in T1, but this did not take account of those who were prescribed sufficient quantities of drugs just before conceiving, and who therefore were exposed early post-conception, particularly if there was any

delay between dispensing and commencing. Current data suggest that such short-lived early exposure may not to be of clinical significance, although this is not absolutely certain – for example, miscarriage is associated with antenatal antidepressants, although this may be due to underlying disease severity (Ban *et al.*, 2012; Ban *et al.*, 2014; Furu *et al.*, 2015).

Table 4-16 – Prevalence of SSRIs during pregnancy

	T0	T1	T2	T3	T4	Overall
Petersen *et al*. (2011)	4.8%	1.9%	0.77%	0.75%	-	2.11%
Margulis, Kang & Hammad (2014)	3.43%	2.06%	0.94%	0.99%	4.44%	-
Charlton *et al*. (2015) (UK)	8.8%	-	-	-	12.9%	3.7%
Charlton *et al*. (2015) Wales)	9.6%	-	-	-	15.0%	4.5%
Wood, Cameron & Julyan (2015)	-	7.43%	3.89%	3.43%	-	7.89%

Figures represent percentage of women exposed to antidepressants during pregnancy, with percentage exposed to SSRIs in parenthesis.

Categories of exposure

Classifying different types of exposure for the purpose of allocating to discrete categories to facilitate statistical analysis of associations poses significant challenges. Pregnant women are exposed to different types and combinations of psychotropics, at different gestations, for varying durations, and for different indications. Given the difficulties in diagnosing depression and rating its severity, it proves difficult to take account of these potential confounding factors when exploring outcomes in relationship to exposure, even before other known, and indeed unknown, confounding factors are taken into account.

Notwithstanding, almost all of those prescribed antenatal psychotropics in our general maternity population were exposed to antidepressants (96.6%, 86/89), mostly to SSRIs (77.5%, 69/89). More than 85% of those on SSRI monotherapy took either Fluoxetine or Citalopram. The trends for timing and duration of exposure to psychotropics as a whole, antidepressants in general, and SSRI monotherapy in particular were similar – around 30% were exposed periconception and discontinued in the first trimester; around 15% were exposed periconception and continued until delivery; around 15% commenced and then stopped in the first trimester; and the others followed a range of patterns (Table 4-13). Most prescribing changes took place in the first trimester, presumably with many women deciding to stop medication when they discovered they were pregnant. These decisions are likely to be taken without the benefits of specialist advice, hence the critical importance of giving appropriate anticipatory information and advice to all women of childbearing potential receiving a prescription for any medication – pregnancy is frequently unexpected, and even non-prescription drugs commonly used antenatally may be associated with as yet unknown risks. For example, even Paracetamol (which is estimated to be taken by >65% of pregnant women), has recently been highlighted as potentially increasing the risk of cryptorchidism (van den Driesche *et al.*, 2015).

As the MLS provides specialist psychiatric input to AMU, several issues emerged from our findings. Firstly, CHIs and Excel should ideally be used to record referrals, appointments, and attendance, to provide a comprehensive, accurate, and useful source of basic data. Secondly, data collection forms are not completed for all patients, and the relevant processes therefore need to be optimised, to eradicate variation between clinicians. However, the MLS forms appeared to have some advantages over the PMHS forms, in that data from follow-up visits were entered to update the forms, and the use of dates to specify exactly when medication started and stopped allowed more accurate characterisation of exposure, comparable to ISD.

Having established the above, we progressed to exploring select outcomes, and establishing what could be gleaned from clinical records.

Key points

- ~1 in 10 women attending AMU were dispensed a psychotropic medication likely taken during pregnancy, the majority SSRI monotherapy.
- ~1 in 6 of those on psychotropics at conception, and ~1 in 7 of those on SSRI monotherapy, continued throughout pregnancy.
- ~2 in 5 women on psychotropics were exposed late in pregnancy.
- Not all women receiving antenatal psychotropics were referred to the MLS.
- Those attending the MLS differed from the general cohort in being more likely to be exposed to medication (mainly SSRIs), continue medication throughout pregnancy, and exposed late in pregnancy.
- The AMU and MLS data were not complete, not fully accurate, and therefore not a reliable source for research purposes.

Chapter 5 - Consequences of antenatal exposure to SSRIs: Clinical outcomes

Phase 1 Admissions to the neonatal unit

Given our findings that almost one in 10 women in the general population were prescribed a psychotropic antenatally, with around one in six of these continuing medication throughout pregnancy, and in light of concerns about potential neurodevelopmental toxicity, comprehensive and accurate data about consequences of antenatal exposure to psychotropics is of paramount importance, not least in supporting mothers and their clinicians in making necessary decisions about care.

In keeping with other studies, we established that the most common type of antenatal psychotropic exposure was to SSRIs. Despite researchers reaching reassuring conclusions regarding their overall safety, a number of inconsistent findings have been reported. For example, in 2015 alone, although Reefhuis *et al*. reported no association between Sertraline and birth defects (including cardiac abnormalities and craniosystosis) in 440 women exposed in the first trimester, Bérard, Zhao and Sheehy did find that Sertraline was linked with cardiac abnormalities and craniosystosis in 366 depressed/anxious women with similar exposure. (Significantly, Sertraline was not associated with an increased risk of malformations overall in comparison to depressed/anxious women not exposed to antidepressants, but only when specific defects were analysed individually.) These conflicting conclusions illustrate the challenging complexities of assessing antenatal exposures, as references can be produced to support apparently opposite conclusions about most drugs.

Some inconsistencies in the literature may be attributable to heterogeneous samples and/or different methodologies, both relevant to the above example. However, in view of the difficulties in accessing and analysing relevant data

highlighted by our work in the PMHS and AMU, what register-based meta-analytic linkage studies gain in power from interrogating large datasets may be offset by the fine detail of individual clinical care, and extensive confounding. For example, in order to clarify the consequences of antenatal exposure to a particular drug, one should ideally take account of each individual medication's pharmacokinetic and pharmacodynamic characteristics, and the dose, gestational stage, and duration prescribed, in addition to the same factors for any co-prescribed drugs, as well as any known or unknown interactions. These data are not easily accessible, nor straightforward to interpret, categorise, or analyse. Moreover, due to the small absolute numbers of fetuses exposed, and the potentially subtle sequelae of exposure, in conjunction with any inaccuracies in the data, or unwarranted assumptions in its analysis, and the countless confounders, the use of retrospective proxy markers for exposure (e.g. the date medication was dispensed) introduces a bewildering array of complex challenges.

Numerous other factors also contribute to outcomes for offspring, including general maternal health and the diagnoses for which medication is prescribed, illness severity, time course, and response to intervention(s), other treatment modalities (e.g. psychological), consistency of adherence to medication, drug metabolism and serum levels achieved, degree of placental transfer, maternal genotype and phenotype, fetal genotype (and therefore paternal genotype and age at conception), obstetric insults, and the myriad of environmental influences, both alone and in combination. Drawing clinically significant inferences from statistical associations in this area is far from straightforward.

Early exposure to psychotropic medication may exert different influences on progeny at different stages of life. For example, some early outcomes may be more related to direct developmental and teratogenic effects of the drug(s) in question, including epigenetic factors, while longer term outcomes may be related more to direct and indirect neurodevelopmental pathways, with greater likelihood of complex gene:environment interactions contributing over time, especially psychosocial factors (Oberlander *et al.*, 2008).

For these reasons, examining naturalistic outcomes of clinical and personal relevance is of value to parents, children, and healthcare workers alike. What do prospective mothers and antenatal prescribers need to know?

The relationship between neonatal admission, antenatal depression, and antenatal antidepressants is complex. For example, in a prospective observational cohort study of 959 women, Chung *et al*. (2001) found that admission rate increased from 19% to 24% in those with BDI scores >14.5, while Engelstad *et al*. (2014), who retrospectively compared select outcomes from a cohort of 254 women with diagnoses of depression with 222 matched controls, reported that antenatal depression (but not SSRIs) was independently associated with an increased risk of admission, from 24% to 42%. Maschi *et al*. (2008) found no association between antidepressants (including SSRIs) and neonatal admission, whereas Lund, Pedersen and Henriksen (2009) established that exposure to SSRIs increased the admission rate to 16.4% from 9.0% (7.4%) in those with a psychiatric history (no psychiatric history) but not exposed to antidepressants. Similarly, in a retrospective register-based analysis of 511,938 deliveries, Räisänen *et al*. (2014) described an increased risk of neonatal admission associated with exposure to antenatal depression, but were unable to account for medication. Conversely, in a study of 76 exposed and 90 unexposed women, Ferreira *et al*. (2007) did not find an independent association between admission and exposure to SSRIs or SNRIs, but did not control for maternal depression. Sutter-Dallay *et al*. (2015) investigated antenatal exposure to different psychotropics in 1,071 women admitted to 13 French Mother-Baby Units providing psychiatric care, and found an association between antidepressants and admission, but did not control for underlying illnesses. Lastly, Wisner *et al*. (2009) reported that neonatal admission rates were 8%, 19%, and 21%, in healthy controls, those exposed to SSRIs, and those exposed to unmedicated depression, respectively. Again, the influences of heterogeneous unrepresentative samples, varying methodologies, and lack of accounting for confounders are evident.

Moreover, the mechanisms by which antenatal exposure to depression and antidepressants may precipitate neonatal admission remain unclear. It is

possible that indirect factors such as preterm delivery are relevant, as well as pharmacological issues such as poor neonatal adaptation, which is closely linked with admission (Craighead & Elswick, 2014; Kocherlakota, 2014; Kieviet *et al.*, 2015).

Although the validity of using admission to neonatal intensive care units as an outcome measure and surrogate for morbidity has been criticised (mainly on the basis of non-comparability of different units), it can serve as a relevant proxy marker of early distress and/or adversity, and therefore we undertook to explore any such association in our sample (Wiegerinck *et al.*, 2014).

Research questions

(1) What proportion of neonates required admission to the local neonatal unit (NNU)?

(2) Did exposure to antenatal psychotropics in general, and SSRIs in particular, increase the risk of admission?

(3) Which types of exposure were associated with the greatest risk of admission?

Methods

AMU is located within University Hospital Crosshouse, a large district general hospital serving Ayrshire. All neonates requiring special care are admitted to the local NNU, unless beds are unavailable, or tertiary-level specialist intervention is indicated. As there was no electronic database at that time, the lead NNU paediatrician arranged for administrative staff to provide details of all admissions between 1 January and 31 March 2012, including linked CHIs for mothers and babies. Neonatal CHIs, DOBs, and gestation at birth were matched

to maternal CHIs, and entered in to an Excel® spreadsheet for statistical analysis. Approval was granted via Information Governance and the Caldicott Guardian, and Healthcare Quality and R&D confirmed that formal ethical approval was not required.

Contributors

EJ generated the research questions; planned the methodology; arranged access to NNU data via SK (NNU consultant); entered and processed relevant data in Excel®; and completed descriptive statistical analysis.

Results

Neonates from 101 mothers in our cohort were admitted to NNU between 1 January and 31 March 2012 (inclusive), i.e. overall admission rate 11.5% (101/875) (none were admitted after 31 March). 19.8% (20/101) had potentially been exposed to a psychotropic during the study period according to ISD. However, eight of these had not been exposed during pregnancy (six exposed preconception only, and two postnatally). SAMS indicated that 40.0% (4/10) had been exposed to Methadone throughout pregnancy. Diagnoses were not immediately available, due to the lack of an established database.

Knowing the gestation allowed us to review the timing of exposure for each neonate both exposed to an antenatal psychotropic and admitted to NNU, resulting in three subjects changing category due to pregnancies lasting less then the assumed 280 days: “92” (exposed to Mirtazapine) changed from 2s2 to 1s2 (gestation 266 days), “174” (Citalopram) from 1s3 to Ps2 (gestation 231 days), and “295” (Fluoxetine) from Ps1 to 0 (gestation 230 days), i.e. exposed preconception only. In other words, 25.0% (3/12) changed timing category as a result of gestation being known.

This left 11 neonates exposed to antenatal psychotropics and subsequently admitted to NNU, all exposed to antidepressants only, and none co-prescribed Methadone, as detailed in Table 5-1. 90.9% (10/11) were exposed to an SSRI (81.8% [9/11] to SSRI monotherapy), 18.2% (2/11) were exposed in the first trimester only, and 27.3% (3/11) throughout pregnancy, with 36.4% (4/11) exposed early and 63.6% (7/11) late in pregnancy. 27.3% (3/11) were born before 37 weeks completed gestation. Significantly, two subjects commenced apparently "high" doses of SSRIs; "398" who commenced Sertraline 100mg in the first trimester, and "569" who commenced Fluoxetine 40mg daily in the first trimester.

Table 5-1 – Neonates exposed to antenatal antidepressants, and admitted to NNU

Subject	Gestation (days)	Gestation category	Drug(s)	Dose[1]	Timing	Exposure	Actual duration
92	266	Term	Mirtazapine	15mg	1s2	Early	28
117	273	Term	Fluoxetine	20mg	Ps1r3	Late	75 + 12
140	184	Pre-term	Fluoxetine	20mg	P	Late	184
174	231	Pre-term	Citalopram	40mg	Ps2	Early	168?
311	275	Term	Fluoxetine	20mg	Ps2r3	Late	164 + 16
398	275	Term	Sertraline	100mg[2]	1s2r3	Late	56 + 56
442	280	Term	Citalopram	20mg	Ps1	Early	17
466	271	Term	Citalopram	20mg	1s1	Early	28
495	231	Pre-term	Sertraline	100mg	P	Late	231
522	287	Term	Trazodone, Mirtazapine, then Citalopram	150mg, 45mg, 20mg	P	Late	287
569	273	Term	Fluoxetine	40mg[3]	1	Late	245

[1] Highest daily dose achieved

[2] Apparently commenced on Sertraline 100mg daily at day 55 – no ISD prescription in preceding 9 months

[3] Apparently commenced on Fluoxetine 40mg daily at day 28 – no ISD prescription in preceding 9 months

Admission rates for different exposure types are summarised in Table 5-2, with statistical significance calculated using Fisher's exact test. The admission rates for those exposed antenatally to any psychotropic, any antidepressant, any SSRI, and SSRI monotherapy were 12.5%, 12.9%, 14.7%, and 15.0%, respectively. Detailed subgroup analyses were not appropriate due to the low absolute numbers, but there appeared to be a trend towards increased risk of admission to the NNU being associated with late exposure to antidepressants in general, exposure to SSRIs in particular, and also 'exposure' to the MLS. Several exposures were significantly associated with admission to the NNU, including Methadone, and exposure to an antidepressant until delivery. Again, there was a trend towards exposure to SSRIs in particular up until delivery being strongly associated with admission. Exposure to antenatal psychotropics that was limited to the first trimester only was significantly associated with a reduced risk of admission to the NNU. There was no statistically significant relationship between gestation at birth and exposure to psychotropics found (Mann Whitney U 2-tailed test).

Results summary

(1) ~1 in 10 babies required admission to the NNU.

(2) Exposure to antenatal psychotropics, antidepressants, and SSRIs was associated with an increased risk of neonatal admission, but this was not statistically significant.

(3) Being exposed to psychotropics late in pregnancy, and receiving care via the MLS were similarly associated with a statistically insignificant risk of admission. However, exposure to any antidepressant until delivery, and exposure to Methadone, were both significantly associated with increased rates of admission, ~1 in 4, and 2 in 5, respectively.

Table 5-2 – Admission rates to NNU for different exposure types

	(N)	Admitted (%)	(N)	Not admitted (%)	(N)	Fisher's exact test (p)
Total	(875)	11.5	(101)	88.5	(774)	-
Exposure						
Unexposed	(787)	11.4	(90)	88.6	(697)	-
Any psychotropic	(88)	12.5	(11)	87.5	(77)	0.73
Any AD	(85)	12.9	(11)	87.1	(74)	0.72
Any SSRI	(68)	14.7	(10)	85.3	(58)	0.43
SSRI monotherapy	(60)	15.0	(9)	85.0	(51)	0.40
Methadone	(10)	40.0	(4)	60.0	(6)	0.02
Referred to MLS	(26)	19.2	(5)	80.8	(21)	0.21
Seen by MLS	(23)	21.7	(5)	78.3	(18)	0.17
Late exposure	(34)	20.6	(7)	79.4	(27)	0.1
First trimester only	(41)	2.4	(1)	97.6	(40)	0.00892
Until delivery						
Any psychotropic	(30)	23.3	(7)	76.7	(23)	0.041
Any AD	(29)	24.1	(7)	75.9	(22)	0.036
Any SSRI	(25)	28.0	(7)	72.0	(18)	0.01
SSRI monotherapy	(22)	27.3	(6)	72.7	(16)	0.025

It proved somewhat labour-intensive to explore neonatal admissions locally, due to the absence of a dedicated electronic database at that time. Paediatric administrative colleagues were very helpful in providing some of the data we sought, but we were unable to establish and therefore categorise reasons for admission to the NNU. Notwithstanding, the lead NNU paediatrician had sight of the reasons for all neonatal admissions during our study period, and did not infer any significant differences between those exposed to antidepressants and those not, with reference either to proportions of preterm births, or diagnoses.

However, having access to the actual gestation at birth enabled us to check the exposure categories to which we had assigned subjects, on the basis of the ISD data. This led to 25.0% (3/12) moving, including one who became 'unexposed'. This has implications for the overall validity of our existing conclusions, and typifies the inaccuracies inherent in defining when pregnancies start and stop, in the absence of relevant data.

Another issue was those who appeared to commence an antidepressant at a higher dose than would be usual (Sertraline 50mg, and Fluoxetine 20mg), according to ISD, who had no record of a corresponding prescription being dispensed in the preceding six months, and four months (respectively). It appears unlikely that a prescriber would initiate these drugs at these doses, particularly during pregnancy (if known), and therefore the patients must have had access to medication from sources other than Scottish community pharmacies, or the ISD data was inaccurate or incomplete. Sources could include pharmacies based either in Scottish hospitals or outwith Scotland, or private prescriptions. ISD subsequently confirmed that the CHI capture rates for BNF Sections 4.2, 4.3, and 4.8 for the period under study were 90.3%, 95.5%, and 95.6%, respectively, indicating that prescriptions for patients in our cohort may have been missed. This could have occurred, for example, if prescribers used only DOBs rather than full CHIs.

Compared to the baseline admission rate in the "unexposed" of 11.4%, it was interesting to note the trend towards higher rates of neonatal admissions in those exposed to antidepressants in general, and SSRIs in particular, albeit not statistically significant. This could represent a "type II error" due to small sample size, and it would be unnecessarily speculative to reach any firm conclusions. Nevertheless, while the increased risk of admission associated with exposure to Methadone was unsurprising and consistent with other reports, the negative association between first trimester exposure only and NNU admission is singular and thought provoking (Cleary *et al.*, 2011; Cleary *et al.*, 2012; Greig, Ash & Douiri, 2012). It is unclear why mothers who were presumably unwell enough to be taking an antidepressant in early pregnancy but stopped should subsequently deliver babies with a lower risk of neonatal admission than the general population. Reverse causality is one possible explanation, in that mothers who were motivated to stop medication for the sake of their baby may also have been driven to be generally healthier, but this seems unlikely, particularly given the increased risk of depressive relapse in those discontinuing antidepressants during pregnancy (Cohen *et al.*, 2006).

The observation that exposure up until delivery was significantly associated with admission is noteworthy, with the associated risk of admission more than doubling. Again, in the absence of knowing the reason(s) for admission, the explanation remains unclear, although poor neonatal adaptation (neonatal adaptation [or abstinence] syndrome [NAS]) is one possibility (Kieviet *et al.*, 2015). This phenomenon is characterised by time-limited neonatal irritability, impaired feeding and sleeping, jitteriness and crying, increased muscle tone, gastrointestinal upset, and respiratory distress, and although previously reported to affect around 30% of babies exposed to antidepressants *in utero*, Kieviet *et al.* (2015) reported that up to 64% were affected in their retrospective cohort study of 247 women and their infants, although the majority of cases were mild. They found an overall admission rate of 21.5%, with 29% of neonates with NAS admitted, while only 9% of those without. (Interestingly, SSRIs were associated with NAS more than SNRIs or NaSSAs (noradrenergic and specific serotonergic antidepressants), but overall drugs less so than feeding – formula feeding was associated with higher rates of NAS, implying that ongoing exposure to

medication in breast milk may moderate symptoms.) Taken together with our findings, this suggests that exposure up until delivery (i.e. not simply "late" third trimester exposure *per se* – see Table 5-2) may put infants at increased risk of NAS, and therefore admission to NNU.

This assumption has influenced some clinicians to withdraw psychotropics in the days leading up to the EDD. In addition to the difficulties in predicting EDD with any degree of accuracy, this practice is no longer common, at least in part due to Warburton, Hertzman and Oberlander (2010), who reported that when confounders are controlled for, withdrawing SSRIs prescribed throughout pregnancy ~14 days before delivery did not reduce neonatal complications such as respiratory or feeding problems (although they did not specifically assess for NAS nor include neonatal admission). They concluded that a discontinuation syndrome or physiological withdrawal may therefore not fully explain poor neonatal adaptation, and that early adverse outcomes may be related to other neurodevelopmental effects of both drugs and the indications for which they were prescribed.

One further finding of note was the increased admission rate in those referred to/seen by the MLS, almost double the baseline rate, although not statistically significant. While this sample did include proportionally more women prescribed antidepressants during pregnancy (73.9%, 17/23), and more who were exposed late in pregnancy (82.4%, 14/17), than the unexposed population, it was not clear that this fully explained the association – five babies born to mothers referred to/attending the MLS were admitted to the NNU, three exposed to antenatal antidepressants, and two not.

This observation illustrates one of the key limitations of this pilot – a relatively small sample size. To perform meaningful subgroup analyses to explore the multitude of relevant common and rare outcomes risks associated with the many different types of exposure requires large numbers.

Having established that it was challenging to access the necessary data to explore neonatal outcomes for those exposed to antenatal psychotropics in Ayrshire, but that those attending the MLS appeared to be at higher risk of admission to the NNU, we elected to consider this service in more detail. The anticipated advantages included access to diagnoses and their severity, as well as select neonatal outcomes, as clinical letters regarding infants of mothers attending the MLS who are admitted to the NNU are routinely copied to the MLS lead psychiatrist.

In collaboration with the NNU lead paediatrician, we learned that a new electronic database for the NNU, BadgerNet (www.clevermed.com), had been implemented, and may be an appropriate source for the clinical details we sought. As BadgerNet was introduced in the NNU in late 2012, and was not being populated with retrospective data, it was not possible to use it for the existing AMU sample.

Due to uncertainties about the utility of BadgerNet, and the limitations experienced with Eclipse, it was agreed that we would access the Scottish Birth Record (SBR) simultaneously, a web-based service provided by ISD which aims to serve as a single comprehensive repository for neonatal health data for all babies born in Scotland, including stillbirths (www.isdscotland.org/Products-and-Services/Scottish-Birth-Record/). This would allow verification of BadgerNet's accuracy, and compensation for any shortcomings.

Early/preterm delivery, low birthweight, low APGAR scores, and neonatal admissions have been linked with antenatal exposure to maternal depression and/or antidepressants (Grote *et al.*, 2010; Jensen *et al.*, 2013; Ross *et al.*, 2013; Hanley & Oberlander, 2014; Forray, Blackwell & Yonkers, 2015; Gentile, 2015). A high proportion of those attending the MLS are exposed to both, and they appear to be at increased risk of delivering babies who require admission to NNU - this was a finding of potential personal importance to mothers, as well as significance to the MLS and NNU clinicians.

Research questions

In pregnant women attending the MLS,

(1) What proportion of neonates required admission to the local neonatal unit (NNU)?

(2) Did exposure to antenatal psychotropics in general, and SSRIs in particular, increase the risk of admission, preterm delivery, shorter gestations, low birthweight, and/or low APGAR scores?

(3) Which types of exposure were associated with admission?

Methods

The MLS records and data collection forms were accessed to identify all women who attended the MLS between 1 January and 31 December 2013 (inclusive). We used the CHIs to interrogate both BadgerNet and the SBR, with the support of administrative staff. Relevant details were entered in to an Excel® spreadsheet for analysis, including maternal date seen, psychiatric diagnoses with rating scale scores (see below), prescribed and other medication, alcohol and tobacco use, and parity; and infant EDD, DOB, mode of delivery, obstetric complications, birthweight, gestation, gender, admission to NNU, and APGAR scores. A multivariate general linear model was employed to explore the relationships between rating scale scores (predictor variables) and gestation at birth, preterm delivery (less than 37 weeks/260 days completed gestation, Appendix 4), birthweight, APGAR scores, and admission to the NNU (response variables). We included exposure to any antidepressants as an additional covariate in the model.

Approval was granted via Information Governance and the Caldicott Guardian, and Healthcare Quality and R&D confirmed that formal ethical approval was not required.

MLS clinicians routinely ask patients to populate a Hospital Anxiety and Depression Scale (HADS) at each visit. The HADS is a 14 item self-completed outcome measure that rates the severity of both depressive and anxiety symptoms via agreement with seven statements related to each, yielding a score of between 0 and 3 for every item, i.e. a score out of 21 for depression (HADS-D), and a score out of 21 for anxiety (HADS-A). Originally developed by Zigmond and Snaith (1983) for use in general hospital patients, it places less emphasis on non-specific somatic complaints common in other conditions, such as fatigue and sleep disturbance. A score >8 on either subscale is generally taken as indicating clinically significant depression and/or anxiety (Bjelland *et al.*, 2002). Although the HADS has not been satisfactorily validated in perinatal populations, nevertheless it has face validity as an appropriate adjunct to standard clinical assessment and monitoring (Bocquet & Deruelle, 2014; Brunton *et al.*, 2015; Evans, Spiby & Morrell, 2015). However, like other rating scales, it is not clear that it is specific for depression/anxiety, and can also be taken as a general measure of stress/distress (Pallant & Tennant, 2007).

APGAR scores, first proposed in 1952, continue to be used to assess heart rate, respiratory effort, reflex irritability, muscle tone, and colour one minute and five minutes after birth (Jepson, Talashek & Tichy, 1991; ACOG, 2006). Despite criticisms and limitations, they remain useful as a predictor of neonatal mortality in term infants, and in identifying those in need of cardiopulmonary resuscitation (Schmidt *et al.*, 1988; Finster & Wood, 2005). However, they are not of value in predicting longer term outcomes, although scores of <8 at one minute may be taken as an indicator of potentially clinically significant early distress.

Contributors

EJ generated the research questions; planned the methodology; arranged access to MLS and NNU data via MC and SK (NNU consultant), respectively; trained, supervised and supported LT and SN (junior doctors working in psychiatry) in transferring relevant data to Excel®; and completed descriptive statistical analysis. RK conducted the multivariate analyses.

Results

116 women attended the MLS at least once, with 106 being seen during pregnancy. Two moved out of Ayrshire before delivering, and data for one of these was not available *post hoc*. Therefore, data were available for 105 subjects, with details of psychotropic exposure summarised in Table 4-3, and timing of exposure for SSRI monotherapy and individual drugs in Table 4-4. Three women delivered twins, which were combined into one exposure for the purpose of analysing admissions to the NNU, but considered individually when evaluating gestations, preterm deliveries, birthweights, and APGAR scores. Diagnoses were available for 99 women, with the primary diagnoses given in Table 4-5. As some subjects had several HADS scores due to multiple attendances at the MLS, the single highest figure was selected for analysis, with the median scores for depression and anxiety being 8 (range 0-20), and 12 (range 0-21), respectively. HADS-D scores were not available for 13 subjects, and HADS-A scores for 12. 16.7% (18/108) of the infants were preterm, including all six twins.

Table 5-3 - Proportion of women prescribed antenatal medication

Antenatal medication	%	(N)
No psychotropics	24.8	(26)
Psychotropics	75.2	(79)
Any antidepressant	71.4	(75)
Antidepressants only	70.5	(74)
Any SSRI	59.0	(62)
SSRIs only	54.3	(57)
SSRI monotherapy	51.4	(54)
Citalopram	16.2	(17)
Escitalopram	1.9	(2)
Fluoxetine	12.4	(13)
Paroxetine	0	(0)
Sertraline	21.0	(22)
Any TCA	1.0	(1)
Any SNRI	5.7	(6)
Other ADs	10.5	(11)
>1 AD	7.6	(8)
Any mood stabiliser	1.0	(1)
Mood stabilisers only	1.0	(1)
Any antipsychotic	3.8	(4)
Antipsychotics only	2.9	(3)

Table 5-4 - Timing of exposure, by type of psychotropic

	(N)	Timing									Exposure	
		P	Ps1	Ps1r1	Ps1r2	Ps1r2s2r3s3	Ps1r3	1	2	3	Early	Late
SSRI monotherapy	(54)	19	9	4	7	1	2	2	5	5	9	45
Citalopram	(17)	8	2	0	3	0	1	0	3	0	2	15
Escitalopram	(2)	0	0	2	0	0	0	0	0	0	0	2
Fluoxetine	(13)	4	4	0	2	0	1	0	2	0	4	9
Paroxetine	(0)	0	0	0	0	0	0	0	0	0	0	0
Sertraline	(22)	7	3	2	2	1	0	2	0	5	3	19

Admissions to the NNU

The overall admission rate was 20.0% (21/105), with few statistically significant differences between those exposed and unexposed to psychotropics, whether taken together as a group, or analysed by subgroup. Preterm delivery was associated with increased risk of admission, and exposure to SSRIs only with reduced admission rate (Table 4-6). However, exposure to SSRI monotherapy did not reach significance, nor did Methadone. There were statistically insignificant trends towards lower admission rates in those exposed to psychotropics in general, and SSRIs in particular.

NNU admission rates in those exposed to SSRIs only, those exposed to other antidepressants, and those not exposed to antidepressants, were statistically significant different using the Freeman-Halton extension of Fisher's exact test for a 2x3 contingency table (Table 4-7). Subsequent dichotomous analysis using Fisher's exact test revealed that this difference was between those exposed to SSRIs and those exposed to other antidepressants.

Table 5-5 – Primary diagnoses for patients attending the MLS

Primary diagnoses	%	(N)	Durrani & Cantwell (2009) (%)
Organic, including symptomatic, mental disorders	**0**	**(0)**	**0.4**
Mental & behavioural disorders due to psychoactive substance use	**0**	**(0)**	**2.5**
Schizophrenia, schizotypal and delusional disorders	**1.9**	**(2)**	**4.7**
Schizophrenia	1.0	(1)	1.4
Schizotypal disorder	0	(0)	0.4
Persistent delusional disorders	0	(0)	0.4
Acute and transient psychotic disorders	0	(0)	1.4
Schizoaffective disorder	0	(0)	1.1
Unspecified non-organic psychosis	1.0	(1)	-
Mood (affective) disorders	**62.9**	**(66)**	**33.6**
Manic episode	0	(0)	-
Bipolar affective disorder	1.0	(1)	5.1
Depressive episode/recurrent depressive disorder	61.9	(65)	26.7 (14.8/11.9)
Persistent mood [affective] disorders	0	(0)	1.8
Neurotic, stress-related & somatoform disorders	**22.9**	**(24)**	**16.2**
Phobic/other anxiety disorders	18.1	(19)	7.6 (1.1/6.5)
Obsessive-compulsive disorder	3.8	(4)	2.9
Reaction to severe stress, and adjustment disorders	0	(0)	5.4
Somatoform disorders	1.0	(1)	0.4
Behavioural syndromes associated with physiological disturbances and physical factors	**0**	**(0)**	**0.4**
Eating disorders	0	(0)	-
Non-organic insomnia	0	(0)	-
Mental and behavioural disorders associated with the puerperium, not elsewhere classified	0	(0)	-
Disorders of adult personality & behaviour	**6.7**	**(7)**	**3.6**
Specific personality disorder (unspecified)	0	(0)	-
Emotionally unstable personality disorder	6.7	(7)	3.2
Intentional production or feigning of symptoms or disabilities, either physical or psychological [factitious disorder]	0	(0)	-
Mental retardation	**0**	**(0)**	**0.4**
Premenstrual tension syndrome	**0**	**(0)**	**-**
Factors influencing health status and contact with health services	**0**	**(0)**	**-**
Diagnosis not recorded	**5.7**	**(6)**	**-**

Table 5-6 - Admission rates to NNU for different exposure types

	(N)	Admitted (%)	(N)	Not admitted (%)	(N)	Fisher's exact test (p)
Total	(105)	20.0	(21)	80.0	(84)	-
Exposure						
Unexposed	(26)	23.1	(6)	76.9	(20)	-
Any psychotropic	(79)	19.0	(15)	81.0	(64)	0.78
Any AD	(75)	18.7	(14)	81.3	(61)	0.60
Any SSRI	(62)	14.5	(9)	85.5	(53)	0.14
SSRIs only	(57)	12.3	(7)	87.7	(50)	0.049
SSRI monotherapy	(54)	13.0	(7)	87.0	(47)	0.09
Methadone	(2)	50.0	(1)	50.0	(1)	0.36
Late exposure	(62)	17.7	(11)	82.3	(51)	0.62
First trimester only	(14)	21.4	(3)	78.6	(11)	0.72
Preterm delivery	(18)	44.4	(8)	55.6	(10)	0.00709
Until delivery						
Any psychotropic	(59)	18.6	(11)	81.4	(48)	1
Any AD	(57)	17.5	(10)	82.5	(47)	0.75
Any SSRI	(49)	14.3	(7)	85.7	(42)	0.24
SSRIs only	(45)	13.3	(6)	86.7	(39)	0.16
SSRI monotherapy	(44)	13.6	(6)	86.4	(38)	0.25

Table 5-7 – Analysis of antidepressant exposures, and admission to the NNU

	(N)	Admitted (%)	(N)	Not admitted (%)	(N)	Fisher's exact test (*p*)
Exposure						
SSRIs only	(57)	12.3	(7)	87.7	(50)	
Other ADs	(18)	38.9	(7)	61.1	(11)	0.0418
No ADs	(30)	23.3	(7)	76.7	(23)	
Dichotomous analyses						
SSRIs only *versus* other ADs						0.032
SSRIs only *versus* no ADs						0.44
Other ADs *versus* no ADs						1

Gestation, preterm delivery, birthweight, APGAR score, NNU admission and relationship(s) to illness severity, and/or exposure to any antidepressant

The median gestation of infants born to mothers attending the MLS was 276 days (range 223-293), median birthweight 3.32 (range 1.4-5.2), and median APGAR scores at one minute and five minutes were 9 (range 1-10), and 9 (range 6-10), respectively. As noted above, 18 of the babies were preterm (including all six twins), and 21 neonates required admission to NNU.

Since HADS-D and HADS-A were significantly correlated ($r=0.704$; $p<0.001$), two separate multivariate general linear model analyses were employed to explore the effects of HADS-D and HADS-A scores (predictor variables) on gestational ages, birthweights, and APGAR scores (outcome variables). We then repeated the analysis, using antidepressant use as an additional covariate in both models.

On the multivariate analysis, without any covariates, there was a significant effect of HADS-D ($F_{(3,87)}=2.8$, $p=0.04$, $\eta_p=0.09$). On further univariate exploration, HADS-D had an inverse relationship with gestational age ($p=0.025$) and birthweight ($p=0.006$), but not APGAR score ($p=0.740$), i.e. greater severity of self-rated depressive symptoms predicted lower birthweights and shorter gestations (Table 5-8).

Adding "any antidepressant" use as a covariate in the above model did not materially affect the results. On multivariate analysis, there was a significant effect of HADS-D ($p=0.05$), but not antidepressant use ($p>0.05$). On further univariate exploration, again HADS-D predicted gestational age ($p=0.027$) and birthweight ($p=0.007$), but not APGAR score ($p=0.745$) (Table 5-9).

On multivariate analysis, there was no significant effect of HADS-A on the outcome variables ($F_{(3,87)}=0.841$, $p=0.475$, $\eta_p=0.03$).

Given that higher HADS-D score predicted shorter gestational age, we conducted an exploratory analysis to see if HADS-D predicted preterm delivery – it did not ($F_{(1,93)}=1.6$; $B=0.009$; $t=1.26$; $p=0.209$).

Similarly, we conducted an exploratory analysis to see if HADS-D score predicted admission to the NNU. There was no significant relationship between HADS-D and admission ($F_{(1,93)}$ <0.001; B<0.001; t=0.008; p=0.994).

Table 5-8 – Multivariate analysis of relationships between HADS-D and select outcomes

Outcome variable	Parameter	B	Standard error	t	Significance (p)	Partial Eta Squared
Gestation	HADS-D	-0.557	0.244	-2.286	0.025	0.055
Birthweight	HADS-D	-0.037	0.013	-2.817	0.006	0.082
APGAR score	HADS-D	0.011	0.034	0.333	0.740	0.001

Table 5-9 - Multivariate analysis of relationships between HADS-D and select outcomes, with "any antidepressant" as a covariate

Outcome variable	Parameter	B	Standard error	t	Significance (p)	Partial Eta Squared
Gestation	Any AD	-0.902	3.054	-0.295	0.768	0.001
	HADS-D	-0.552	0.246	-2.248	0.027	0.054
Birthweight	Any AD	-0.081	0.163	-0.496	0.621	0.003
	HADS-D	-0.036	0.013	-2.763	0.007	0.080
APGAR score	Any AD	0.022	0.430	0.051	0.959	0.000
	HADS-D	0.011	0.035	0.327	0.745	0.001

AD = antidepressant

Results summary

In pregnant women attending the MLS,

(1) ~1 in 5 babies required admission to the NNU.

(2) Exposure to antenatal psychotropics and antidepressants was associated with a reduced risk of neonatal admission, but this was not statistically significant, except for exposure to SSRIs only (but not SSRI monotherapy).

(3) Exposure to SSRIs only was associated with a reduced rate of admission, in comparison with exposure to other antidepressants, or non-exposure. Otherwise psychotropics were not associated with preterm delivery, gestation at birth, birthweight, or APGAR scores, although increasing severity of depressive symptoms was associated with shorter gestations and lower birthweights, and preterm delivery predicted admission to the NNU.

Data integrity

As established in Chapter 3, the MLS records were a reliable record of patients seen, while the data collection forms, when completed, were an adequately accurate source of data on medication type and timing. Where there were gaps, we assumed that no drugs had been taken. Where dates were missing, we used EDD to estimate DOB, and gestation seen to estimate date seen.

BadgerNet proved to be an acceptable repository of relevant details for babies admitted to the NNU, although like other databases, not all fields had been completed. However, it was a true record of neonatal admissions, and the SBR both confirmed and supplemented BadgerNet data, as well as including details for infants not admitted to the NNU. Other parameters such as length of stay, head circumference, and postpartum haemorrhage were also obtainable.

Again, when date first seen was compared to the timing of medication changes, the majority of prescribing decisions had already been taken before attending the MLS. Several patients were seen more than once during pregnancy, and it was not possible to correlate the diagnosis and dates of HADS scores with type, timing, and dose of medication with any degree of validity. We assumed that HADS scores would have a complex relationship with medication, in that some patients would remit either spontaneously or with drugs, others would exhibit partial recovery, and still others would fail to respond at all (or deteriorate). Either partial or non-response could have precipitated a change in medication dose or type, and without explanatory documentation, it was not possible to establish this retrospectively.

There were a wide range of values for both the HADS-D and HADS-A, and it was encouraging to note that the median HADS-D score was 8, i.e. approaching non-clinical levels, perhaps indicative of effective therapeutic intervention. However, the median HADS-A score was somewhat higher at 12, and although

not necessarily consistent with significant neurotic illness, this may reflect the general distress levels of expectant mothers attending the MLS.

Twins were born to three women attending the MLS – each mother was only counted once with regards to analysing the relationships between psychotropic exposure and neonatal admission, while the details for each twin were included for the statistics on gestation, birthweight, and APGAR scores, thereby increasing the sample size to 108.

Diagnoses, medication, and outcomes

In comparison to the PMHS, there were proportionately less women with diagnoses of psychotic and bipolar disorders, and more with unipolar depression, anxiety, and personality disorder (Table 5-5). This may reflect the different resources and remits of the PMHS and the MLS as regional and local services, respectively, as the pattern of referrals received by each is similar, with 62% of referrals coming from maternity (Durrani & Cantwell, 2009).

The most common SSRI prescribed was Sertraline, accounting for 40.7% of SSRI monotherapy (Table 5-3). Significantly, it was the only psychotropic commenced in the third trimester, in five women who all had a primary diagnosis of depression. Sertraline is the antidepressant of choice in the MLS, due to its generally favourable safety profile in pregnancy and breastfeeding in comparison with other antidepressants, in addition to its efficacy and tolerability (Cipriani *et al.*, 2009; Taylor, Paton & Kapur, 2015)

The higher NNU admission rates for infants born to mothers attending the MLS in comparison to the general AMU population were again noted, 20.0% (cf. 11.3% of those not seen in Phase 1 (Table 5-6). The absolute numbers were low, and therefore care over interpretation is required. However, despite 14 of the 21 babies admitted having been exposed to antenatal psychotropics (all antidepressants, and 64.3% SSRIs), this was not a statistically significant

difference. In the AMU sample it had appeared that exposure to medication, including SSRIs, conferred greater risk of neonatal admission, but the opposite trend emerged in this MLS cohort – exposure to SSRIs only was associated with a statistically significant lower rate of admission than exposure to other psychotropics and non-exposure combined. However, the observation that significance disappeared when SSRI monotherapy was analysed raises some uncertainties over this interpretation. It should be noted that the absolute numbers were small.

However, overall it appeared that the increased risk of neonatal admission for infants of mothers attending the MLS is a true association. The data presented in Tables 5-6, 5-7, and 5-8 are consistent with the hypothesis and existing observations that psychiatric illnesses are associated with adverse outcomes, and that appropriate pharmacological interventions may moderate (or at the very least not exacerbate) some of these risks (Wisner *et al.*, 2009; Engelstad *et al.*, 2014). Although Malm *et al.* (2015) did find that antenatal exposure to SSRIs was independently associated with a risk of neonatal admission over and above the risk attributable to illness, they acknowledged that they had been unable to control for illness severity. Moreover, they analysed affective and neurotic disorders together, and did not take account of timing or duration of exposure to SSRIs.

It is noteworthy that exposure to SSRIs only was associated with reduced risk of admission, and exposure to other antidepressants was associated with an increased risk of admission, while neither was linked with other outcomes. Rather, severity of depression (but not anxiety) as measured by HADS analysed as a continuous variable, was linked with shorter gestations and lower birthweights, but not preterm delivery, reduced APGAR scores, or admission. (It should be noted that, as illustrated by HADS-D's association with shorter gestations but not increased preterm birth, not all statistically significant findings are necessarily of clinical concern.)

These findings are consistent with the hypothesis that it is severity of illness (for which prescribing is a surrogate marker) more than antidepressants that is

associated with risk. That exposure to non-SSRIs (mainly SNRIs, Trazodone, and Mirtazapine) was associated with an increased risk of admission raises the possibilities that these antidepressants cause more adverse effects, or that their use indicates either increased depressive severity and/or treatment resistance (to SSRIs), or medication (and therefore illness) that predates the current pregnancy, thus indicating chronicity. However, further work on a larger sample including infants admitted to the NNU is indicated, as both the reasons for admission and their associated risk factors remain covert. While it appeared that exposure to both unmedicated illness and non-SSRI antidepressants were associated with neonatal admission, HADS-D did not predict admission, suggesting that other factors may be involved. A larger sample would help to explore the consequences of different exposures in more detail, teasing out any differences due to severity, duration, and timing of individual disorders and drugs. The current consensus is that tricyclic antidepressants, the SNRIs Venlafaxine and Duloxetine, the NaSSA Mirtazapine, and Trazodone are broadly comparable to SSRIS with regards to perinatal sequelae, although they have been studied less than SSRIs, and the few studies that do exist are subject to the same caveats and cautions regarding confounding and methodological weaknesses (Simoncelli, Martin & Bérard, 2010, Udechuku *et al.*, 2010; Grigoriadis *et al.*, 2013; Andrade, 2014; Osborne *et al.*, 2014; Bellantuono *et al.*, 2015).

The leitmotif of confounding is woven throughout studies and conclusions pertaining to the consequences of antenatal psychiatric disorders and their pharmacological treatments. Even where authors claim that known confounding factors have been controlled for, there remains interpretative uncertainty. For example, while Englestad *et al.* (2014) list one of their study's strengths as women with depression having "similar disease severity" whether on SSRIs or not, they did acknowledge that this could represent symptom reduction due to medication in those taking SSRIs, i.e. the group exposed to SSRIs may have had more severe depressive illness, which had responded sufficiently to antidepressants, thus appearing comparable to the unmedicated subjects. This remains a significant challenge to researchers in this area, as randomised-

controlled studies to ensure parity of illness severity in medication-exposed and unexposed groups would be unethical (Barbui & Ostuzzi, 2014).

It is a reasonable assumption that there are likely to be systematic differences between depressed women taking medication, and those not. Current clinical practice tends towards using antidepressants when depression is of moderate severity or worse, and recommending non-pharmacological interventions in milder cases (NICE CG90, 2009). This means that even where rating scales yield similar scores in antenatally depressed women exposed and not exposed to antidepressants, this is unlikely to indicate that they have had exactly the same experience of depressive illness and is consequences throughout pregnancy.

One way of seeking to address this is via propensity score matching, where one adjusts for biased distribution of known covariates between observational cohorts by matching subgroups that do not differ significantly with regards to these factors (Drake & Fisher, 1995). A seminal study in this regard is Oberlander *et al*. (2008). They interrogated the British Columbia Linked Health Database, and identified 119,547 live births between 1 January 1998 and 26 March 2001, matched with maternal prescriptions for SSRIs from 1 April 1997 to 31 March 2002. They defined exposure during pregnancy using the date the drug was dispensed plus the number of days for which tablets were supplied to establish any overlap with pregnancy, which was estimated from infant birth date and length of gestation. The trimesters were taken as from conception until day 92, day 93 until day 185, and day 186 until delivery. As per Chambers *et al*. (1996), who first highlighted the potential risks of exposure to SSRIs later in pregnancy (defined by continuing into the third trimester/beyond 24 weeks of gestation), Oberlander *et al*. compared neonatal outcomes in those exposed early in pregnancy (discontinuing before day 185) and those exposed into the third trimester. (One interesting observation is that there is no agreed definition of the trimesters of pregnancy, hence we used Oberlander *et al's* specification throughout – see Appendix 5.) 1.3% (1,575/119,547) were exposed early, and 1.6% (1925/119,547) late.

They found that late exposure was associated with lower birthweights, shorter gestations, and increased rates of respiratory distress, but these associations did not remain significant following propensity score matching, when they compared a subgroup of 429 infants in each exposure group, matched for diagnoses of depression, visits to a psychiatrist, and duration of exposure to an SSRI during pregnancy (all considered to be proxy markers for depression severity). Following this, the only statistically significant findings were that duration of exposure to an SSRI during pregnancy was linked with lower birthweights, shorter gestations, and increased rates of respiratory distress. SSRI dose was not associated with adverse neonatal outcomes, although Roca *et al*. (2011) subsequently reported (after accounting for, but not necessarily controlling for maternal illness severity) that higher doses of SSRIs are associated with increased rates of preterm birth.

It appears that antenatal SSRI exposure may contribute to, confound, or curtail adverse outcomes, and in the absence of randomised controlled studies to establish causality, there remains a need for high quality prospective research that takes account of the plethora of parameters that can influence inferences.

Key points

- ~1 in 10 babies required neonatal admission, and this rate doubled to ~1 in 5 in those exposed to antenatal maternal depression significant enough to warrant referral for specialist care, and/or medication.
- Antenatal exposure to SSRIs may reduce the risk of some adverse perinatal consequences, and increase the risk of others.
- However, antenatal exposure to SSRIs may also serve as a proxy measure of maternal illness severity, which is independently associated with sequelae.

Chapter 6 – Methodological issues in determining the characteristics and consequences of antenatal exposure to SSRIs

Throughout our overview of the literature in Chapter 1, outlining the challenges in diagnosing and treating depression, especially perinatally, and the difficulties in disentangling the sequelae of antenatal depression from antidepressants; our systematic review of publications on the characteristics of antenatal exposure to SSRIs in the UK in Chapter 2; our exploration of prescribing patterns and data integrity within different perinatal settings using clinical datasets in Chapters 3 and 4; and our subsequent analyses of select clinical outcomes of fetal exposure to depression and antidepressants in Chapter 5; we have highlighted and discussed in context diverse methodological issues in this area of research. A comprehensive account is beyond the scope of this thesis, as demonstrated by Grzeskowiak (2012) in the pursuit of his PhD on "Feasibility of Using Routinely Collected Health Data to Examine Long-Term Effects of Medication Use During Pregnancy". Therefore, the focus of this chapter is to summarise and discuss key matters relating to mining the UK datasets to determine the characteristics and consequences of antenatal exposure to antidepressants in general, and SSRIs in particular, in the UK.

Prospective parents and perinatal practitioners alike desire accurate, reliable and up-to-date evidence on how to prevent and treat perinatal depression effectively – and safely. Management options and recommendations prefaced and enveloped by qualifications such as "In general terms …", or "As far as we know …" are less than reassuring to patients and fall short of professional aspirations (Mulder *et al.*, 2012). Clinical practice based on research conclusions derived from reviewing individual patients' records has been at the heart of medical research for centuries, and has a long and distinguished profile (Balas *et al.*, 2015). This approach is limited, however, by the inadequate statistical power of insufficiently large samples to reliably identify small increases in risks

of relatively common adverse outcomes, and/or significant sequelae associated with rare exposures. The rise of evidence-based medical practice and use of epidemiological databases incorporating and linking individual electronic health records and other registers over the past few decades has made it possible to access millions of records at a time, and has led to the accumulation of vast amounts of so-called "big data". "Big data" merits a big definition, which can be simplified as six "Vs"; variety (different datasets with different sources), volume (numerous measurements), velocity (contemporaneous or frequent updates), value (clinical relevance), variability (longitudinal trends) and veracity (data quality) (Andreu-Perez *et al.*, 2015; Baro *et al.*, 2015; Ehrenstein *et al.*, 2017). "Big data" can be particularly valuable when exploring rare exposures and outcomes, and phenomena not amenable to interventional evaluation.

However, quantity does not always guarantee quality. In addition to the technical, ethical and legal issues surrounding the storage, international sharing and use of routinely collected clinical data by researchers (and for purposes) unknown to individual patients, suboptimal data integrity due to incomplete, invalid, inaccurate, unreliable, out-of-date or inconsistent entries has the potential to "amplify systematic error" (Roth *et al.*, 2009; Balas *et al.*, 2015; Auffray *et al.*, 2016; Ehrenstein *et al.*, 2017; Lee & Yoon, 2017). As in computer science, where "garbage in" equals "garbage out", inferences based on suboptimal datasets are to be avoided. Moreover, statistical does not necessarily imply clinical consequence.

Since 2000 the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group has become increasingly influential in standardising guideline developers' grading of the evidence and recommendations, and has been used by NICE since 2009, and SIGN since 2013 [Guyatt *et al.*, 2008a; SIGN, 2013; NICE, 2014]. GRADE has built on the established "hierarchy of evidence", with randomised controlled interventional trials (RCTs) representing higher quality data on which to base policy and decisions, due to their explicit designs to address and minimise the methodological limitations of observational studies, such as those employing cohort and case-control designs [Guyatt *et al.*, 2008b]. While observational

studies can identify associations between exposures and outcomes, they do not prove causality, with chance, bias, confounding and reverse causality mimicking true causal relationships (Skapinakis & Lewis, 2001; Rutter, 2007). The use of "big data" via epidemiological databases has served to magnify the potential both to identify and be misled by small non-causal associations between exposures and outcomes, and remains an important (if not convenient and necessary) means to answer questions that are difficult to address via interventional trials, whether technically, ethically or legally (Ehrenstein *et al.*, 2017). Assessing the safety, effectiveness and tolerability of antidepressants during pregnancy via RCTs is one good example, as many (but not all, e.g. Coverdale, McCullough & Chervenak, 2008) hold this to be unethical, mainly due to the potential unknown adverse effects on the fetus, and likely impractical due to the understandable attitudes and anxieties of mothers-to-be (Healy, Mangin & Mintzes, 2010; Turner *et al.*, 2008; Barbui & Ostuzzi, 2014). (RCTs of antenatal pharmacological interventions have been possible in certain circumstances, which admittedly differ from assessing antidepressants for antenatal depression, due to greater certainty about risk:benefit ratios, e.g. Unger *et al*. [2011].) The common practice of using pregnancy as an exclusion criterion in RCTs, and the need for statistical power to identify small influences on rare outcomes lead inexorably to the use of "big data" in addressing questions on the characteristics and consequences of antenatal exposure to antidepressants.

At present, therefore, combining and using the routinely collected longitudinal clinical data from millions of records to explore the associations between exposure to antenatal depression and antidepressants and outcomes for women and offspring remains the primary means of reaching conclusions on which to base clinical decisions, necessitating a clear understanding of the methodological issues, and consequent uncertainties and caveats. These have been described in the literature, with key references including Colvin *et al*. (2011), Bromley *et al*. (2012), Grzeskowiak, Gilbert & Morrison (2011), Grzeskowiak, Gilbert & Morrison (2012a and b) and Colvin *et al*. (2013). Significant areas of challenge in using "big data" are summarised in Table 6-1.

Table 6-1 – Methodological issues in using epidemiological data

Data integrity representativeness; missing data; interpreting ambiguities; prospective and retrospective data; bias and confounding; technical, ethical and legal challenges
Defining pregnancy beginning and end; spontaneous and induced abortion; live births, stillbirths and neonatal deaths
Defining exposure to antidepressants prevalence, type, dose, timing and duration; prescribed, paid for, dispensed and ingested; comorbidity and co-prescriptions; genetic, epigenetic and maternal-obstetric factors
Relating outcomes to exposures underlying illness type and severity, versus intervention characteristics

Data integrity

Data integrity may be defined as the validity, accuracy, reliability, timeliness and consistency of the data (Balas *et al.*, 2015). Completeness is implied in this definition, although worthy of specific mention. Selecting a study sample representative of the general population is the first step in reaching conclusions regarding antenatal antidepressants, and presents several challenges. Three main data sources described in the perinatal literature are the linking and mining of national registers (mainly in Nordic countries, e.g. Jimenez-Solem, 2014), primary care databases (including in the UK; see Chapter 2), or information derived from healthcare insurance and/or claims (commonly in the USA, e.g. Hanley & Mintzes, 2014).

The limitations of the latter datasets are immediately apparent – socioeconomic factors influence outcomes, and patients with private health insurance are not directly comparable with those reliant on government funding. For example, Hanley and Mintzes (2014) reported that 6.5% of pregnant women with private health insurance were exposed to an antidepressant between 2006 and 2011, while Huybrechts *et al*. (2013) found that 8.1% of women eligible for Medicaid (a joint federal and state programme that helps to fund healthcare for the less affluent) between 2000-2007. However, even within the datasets used there was significant temporal, regional, diagnostic and demographic variation – older, white women were prescribed antenatal antidepressants more frequently, different proportions of those diagnosed with depression received prescriptions in different states, and exposure rates varied more than twofold geographically (from 6.44% in New York to 15.41% in Idaho). Clearly, conclusions based on individual datasets are not necessarily generalisable. Moreover, pooling data over time, from different subjects, of varying ethnicities and socioeconomic backgrounds, residing in diverse locations, even although they are in a particular dataset, simply leads to an overall estimate of the average exposure within that population during the time period studied.

The Nordic registers are more inclusive than their US counterparts, thus ensuring that all residents are included, and allowing known confounding factors to be taken into account in analyses; therefore, conclusions are relevant to the population of the country under consideration. However, they are not exempt from other limitations discussed below, including lack of data on women's adherence to dispensed medication, nor pregnancies ending in spontaneous or induced abortion (Jimenez-Solem *et al.*, 2013).

The characteristics of the UK primary care databases have been outlined in Chapter 2, with Petersen *et al*. (2016) providing a summary of their strengths and limitations (including that THIN contains slightly more patients who live in affluent than CPRD, data is not complete for medication quantities and doses, mother:infant data can only be linked if the child is registered at the same practice as the mother, and the dates of birth for children under 15 are restricted to month and year only – see below). Similar to the Nordic registries,

and due to the structure of healthcare in the UK, the CPRD and THIN datasets are inclusive and broadly representative of the British population, although do not include information about patients not registered with a GP or receiving care from other sources, e.g. private or specialist settings. This introduces the potential for bias, e.g. by systematically excluding socioeconomically deprived patients such as the homeless, more affluent patients accessing private care, or more unwell patients requiring specialist management. Each of these could influence findings and conclusions in different directions, given that diagnoses of and prescriptions for antenatal depression are associated with socioeconomic factors, and patients managed in perinatal or psychiatric settings are likely to suffer from more severe, chronic and/or complicated depressive illnesses necessitating interventions not common in the general population (see Chapters 1 and 8). Moreover, changes in service provision over time may also affect data integrity; for example, pregnant women in the UK no longer require contact with their GP to have pregnancy confirmed due to the reliability of over-the-counter pregnancy tests and, in recent years, have been able to self-refer for antenatal care, thus bypassing their GP, potentially throughout pregnancy. As the data is collected prospectively the potential biases associated with retrospective recall may be minimised (although not absent – some of the "prospective" information collected during clinical contacts is based on the patients' history); however, accessing and interpreting relevant data retrospectively is not always straightforward (Margulis *et al.*, 2013).

Missing data is a significant issue, leading to limitations such as relevant subjects being overlooked (e.g. if their pregnancies or prescriptions were not identified or recorded) or excluded (e.g. due to strict methodological criteria, such as omitting those with certain [comorbid] conditions or co-prescriptions), or compensatory measures being employed, such as assumptions about length of pregnancy, gestational age at birth, and/or timing of prescriptions) (see Table 2-2). Again, each of these has the potential to bias findings and conclusions.

The same is true of ambiguities, such as inconsistent birth details between maternal and neonatal records, or translating prescription details for dates, doses and number of tablets prescribed and/or dispensed into timing and

duration of exposure, in correlation with gestation dates and stages (Chapter 4). Some of the most basic parameters foundational to exploring associations between antenatal exposure to depression and antidepressants and outcomes such as simply identifying pregnancies are not necessarily straightforward. While many studies do not go into detail about how exactly they identified pregnancy women from datasets such as CPRD and THIN, Cea-Soriano *et al*. (2013) did, demonstrating that categorising subjects as pregnant as opposed to non-pregnant is not an unambiguous digital process.

Defining pregnancy

Using THIN to assess medicines prescribed during pregnancy Cea-Soriano *et al*. (2013) defined their study population as women of childbearing age (13-49) who were registered with a participating practice for at least one year during the study period (1996-2010), including either at least 280 days following the recording of their last menstrual period (LMP) or before any date of delivery or pregnancy loss (including abortion, termination, ectopic pregnancy, and stillbirth [incorporating fetal and neonatal death]). In other words, THIN (and other databases do not necessarily provide a data field to indicate "pregnant" as opposed to "not pregnant"; pregnancy must be inferred. While several outcomes do unequivocally indicate a pregnancy (live birth, pregnancy loss or neonatal death), very early miscarriages may be missed, and subjects who were not registered throughout pregnancy will be excluded – the former is a practical artefact of the dataset itself, and the latter a consequence of researchers using exclusion criteria to minimise missing data. Moreover, even apparently unequivocal data require checking – Cea-Soriano *et al*. found that 2% of women recorded as experiencing pregnancy loss had subsequent entries indicating live birth, suggesting threatened rather than completed miscarriages in the earlier entries.

In an attempt to ensure that their conclusions were accurate, Cea-Soriano *et al*. defined pregnancies in women via three groups: (1) a *conception* group, where

those with an LMP recorded were included if a code consistent with end of pregnancy was recorded within 320 days (to capture late deliveries); (2) an *end of pregnancy* group, made up of those with a code for loss or delivery; and (3) an *other pregnancy codes* group, comprised of those without LMP or pregnancy outcome data, but with other pregnancy-related codes, e.g. pregnancy tests or prenatal visits.

Cea-Soriano *et al*. noted that using LMP alone as a marker for pregnancy was misleading, as this was not infrequently recorded as part of contraceptive care. Therefore, they attempted to link all women with LMP recorded to infants born within 180-380 days of that LMP, using THIN's family identification codes. Again, this process involved a degree of estimation and inference, as while mother's dates of delivery may have been recorded accurately, neonates' dates of birth were provided to the researchers as month and year of birth only, to protect confidentiality. This necessitated assigning the 15th of the month as the putative date of birth for all infants, necessitating further interpretation – if there was more than a 30 day discrepancy between mother's date of delivery and their infant's putative date of birth the latter was used; otherwise, the researchers employed the date of delivery. A relatively high proportion of pregnancies identified as completed had missing linkage data, again leading to date of delivery being used.

Furthermore, as (by definition) subjects in the *end of pregnancy* group had no LMP date, LMP (i.e. beginning of pregnancy) was simply assumed to be 280 days before the date of birth (or date of delivery), unless codes indicated pre- or post-term births, in which cases 245 days or 285 days were substituted, respectively. Ultimately those with possible pregnancy-related codes (including LMP) but no infant linkage were excluded, with the assumption that these codes did not imply actual pregnancy.

Thus it can be seen that simply identifying pregnant women from datasets such as THIN is not an unambiguous process. Even where LMP is clearly recorded, this does not exclude the potential for individual retrospective recall bias regarding exact dates, nor inaccuracies in ultrasonography (as LMP may be calculated or

corrected using early scans). Cea-Soriano *et al*. acknowledged that their "conservative" approach may have underestimated the pregnancy rate in THIN, and sought to evaluate this by repeating their study, identifying 11% more "suspected" pregnancies, but ultimately ending up with the same number of subjects for whom data of acceptable accuracy was available. Notably, they achieved 88.5% linkage between mothers and infants – this still indicates that data for more than one in 10 potential participants were missed.

In broad terms, therefore, even primary care databases such as THIN, validated and viewed as being comprised of high quality data and representative of the general population, are not 100% definitive with regards to identifying pregnant subjects, nor specifying the beginnings, ends or durations of pregnancies. Thus, they are neither exempt from uncertainties nor immune to ambiguities, and require careful post-hoc interpretation and algorithmic manipulation. Margulis *et al*. (2015) reviewed the main approaches used by researchers in this area, categorising them into five main groups, which, while varying in their strengths, complexity and utility, are all associated with unavoidable inaccuracies relating to actual gestation length, and therefore prone to introducing bias, e.g. by systematically overestimating pregnancy length in pre-term births, which may be over-represented in those exposed to antenatal antidepressants (Oberlander *et al.*, 2008; Ross *et al.*, 2013).

Even without reference to databases and registers, precisely defining the beginning of pregnancy is challenging clinically and practically, including for obstetricians, (Chung *et al.*, 2012). Similar to many perinatal researchers, Petersen *et al*. (2016) took LMP as the start of pregnancy in "accordance with clinical practice in the UK". However, basing gestational age on LMP is not exact, as although ovulation occurs 14.6 days later, with fertilisation one day after that, and implantation after a further seven days, these are average epochs, affected by a variety of factors, including the length of each woman's usual menstrual cycle (Geirsson, 1991). In other words, using gestational age (based on LMP, or fetal size in reference to standardised ultrasonographic findings) adds an extra 15.6 days (on average) to so-called fertilisation (fetal, embryonic) age, potentially artificially inflating estimates of rates of very early

fetal exposure to antidepressants prescribed in the weeks before conception. Moreover, as the gestational ages associated with even normal, uncomplicated, term pregnancies can vary by up to 37 days, it appears clear that it is practically impossible to be precise when defining the true beginning of pregnancy using LMP alone (Jukic *et al.*, 2013).

Therefore, using "end of pregnancy" outcomes to define not only the occurrence but also the length of pregnancy is perhaps the most useful and accurate approach as, if date of mother's date of delivery/infant's date of birth and infant's gestational age at birth are recorded, then the start and duration of pregnancy can be calculated with a degree of certainty. Depending on data outcomes used, ectopic pregnancies, spontaneous miscarriages and induced abortions, and stillbirths and neonatal deaths can be identified as well as live births, thus minimising biases introduced by excluding these phenomena, given that they are associated with exposure to antidepressants (excluding non-live births has the potential to lead to underestimates of true overall exposure rates) (Ban *et al.*, 2012; Kieler *et al.*, 2014). One further issue to be noted rather than addressed is that a high proportion (perhaps up to 70%) of fertilised embryos may not implant and therefore result in an identifiable pregnancy - if exposure to antidepressants periconception is associated with early pregnancy this may go undetected (Smart *et al.*, 1982; Wilcox, Baird & Weinberg, 1999; Wang *et al.*, 2003). Given the significant difficulties in being accurate to the day regarding the start of pregnancy, perhaps taking fertilisation age as the start of pregnancy when evaluating exposure to antidepressants would be a reasonably pragmatic default, i.e. LMP plus 15 days, or gestational age minus 15 days. No studies to date have done this, with even the most methodologically rigorous using gestational age to define pregnancy, thus defining exposure a full two weeks before an embryo even exists, and three weeks before implantation

Two further variables related to defining pregnancy merit discussion, both relevant to confounding factors: serial pregnancies, and multiple pregnancy. It would simplify matters greatly for researchers if all mothers had only one pregnancy, and each was singleton. However, given that many of the studies span several years, it is not infrequently the case that some women may have

several pregnancies, precipitating methodological decisions about how to accommodate these. Including more than one pregnancy in the same women introduces the potential for bias via clustering, as a past history of an adverse outcome is associated with a significantly increased risk of repetition (for a detailed discussion see Louis *et al.*, 2006). Failing to take account of this statistically, including by simply incorporating obstetric history as a covariate, may obscure important exposure:outcome relationships. In an attempt to minimise bias due to clustering, some studies exclude multiparous women, or select only one pregnancy during the study period, either randomly, or the first or last. Others include all pregnancies. This makes it difficult to compare different studies, as well as limiting the power to identify potential exposures of significance.

Similar issues affect multiple pregnancy – counting this as one exposure without controlling for the reduced growth rates and adverse outcomes in comparison to singleton pregnancy introduces one type of bias, while counting each infant as a separate outcome introduces another (Grzeskwoiak, Gilbert & Morrison 2012a). For these reasons, some researchers elect to include only singleton pregnancies in primiparous women when exploring the outcomes of antenatal exposure, not least because of the potential adverse effects of multiparity on offspring (Lahti *et al.*, 2014).

In summary, therefore, identifying pregnant women and the timing and duration of pregnancy from clinical and administrative datasets for the purpose of retrospective research is neither routine nor infallible. The best approach appears to be to use outcomes which confirm that pregnancy occurred, e.g. ectopic, spontaneous miscarriage, termination of pregnancy, live birth or stillbirth, and to use the date of delivery/date of birth and gestation at birth to fix the beginning of pregnancy, whether gestational age or fertilisation age. Depending on what exposures and/or outcomes are being assessed, either singleton or multiple pregnancy, in primiparous or multiparous women, included once or serially in the study sample should be considered and described.

Defining exposure to antidepressants

In addition to the challenges in ensuring data integrity and defining pregnancy from routinely collected data, characterising antenatal exposure to antidepressants is similarly complex. In their paper paper on classifying exposures Grzeskowiak, Gilbert and Morrison (2012b) highlight the inconsistencies in evaluating dose, duration and timing of exposure; variability in categorising exposures (including how to process and analyse women who stop medication before or in early pregnancy)' and assumptions surrounding whether medicines dispensed perinatally result in actual fetal exposure. The key issues in defining exposure are what and when.

While it is generally possible to define the type(s) of medication prescribed, it is common practice to assess broad outcomes (e.g. any cardiac malformation, whether clinically insignificant or life-threatening) of exposure to classes of medication (e.g. SSRIs) rather than individual drugs. Although this makes sense in terms of increasing sample size, and avoiding the need to take account of potentially confounding reasons for clinicians choosing one particular drug over another, it assumes that all drugs within that class are similar with regards to their teratogenicity and effects on longer term neurodevelopment. As discussed in Chapter 5, this is not clearly the case for SSRIs. Partly in relation to this, defining rates of exposure is confusing – studies vary in reporting incidence, point prevalence and/or period prevalence, depending on which methodology they employ to address the specific research question(s) they are seeking to address. While establishing total exposure rates, i.e. period prevalence, is useful from epidemiological, economic and service provisions perspectives, it is less helpful for evaluating outcomes, due to the varying effects of different types of exposure at different gestations.

Detailed data on doses is generally absent from the antenatal literature, not because they is not available, but presumably because taking account of doses is impractical on a number of levels. Firstly, and as outlined in Chapter 4, the actual daily dose taken is not necessarily clear from the prescription data itself. Secondly, unless confounding factors such as the underlying diagnosis and illness

severity, and maternal adherence and pharmacokinetic issues are taken into account, relating doses to outcomes may be misleading. However, SSRI doses do represent an important area for future study, as there is evidence of dose-related teratogenic risks with some SSRIs (higher doses of Paroxetine may be associated with a higher risk of cardiac malformations), similar to anticonvulsants (Vajda *et al.*, 2004; Bérard *et al.*, 2007).

Clarity about timing and duration of antenatal antidepressants is critical, however, due to concerns about adverse consequences at different developmental stages, and/or length of exposure. This is dependent on accurate information on gestational age and stage, discussed above. Challenges relating to defining timing and duration of exposure have been discussed in Chapter 4, and include a wide range of factors. The CPRD and THIN datasets specify when prescriptions were issued by the provider, but this is not necessarily the date when the medication was dispensed (although this is specified by some sources, including ISD), collected or commenced. Some women may collect their next supply of drugs in good time to continue without a break, while others may be late, for a variety of legitimate or less than ideal reasons. Unless datasets specify the intended daily dose, this and therefore duration cannot necessarily be inferred from the quantities and strengths of the tablets supplied.

Adherence to medication is another obvious complication. Even in the general population prescriptions for antidepressants do not translate exactly into medication taken – in the Netherlands van Geffen *et al*. (2009) found that more than one in four patients issued with a prescription for an antidepressant either did not start it at all, or persisted for less than two weeks, with the elderly, those with non-specific symptoms and immigrants two-, three- and five-fold more likely to decline treatment, respectively. In Scotland, Beardon *et al*. (1993) reported that around one in four women aged 16-39 did not redeem prescriptions, concluding that "observational studies of drug exposure can be more accurately estimated from dispensing rather than prescribing data". This was reinforced by Mabotuwana *et al*. (2011), who found that while prescribing data indicated that 39% of patients demonstrated poor adherence to antidepressants, dispensing data revealed poor adherence to be 68%. With

specific regards to pregnancy, van Gelder *et al*. (2012) compared retrospective questionnaires on perinatal medication with accurate dispensing records, demonstrating a sensitivity of 39% for detecting antidepressants (and a wide range of sensitivities for identifying other antenatal drugs), meaning that putative recall bias dramatically reduces the utility and validity of retrospective data collection for establishing exposure. Skurtveit *et al*. (2014) reported comparable findings, with sensitivity being higher at 66.9% for antidepressants, but lower at 27.8% for benzodiazepines prescribed for sleep. Källén, Nilsson and Olausson (2011) found that relying on prescription data in early pregnancy can lead to overestimates of exposure in comparison with clinical interviews, presumably due to erroneously assumed adherence. However, recall bias would lead to the opposite error, as may a reluctance to take (or to admit to taking) antidepressants during pregnancy – Lupattelli *et al*. (2015) found that around 50% of pregnant women adhered poorly to prescribed antidepressants, especially those who had more severe depressive symptoms, those who perceived risk to be high and/or outweigh benefits, and those who smoked. However, those prescribed more than one psychotropic during pregnancy adhered better, consistent with the observation that those who perceive benefits to outweigh risks demonstrate higher concordance.

The above issues are particular problems with regards to ascertaining early exposure. Knowing exactly when a woman who was prescribed an antidepressant before pregnancy started it, took it, and/or discontinued it would, in conjunction with actual or retrospectively calculated LMP and/or ultrasound-estimated gestational age, allow this. However, short of asking each individual contemporaneously (or observing, or supervising), there appears to be no practical way to improve upon the methods currently employed by the published studies, other than to acknowledge their limitations. This obviously affects estimates of exposure, with regards to incidence and prevalence, timing and duration, and thus accurate assessment of outcomes.

Even if exposures could be ascertained accurately, this would not obviate the issues in categorising exposure types to study outcomes. While stopping antidepressants prescribed periconception in the first trimester, or persisting

throughout pregnancy are the most common patterns, a substantial proportion of patients stop and start at various different gestations, sometimes more than once, in addition to being exposed to more than one type of psychotropic concurrently or consecutively, as well as non-psychotropics and other psychoactive substances, whether legal (including alcohol and tobacco), novel or illicit (Riley *et al.*, 2005; Colvin *et al.*, 2011; Huybrechts *et al.*, 2017 – see also Chapter 3 and 4). Lumping these disparate exposures together to increase statistical power lacks research and ultimately clinical validity, by diluting and obscuring potentially significant causal associations between specific exposures and sequelae (Grzeskowiak, Gilbert & Morrison, 2011).

In summary, therefore, accurate classification of exposures is dependent on defining the type (which drug, at what dose) and timing (at what gestation(s), and for how long), for which data may not be available at the level of accuracy or indeed detail required, given that there is no way of confirming retrospectively from datasets exactly what dose of medication was taken and when (or if at all). The myriad of confounders discussed in Chapter 1 are considered in relation to outcomes (below), with Table 6-2 summarising the main factors. At least part of the complexity in this area is that outcomes may also act as subsequent exposures and/or confounding factors.

Table 6-2 – Select outcomes and exposures/confounders relevant to perinatal depression and antidepressants

	Outcomes*	Exposures/confounders
Prenatal	Reduced fecundity Ectopic pregnancy Miscarriage Termination of pregnancy Neuroendocrine dysregulation Epigenetic phenomena Obstetric complications, e.g. reduced fetal, growth, eclampsia, operative deliveries Stillbirth Pre-term delivery Low birth weight Congenital malformations Neonatal adaptation syndrome Specific neonatal problems & conditions, e.g. respiratory distress Feeding difficulties Failure to thrive Neuroendocrine dysregulation & physiological abnormalities Attachment difficulties Temperament & personality Neurodevelopmental delay & deficits Socio-emotional, psychomotor, cognitive, academic, intellectual & behavioural problems General health complications Childhood/adolescent/adulthood psychopathology & mental health problems, including depression	Maternal (& paternal) • Genotype • Socioeconomic status • Age • Medical/obstetric history • Current health status • Depression • Smoking, alcohol & substance use Maternal stress Depression • Severity • Chronicity • Response to medication • Comorbidity Medication • Type • Dose • Timing • Duration • Adherence • Co-prescriptions • Placental transfer of drugs Fetal genotype Early neonatal environment
< - >		
Antenatal		
< - >		
Postnatal		

* outcomes may also act as subsequent exposures and confounders

Relating outcomes to exposures

Compounding the complexity of ensuring data integrity, identifying a representative sample population, defining the boundaries of pregnancy and categorising exposures are the challenges of relating outcomes to exposures. The main issues are specifying the outcomes to be assessed, while minimising and accounting for bias and confounding.

Bias is systematic error that that leads to an incorrect estimate of effect or association, while a confounding variable is one that distorts associations between exposures and outcomes. Known confounders may be controlled for, but unknown confounding factors may lead to bias. Interventional trials frequently employ randomisation and blinding to minimise bias and confounding, but the observational approaches used to evaluate perinatal exposures and outcomes are unable to utilise these. Due to the overlap between the outcomes of exposure to antenatal depression and antidepressants, and many of these sequelae further confounding associations (e.g. low birthweight and preterm delivery, both of which are independently associated with numerous adverse outcomes also linked with both antenatal depression and antidepressants), it has proven difficult to discriminate between consequences of the underlying disorder and its pharmacological treatment.

It should be noted that neither of these (illness and treatment) is a simple digital phenomenon. Just as antidepressant exposure can vary in type, dose, timing and duration, depression may fluctuate in severity, chronicity and response to treatment. For example (and using a BDI-II cut-off for moderate depression as 20), a pregnant woman scoring 20 in the second trimester may represent an individual experiencing transient emotional distress, a new onset or recurrence of a depressive episode, or an improvement from a score of, say, 40 two weeks earlier. Equally, a BDI-II score of 20 could represent an unmedicated patient who is deteriorating, a patient recently prescribed an SSRI which is proving ineffective, or a patient who has improved significantly on a tricyclic which was prescribed before pregnancy for a pre-existing and chronic depressive illness. As noted in Chapter 5, there are likely to be systematic differences

between depressed women taking medication, and those not. Few studies investigating antenatal antidepressants have taken account of characteristics of the underlying illness (or comorbidity or co-prescriptions for non-psychotropics), and none have given comprehensive attention to the all the known factors of relevance – this is due in large part to this level of dynamic detail being unavailable from the datasets. As per our observations in Chapters 3 and 4, the information in the CPRD and THIN was not collected with the aims of the researchers in mind (Grzeskowiak, Gilbert & Morrison, 2011).

In their review and critical appraisal of methodological issues in studying consequences of antenatal exposure to SSRIs Grzeskowiak, Gilbert and Morrison (2011) noted the above issues, in addition to teasing out specific effects of individual SSRIs on discrete outcomes, e.g. Paroxetine and congenital malformations. However, on closer inspection even these two apparently clearly defined phenomena are heterogeneous groups: Paroxetine exposure needs to be defined more precisely in terms of dose, timing and duration, as well as the underlying condition for which it was prescribed (presumably, but not necessarily depression) and all its characteristics; and "cardiac malformations" may include everything from clinically insignificant and self-limiting septal defects to major structural pathology associated with stillbirths and/or neonatal deaths. Moreover, as those prescribed SSRIs may (for a variety of reasons) be monitored more closely during pregnancy (e.g. via detailed ultrasonography), and exposed neonates may be admitted more frequently to hospital, it is possible that increased rates are more apparent than real, and attributable to detection bias. Furthermore, as definitions of congenital malformations vary between studies, conclusions and even rates of abnormalities are not necessarily comparable. Unmedicated mothers with comparable depression were not used as a reference group for comparison, thus meaning that any consequences of exposure to antenatal depression may have been misattributed to Paroxetine.

Similar issues of heterogeneity and detection bias, in addition to confounding, apply to exploring associations between antenatal exposure to SSRIs and other sequalae, including miscarriage, neonatal outcomes and longer term neurodevelopment. Three additional factors that compromise conclusions are

the risks of chance findings due to multiple testing and subgroup analyses common in the studies, inadequate sample sizes leading to "type II' errors (with attempts to increase sample size leading to heterogeneous exposures), and insufficient discrimination between statistically and clinically significant findings. Indeed, as Grzeskowiak, Gilbert and Morrison (2011) observe, a preferable approach to manage the challenges would be via a prospective cohort study, although the costs would be prohibitive, and the losses to follow-up over the decades required to address questions regarding longer term outcomes would be difficult to minimise.

Summary and conclusions

Methodological challenges in evaluating the consequences of antenatal exposure to SSRIs via retrospective mining of British primary care databases are far from insignificant. Some can be managed via careful, detailed and nuanced approaches, e.g. defining pregnancy, and classifying broad categories of exposure. Actual ingestion of prescribed/dispensed medication cannot be confirmed, nor the degree to which drugs were metabolised by individuals, nor crossed the placenta to affect fetuses, whose genotypes remain unspecified. Many known and all unknown confounding variables cannot be adequately controlled for, including factors relating to underlying depression, exposure to which is associated with outcomes which overlap with those linked to SSRIs. Equally, psychiatric and other comorbidities cannot be accounted for, nor can co-prescriptions or tobacco, alcohol or other psychoactive substance use. Tensions remain between employing sample sizes large enough to provide adequate statistical power to identify clinically significant associations, categorising different exposures into meaningful and specific subgroups, and caution over chance findings attributable to multiple testing of too many subgroups. While researchers have sought to refine methodologies that address these issues as far as possible, and existing data provides broad reassurance, there remains significant uncertainty about the consequences of antenatal exposure to SSRIs.

Chapter 7 - Consequences of antenatal exposure to SSRIs: Structural neuroimaging

Depression during pregnancy is common, and may be under-recognised and undertreated (Geier *et al.*, 2014). Antenatal exposure to untreated depression is associated with potentially significant adverse outcomes for both mothers and offspring, while antenatal pharmacological treatment may ameliorate some of these risks at the expense of increasing others, including long term neurodevelopmental consequences, and depression in adulthood (Suri *et al.*, 2014). Various mechanisms have been postulated as explaining the link between maternal antenatal and postnatal depression and sequelae for offspring, including neuroendocrine dysregulation, immunological influences, epigenetic phenomena, and environmental factors (Field, Diego & Hernandez-Reif, 2006; Christian, 2012; Waters *et al.*, 2014).

One additional mechanism that may also explain the overlapping consequences of exposure to both antenatal depression and antidepressants is perturbation of serotonin-dependent neurodevelopmental processes via SERT-mediated effects. The structural and functional effects of SERT gene polymorphisms are associated with increased risk of trait neuroticism and depression (Canli & Lesch, 2007; Willner, Scheel-Krüger & Belzung, 2013). Significantly, the murine phenotype attributable to congenitally reduced SERT expression and activity associated with the "short" SERT allele may be mimicked by early exposure to SSRIs (Murphy *et al.*, 2008). This was reported by Ansorge *et al.* (2004), who demonstrated that mice exposed to the SSRI Fluoxetine during developmental phases approximating to the third trimester *in utero* and early postnatal life in humans evidenced abnormal emotional behaviours as adults, thought to be analogous to anxiety- and depression-like states in humans. As the neurodevelopmental consequences of "short" SERT gene alleles are associated with anatomical and physiological abnormalities in limbic structures, with smaller hippocampal, amygdalar and cingulate cortical volumes, altered

functional connectivity between the amygdalae and cingulate cortices, and a dysregulated control loop for fear responses, Ansorge *et al's* findings suggest that the apparent consequences of genetically-mediated attenuated SERT function in early life (i.e. trait neuroticism, and the increased risk of adult depressive illness) may also be induced by drugs with serotonergic activity (Hariri & Weinberger, 2003; Pezawas *et al.*, 2005; Frodl *et al.*, 2008a; Frodl *et al.*, 2008b; Kobiella *et al.*, 2011; Little *et al.*, 2014). Of clinical concern is that fetal exposure to antidepressants intended to ameliorate antenatal depression and its consequences for mothers and babies may actually increase the risk of offspring developing depression later in life, via trait neuroticism and associated sequelae, by disrupting serotonergically-mediated neurodevelopmental process. In other words, does human exposure to antenatal SSRIs predispose to longer-term risks of developing depression via abnormal limbic neurodevelopment?

It was in this context that we noted with interest the work of colleagues in the Sackler Institute based at Columbia University in New York, USA. They had been performing scans on babies born to mothers misusing substances during pregnancy, to identify structural neurodevelopmental consequences of exposure to opiates *in utero*. In keeping with our concerns regarding fetal exposure to SSRIs they attempted to extend their investigations to depressed mothers to investigate early neurodevelopmental effects of antidepressants, but despite having a dedicated team and resources, and offering incentives to potential participants, they had encountered difficulties in recruiting subjects. The reasons for this were unclear.

As the Glasgow Sackler Institute has a close working relationship with the PMHS, which provides care for around 100 women each year taking antidepressants during pregnancy, we agreed to try and recruit patients for a similar study in Glasgow. Consistent with clinical experience, mums-to-be with mental health problems have been reported to overestimate the teratogenicity of prescribed medication, with this phenomenon being even more marked in those suffering antenatal depression, even to the extent of increasing the likelihood of termination of pregnancy (Koren *et al.*, 1989; Walfisch *et al.*, 2011). As women taking antenatal antidepressants may feel anxious (and possibly even guilty)

about the potential consequences for their babies, we predicted that some at least would therefore be motivated to contribute to a study offering neonatal neuroimaging to investigate and identify potential sequelae.

The PMHS appeared to be a viable source of scanning subjects. In 2008 the PMHS was located within the Southern General Hospital (SGH) in Glasgow, a large teaching hospital with a sizeable maternity service overseeing approximately 3,500 deliveries annually, alongside a psychiatric service covering both inpatients and outpatients. Additionally, the Glasgow Sackler Institute was colocated with the Institute of Neurological Sciences (INS), a European centre of excellence for neurological clinical care and academic research, with access to neuroradiological expertise and an MRI scanner, with research scanning slots available and funded.

As the latest MRI scanning technology (including DTI and MRS) affords an opportunity to measure the structural and biochemical consequences of perturbation of serotonergic function early in life, we aimed to define the effects of fetal exposure to SSRIs on brain anatomy and metabolite concentrations by comparing scans in infants born to mothers in three distinct categories; (1) healthy controls; (2) women with antenatal depression not exposed to antidepressants; and (3) women with antenatal depression who received SSRIs during pregnancy.

We reasoned that the SSRI-exposed phenotype demonstrated in mice by Ansorge *et al*. (2004) might be associated with biomarkers in the form of structural changes similar to those seen in humans with "short" SERT alleles. However, although limbic structures (hippocampus, amygdala and cingulate gyrus) are implicated in affective regulation and have a rich serotonergic innervation, and it is feasible that antenatal exposure to SSRIs may interfere with the development of this neural circuitry, there are numerous challenges in imaging these nuclei in the rapidly developing infant brain, including difficulties in keeping subjects sufficiently still, as well as properties of the brain tissue itself (Choe *et al.*, 2012; Sled & Nossin-Manor, 2013; Guo *et al.*, 2014; Holland *et al.*, 2014). As Frodl *et al*. (2008a) reported an association between "short" SERT

alleles (including the "L_G" variant which has comparably reduced activity) and reduced grey matter volume in all regions studied, and the cerebellum is the fastest growing region of the infantile brain, we therefore aimed to assess differences in total brain and cerebellar volumes, in addition to amygdalar and hippocampal volumes, between the three study groups (Holland *et al.*, 2014*)*.

Key hypotheses

1. Based on animal models of perinatal SSRI exposure, we hypothesised that structural MRI would reveal reduced total brain volume, as well as reduced cerebellar, amygdalar and hippocampal volumes, in infants exposed to antenatal SSRIs.

2. Furthermore, we anticipated that DTI measures would demonstrate differences in the white matter of SSRI-exposed infants.

3. Similarly, we predicted that MRS would show significant reductions in N-acetyl aspartate (NAA) concentrations in the cerebellums of SSRI-exposed infants.

Methods

Subjects

We aimed to identify primiparous women aged between 18 and 35, with uncomplicated singleton pregnancies, booked at the SGH Maternity Unit (SGHMU), and/or receiving antenatal psychiatric care via the PMHS. Eligible woman would be allocated to one of three discrete study groups: (1) healthy

controls, i.e. mentally and physically well, and not prescribed psychotropic medication; (2) women with antenatal depression, in the absence of mental or physical comorbidity, and not exposed to psychotropics during pregnancy; and (3) women taking SSRI monotherapy for uncomplicated antenatal depression. Any potential participants with characteristics not consistent with the above allocations would be excluded. As it quickly became clear that these criteria were too restrictive to allow adequate numbers to be recruited, it was agreed that we would allow multiparous women, and those on any antidepressants, to participate if they wished. We set out to recruit 10 women into each study group for the purposes of this pilot, to generate data, as well as to demonstrate feasibility, with the aim of securing grant funding for a proposed bigger study.

Recruitment strategy

Obstetricians and midwives at the SGH, and psychiatrists and nurses in the PMHS were personally informed about our study, including its purposes, practicalities, and inclusion criteria. Literature was provided, and their feedback sought. We asked these colleagues to tell all antenatal patients about our study, at their discretion. Posters were displayed within waiting areas in the SGHMU and the PMHS, and information leaflets made available for distribution by clinical staff in both locations (Appendix 6 - the first page of the information leaflet was used as the poster, printed as size A3, with the leaflets being A3 folded, double-sided, i.e. four sides of A4). Moreover, the SGHMU midwives included an information leaflet in each Bounty Pregnancy Information Pack compiled (a compendium of information and vouchers issued to every mum-to-be booking for antenatal care in the UK).

The posters directed potential participants to speak to their midwife, visit our website, and/or email/'phone/text us for details, while the leaflets gave further information about both the reasons for our study, and the practical commitments involved. We asked a number of mothers, midwives and colleagues to review the wording, pictures and formatting, to ensure that the posters and

leaflets were quick to read, easy to assimilate, interesting, and attractive, while being factual, accurate, and not misleading. 250 posters and 10,000 information leaflets were printed at a cost of £700, paid for from the Sackler budget - enough to cover almost three years of deliveries at SGHMU.

The website www.helpingmums.org.uk gave the same information as the leaflets, with a few extra details. It also contained links to the information leaflet in Portable Document Format (PDF), as well as another PDF giving specific detailed information on the scans themselves (Appendix 7). Finally, the website provided a contact page with a form delivered to us via email. The website was not submitted to search engines, nor added to online directories, to ensure that only women who had seen a poster or received an information leaflet would visit (in an attempt to avoid ineligible women outwith our recruitment cohort volunteering). We coded the website in the plain text editor Smultron using hypertext markup language (HTML), and a free PHP: Hypertext Preprocessor (PHP) script for the contact form, and registered the domain name via the www.1and1.co.uk hosting service. High resolution royalty-free images were purchased from www.iStockphoto.com. (We commenced this study before social media such as Facebook became mainstream, but these would now be a preferable option for a customisable, easily updated, accessible online presence.) The website allowed additional and updated information and resources to be added as required, without the costs associated with print media.

The website also provided "brand identity", in that creating a recognisable name and theme for our project may help potential participants to have confidence in contacting us, and establish a study persona on which to build future research. While we had used the title "Prescribing in Pregnancy: Helping Mothers without Harming Babies" when presenting the findings from our initial audit, we agreed to change this to "Helping mums, caring for babies", both to soften and de-formalise the maternal descriptor, and to avoid using the lexeme "harming", a term with connotations that, on reflection, we wished to disassociate from our work (Julyan, Cavanagh & Cantwell, 2009).

Initial contact

Eligible women could therefore make contact via their midwife or the PMHS staff, or directly by text, 'phone, email or web. This initial interaction was used to (arrange a time to) speak by 'phone, to explain the purpose and practicalities of our study, and then to establish some basic details and eligibility if the potential participant wished to proceed. Estimated date of delivery (EDD) by ultrasound scan was ascertained, and the likely exposure group assignation identified, before arranging to meet as soon as possible after booking. If the person was willing to proceed to meet in person they were sent a copy of the latest version of the approved Information Sheet (Appendix 8), by email or post as preferred, to read in advance of meeting.

Antenatal assessment

In an attempt to make the process as easy as possible for potential participants they were assessed at a venue of their choice, although initially our preferred option was to use a bookable multipurpose room next to the MRI scanning suite within the Department of Neuroradiology, INS, at the SGH. This allowed privacy, as well as a limited tour of our facilities, should the woman wish to proceed. (The tour was limited, as access to the MR scanning suite was tightly controlled, to avoid adverse incidents, and to preserve peace, discretion and confidentiality for patients undergoing scans.) If the individual wished to meet at a different venue, we sought to facilitate this, with the exception of their home, to maintain appropriate ethical and professional boundaries.

Transport costs were met out of the Sackler Institute budget, and detailed directions, travel information and a map were provided. As parking was limited at the SGH, we secured agreement from the SGH Facilities Administrators that if a mother and baby arrived but could not park, one of the parking attendants would arrange a space. Furthermore, as the SGH operated a strict parking policy

of no more than four hours for patients or visitors, we obtained assurances that our subjects would not be penalised if they breached.

After meeting, re-explaining our study in greater detail with reference to the Information Sheet, and answering any questions, each participant was asked to (re-)read the Information Sheet, and then sign and date two copies of the Consent Form, which the researcher then countersigned and dated, retaining one copy for our records, and giving the other copy to the subject.

Thereafter we assigned each participant a unique study number to allow later anonymisation, and gathered basic epidemiological and clinical data, before completing our battery of assessments (see below). To ensure that all relevant details were collected, the research team developed an assessment proforma, and a checklist (Appendices 9 and 10). Completed paperwork was stored in a locked filing cabinet thereafter, except when in transit, or when data were being analysed.

Assessment documentation and rating scales

Given that there were a number of known potential confounding factors (including maternal [and fetal] genotype, socioeconomic status, alcohol, smoking and substance misuse, family history of affective disorder, life experiences, recent/current stressors, and obstetric/fetal outcomes), we attempted to capture as many details as possible via the assessment proforma, which provided a structure to record essential demographic, contact and clinical data. As type, dose, timing, duration, and adherence to psychotropics may significantly affect our findings, one specific challenge was how to assess and document accurate information on prescribed and other medication during pregnancy, as this had been a source of ambiguity and inaccuracy in the PMHS and the MLS data collection sheets and clinical records. Therefore, we constructed a table with columns for drug name, dose, frequency, and dates commenced and changed/stopped, with sufficient rows to accommodate

polypharmacy and/or several changes in medication – this allowed accurate timing of fetal exposure to medication, and could be easily updated at each encounter (although it did not solve the problems of recall bias, poor memory, or inaccurate disclosure). Although we acknowledged that there might be significant variation in maternal pharmacokinetics, with rate of metabolism, serum levels, placental transfer, and fetal cerebrospinal fluid (CSF) levels, that would also exert subtle effects on the parameters under scrutiny, assessing these was beyond the scope of this study.

As timing, duration, and severity of depression could similarly affect findings, subjects were assessed by experienced clinicians; one higher trainee in psychiatry (JM), and a consultant psychiatrist (EJ). As NHS doctors, both were experienced in assessing patients with depressive disorders, and in using ICD-10 criteria to ensure that reliable diagnoses were made. We made this the focus of the interview, as clearly a diagnosis of antenatal unipolar depression, in the absence of other psychiatric disorders, was essential in assigning subjects to the correct group. A retrospective judgment was made for those on antidepressants, as the absence of depressive symptoms at the time of assessment would not preclude a diagnosis, but rather indicate remission as a consequence of pharmacological intervention. We anticipated challenges in allocating some participants, as depressive illness and antidepressant pharmacotherapy may not persist throughout pregnancy, nor at the same severity or dose (respectively), as well as not being mutually exclusive factors, e.g. women may start off well, then become depressed, then be prescribed one or more antidepressants, to which they may experience variable responses; or start off on medication, then stop, then relapse, then restart. We therefore agree to allocate those with any experience of antenatal depressive illness but not exposed to medication to the depressed unmedicated group, and those on antidepressants (whether depressed during pregnancy or not) to the depressed medicated group, discussed below.

To standardise assessments we initially based our battery of diagnostic interviews, rating scales, and psychological tests on that of our Columbia University colleagues, namely the Structured Clinical Interview for DSM Axis-I disorders (SCID), the Hamilton Rating Scale for Depression (HRSD), the Clinician-

Administered PTSD Scale for DSM-IV (CAPS), the Stroop Test, and the National Adult Reading Test (NART) (Appendix 12).

The diagnoses based on clinical interview were confirmed via the SCID. The SCID is a clinician-administered semi-structured clinical interview based on DSM-IV criteria, designed to make reliable diagnoses when used by mental health clinicians or trained associates. It presents the DSM-IV criteria for Axis I disorders as questions, with accompanying probes and qualifiers, with four levels of response rated by the interviewer; ?=inadequate information; 1=absent or false; 2=subthreshold; and 3=threshold or true. Thus it can generate diagnoses of current and historical mood disorder, and is extensively utilised in studies to ensure that subjects are correctly diagnosed and allocated. However, it is not without controversy or criticism, and can take several hours to complete with complicated patients, although as little as 15 minutes in straightforward healthy controls (SCID – frequently asked questions www.scid4.org/faq/scidfaq.html accessed 21 July 2015).

The HRSD is an observer-rated scale used to measure depression severity, and is the accepted "gold standard" for assessing response to antidepressant therapy. It has been validated in various clinical and non-clinical populations, although its limitations have been criticised, not least the utility of its total score, and redundancy of some of the items (Hamilton, 1960; Gibbons, Clark & Kupfer, 1993; Faries *et al.*, 2000; Entsuah, Shaffer & Zhang, 2002; Bagby *et al.*, 2004; Bech, 2006; Bech, 2012; Leucht *et al.* 2013). Hamilton's original 17 items have been supplemented by an additional 4 items whose scores are not added to the 17, and higher scores are taken to indicate increasing severity of depression. Variations of the HRSD have been developed in an attempt to address some of criticisms and increase its validity and clinical utility, including the HAM-D6, a shorter six item scale, the MHRSD, a longer 25 item variant, and the GRID-HAMD, which separates frequency of symptoms from severity, as well as providing a structured interview guide (Bech *et al.*, 1975; Miller *et al.*, 1985; Williams *et al.*, 2008). The HRSD takes an average of 20 minutes to complete, depending on the subject.

Similar to the SCID, the CAPS is an clinician-administered semi-structured interview employed to reliably assess the essential features of post-traumatic stress disorder (PTSD), as well as acute stress disorder. Its applications include diagnosis, assessment of severity, and monitoring of response to treatment, and it is considered to be the "gold standard" in PTSD assessment, and takes between 30 and 60 minutes to complete (Blake *et al.*, 1995; Weathers, Keane & Davidson, 2001; US Department of Veterans' Affairs www.ptsd.va.gov/professional/assessment/adult-int/caps.asp accessed 21 July 2015).

The Stroop test is a non-specific neuropsychological assessment used to investigate subjects' attention, processing speed, and executive functions, by firstly reading out loud the names of colours printed in ink of a different colour, and then by stating the colour of ink in which each word is printed, regardless of the word, e.g. if one saw "**BLUE ORANGE PURPLE**", in the first task one would say "blue orange purple", and in the second task, "red green blue". It is immediately apparent that the former is easier than the latter. The Stroop test is essentially an interference task, and takes less than 5 minutes to complete (Jensen & Rohwer, 1966).

The NART is utilised to appraise an individual's premorbid level of intellectual functioning, and is to some extent related to demographics and educational attainment, as well as abilities that tend to be relatively spared in states of cognitive impairment. It is well recognised that pathological mood states can have a significant deleterious effect on cognition, and the NART therefore allows an estimation of a subject's baseline functioning, taking around 5 minutes to complete (Crawford *et al.*, 1990).

We reviewed our use of the HRSD, CAPS, Stroop test, and NART during the first few assessments, and agreed that they appeared suboptimal in our cohort, not least because of the time taken to complete, and what they yielded in terms of relevant data. The HRSD places significant emphasis on somatic signs and symptoms of depression such as changes in sleep, appetite, weight, and libido, as well as fatigue-related features, with 23 (43.4%) of the total 53 points

associated with these – normal pregnancy includes all these features, and we were concerned that the HRSD had not been validated in pregnancy. After reviewing the literature on other depression rating scales (such as the Hospital Anxiety and Depression Scale, the Patient Health Questionnaire, the Quick Inventory of Depressive Symptomatology, and the Edinburgh Postnatal Depression Scale) and establishing that all had limitations in pregnant and non-pregnant subjects, we sought expert opinion from Drs Roch Cantwell and Ian Jones, who agreed that using the Beck Depression Inventory (BDI-II) instead of the HRSD would be reasonable, particularly in view of its ease of use, short time required for completion, and patient-completed nature (Holcomb *et al.*, 1996; Ji *et al.*, 2011; Wang & Gorenstein, 2013; Brunton *et al.*, 2015). Furthermore, as the BDI-II has a greater emphasis on cognitive depressive features, it therefore has a degree of face validity in antenatal depression (15 [23.8%) of the total 63 points relate to somatic symptoms). The BDI has also been shown to correlate with adverse obstetric/neonatal outcomes (see Chapter 8) (Steer *et al.*, 1992).

The CAPS appeared redundant, as comorbid PTSD was an exclusion criterion for our study, and focusing on severity of anxiety and stress-related features appeared more relevant, hence switching to using the Beck Anxiety Inventory (BAI) for similar reasons to the BDI-II, and the Holmes-Rahe Social Readjustment Rating Scale (SRRS), both self-completed (Holmes & Rahe, 1967; Beck *et al.*, 1988). These changes saved significant time in assessing subjects, without any obvious loss of data relevant to our study, and allowed quick updates at the one month and four month scans, when time for maternal re-assessment was limited. Table 7-1 summarises the recommended cut-off points for normal, mild, moderate, severe, and very severe scores for each of the rating scales, with low, moderate, and high risk of illness being shown for the SRRS (Hamilton, 1960; Holmes & Rahe, 1967; Beck *et al.*, 1988; Beck *et al.*, 1996).

Table 7-1 – Cut-off scores for severity

Severity	HRSD	BDI-II	BAI	Risk of illness	SRRS
Normal	0-7	0-13	0-7	**Low risk**	<150
Mild	8-13	14-19	8-15	**Moderate risk**	150-299
Moderate	14-18	20-28	16-25	**At risk**	>299
Severe	19-22	29-63	26-63		
Very severe	>22	-	-		

HRSD – Hamilton Rating Scale for Depression; BDI-II – Beck Depression Inventory-II; BAI – Beck Anxiety Inventory; SRRS – Social Readjustment Rating Scale

A checklist was utilised to summarise salient points for each participant, as well as to minimize omissions. The checklist served as the front sheet in the polypocket containing paperwork for each subject, and included the unique study number and EDD, a column for each anticipated contact (immediately after booking, at the start of the third trimester and at the one month and four month scans), rows to note actual dates and gestations, in addition to next planned assessment, rows to tick off the consent and each assessment when completed at each meeting, a section to categorise subjects by health status and antidepressant exposure, and a section for any additional notes (Appendix 10, and the updated version, Appendix 11).

Timetable

Existing data indicated that the majority of women taking antenatal psychotropics throughout pregnancy are already prescribed them before conceiving. We therefore aimed to recruit and assess subjects as early in pregnancy as possible, ideally in the second trimester, immediately after booking (which tends to take place around 11-13 weeks gestation). This allowed us to follow women through a greater proportion of their pregnancies, thus reducing recall bias and significant factual omissions and inaccuracies. In

particular, this should make our data on prescribed and other drugs more accurate.

However, this also permitted re-assessment of each subject at a standardised timepoint, at the start of the third trimester, between 24 and 28 weeks, facilitating more consistent comparison of the depression rating scale scores. Moreover, a second review allowed completion of any assessments outstanding following the first meeting – some subjects were unable to complete them all in one interview, especially if unwell, or if their history was complicated.

Over time, however, and particularly when scanning started and reduced the time available for assessing other subjects, it became desirable to rationalise the number of antenatal contacts to just two; the initial 'phone discussion, and then a face-to-face assessment at the start of the third trimester. This made it less onerous for the participants (and assessors), with no discernible deleterious effects on the quality of data collected. However, this may have been related at least in part to our recruits mainly being healthy controls (see below).

At the first meeting, and after informed consent was obtained, we agreed provisional scan dates for as close to 44 weeks and 56 weeks gestational age by EDD as possible. All future dates were entered into a private "Helping mums" Google calendar using the anonymised unique study numbers, accessible only by the researchers, with email alerts set up, to prompt contacting subjects in advance of each meeting, and ensure that any issues were resolved. For example, it sometimes became necessary to reschedule assessments or scans, due to accommodating other subjects, the MR scanner being unavailable due to servicing or malfunction, or life events affecting participants' availability.

Rooms and resources

Another factor was the availability of an assessor, as all scans had to be scheduled on Wednesdays between 9am and 1pm. However, this slot did not suit

some potential participants. Moreover, it was not always possible to book the neuroradiology multipurpose room for assessments at that time, as others tended to book the room regularly for various purposes, and booking well in advance was not always possible, depending on what stage of pregnancy the mums-to-be contacted us, or were able to meet. We therefore met and assessed some subjects at their place of work, or in a coffee shop if preferred. However, after negotiation with the Sleep Centre Service Manager (the University of Glasgow Sleep Centre was hosted within the Sackler Institute until 2012) it became possible to use one of the sleep study rooms in the INS for assessments.

Furthermore, assessing participants at the INS, two floors above the Department of Neuroradiology, allowed them to have a limited tour of and orientation to the MR scanning suite, a desirable factor in reducing anxiety on the day of the first scan.

Supporting staff and colleagues

As assessments and scanning progressed, it became clear that one researcher alone would be unable to complete and supervise all the work involved, particularly as timing for both assessments and scans was critical, and meetings could not be rescheduled to accommodate limited availability of staff due to annual leave, or scans and assessments being booked at the same time.

Higher Trainees in Psychiatry in the West of Scotland were therefore invited to participate in the study. This was of mutual benefit, as trainees are expected to obtain research experience. Three doctors volunteered, who shadowed the consultant psychiatrist when completing assessments and scans at least twice, in addition to receiving detailed tutorials, and ensuring registration/approval with the Research Ethics Committee, through submission of their curriculum vitaes, before carrying out interviews and supervising scans on their own. JM assessed one and supervised scans for three subjects, and FC supervised one scan.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-ionising, non-invasive scanning technology that exploits the varying water (H_2O) content of different tissues to produce high resolution images (Currie *et al.*, 2013a). By subjecting static subjects to a strong and uniform magnetic field within the scanner, protons (hydrogen atoms) are then "excited" by radiofrequency pulses at a characteristic frequency. Magnetic field gradients are further applied to facilitate the spatial localisation of the signals. It is these gradients which contribute to the noise the MRI scanner produces, which can be considerable (>100dB). Following the radiofrequency stimulation and gradient applications, radio waves emitted from the subject are detected by a receiver coil. The rate at which excited atoms return to baseline provides the contrast between different tissues, and can be viewed on a computer screen. Magnetic field strength is measured and expressed in teslas (T). MRI scanners utilising field strengths of 1.5T are frequently used in humans for clinical diagnostic, staging, and monitoring purposes, while 3T scanners are common in research environments. Since the beginning of this project 7T MRI systems are being used more frequently for research, and there are now more than 50 7T MRI systems worldwide.

Image contrast can be weighted according to what tissues or lesions are under study, by altering parameters relating to technical issues such as repetition time or echo time, associated with spin-lattice relaxation, and spin-spin relaxation, respectively. These are referred to as T1 and T2 (not to be confused with teslas). Among other things, T1-weighted images highlight fatty tissues well, for general anatomical imaging and in post-contrast examination, while T2-weighted scans are useful for demonstrating pathologies such as oedema, inflammation, and white matter lesions.

MRI scans excel in revealing the detail of organs comprised of varying soft tissues such as the brain, and can thus yield high resolution data on the size, shape, and integrity of intracranial structures. In addition to straightforward spatial and volumetric imaging, MRI can also be deployed in demonstrating anatomical

connectivity via Diffusion Tensor Imaging (DTI), which detects the anisotropic movement of molecules along axons forming white matter tracts (Abhinav *et al.*, 2014). Magnetic resonance spectroscopy (MRS) can measure cellular metabolism (a measure of cell turnover and membrane integrity) via spectral resonances associated with different molecules (Currie *et al.*, 2013b). Moreover, functional MRI (fMRI) can be used to detect neuronal activity without the need for contrast media, using the different signals associated with oxygenated and deoxygenated blood flow as a proxy marker for increased cerebral activity. All these techniques have been used in studying the developing brain (Rivkin, 2000; Almli, Rivkin & McKinstry, 2007; Cascio, Gerig & Piven, 2007; Hunt & Thomas, 2008; Marsh, Gerber & Peterson, 2008; Silk & Wood, 2011; Gilmore *et al.*, 2012; Blüml *et al.*, 2013; Giedd *et al.*, 2015).

MRI scanning is, generally speaking, considered to be safe, given that it employs non-ionising radiation to produce images. However, due to the strong magnetic fields, there were a number of considerations relevant to our project. Firstly, ferromagnetic objects are attracted strongly to the centre of the magnet, necessitating such potential missiles to be banned from the scan room. Secondly, scanning subjects can heat up due to absorbing the radio waves used to generate the magnetic fields (although this is monitored by the scanner, and scanners are designed to ensure internationally agreed limits are not exceeded). And thirdly, although MRI has not been demonstrated to cause tissue damage or increase the risk of cancer in humans, it has been associated with minor DNA damage similar to that of other ionising imaging modalities (Knuuti *et al.*, 2013). Notwithstanding, MRI is considered to be safe for infants, and has even being utilised during pregnancy to detect and monitor congenital defects *in utero*, although its use during organogenesis in the first trimester is avoided unless essential (Alorainy *et al.*, 2006; Girard & Chaumoitre, 2012). There are no known developmental sequelae of MR neuroimaging in neonates (Bulas & Egloff, 2013; Tocchio *et al.*, 2015).

One major challenge, however, is that scanning subjects need to remain as still as possible, to allow high quality images to be produced. This is a particular issue in imaging neonates, especially given the noise of the gradient coils.

Despite providing ear plugs and larger headphones feeding white noise to babies, there is still sufficient noise to disturb them, resulting in movement. Many young children undergoing MRI are anaesthetised because of the noise and the claustrophobic tunnel, but this was not appropriate for our study. The advice of our colleagues in Columbia in this regard was invaluable, as detailed in Appendix 12, and described below.

We aimed to use structural MRI to measure and compare total brain volume and cerebellar volume for all neonates at one month and four months postnatally; to use DTI to measure and compare diffusion tensor maps for all neonates at one month and four months postnatally; and to use MRS to measure and compare N-acetyl aspartate for all neonates at one month and four months postnatally.

Preparation for scanning

One week after the EDD participants were contacted to inquire after their health and progress, and to remind them about the provisionally agreed scan date. After confirming availability and willingness to proceed, and arranging any necessary rescheduling, each received a copy of our leaflet giving detailed information about the scan (Appendix 7). Transport arrangements were made, with taxis being booked for those without private transport, with advice to contact the researcher by text/'phone upon arrival, to provide help in locating a parking space, and escorting mother and baby to the scanning suite. Subjects were advised to attend between 9am and 9:30am, and to bring baby hungry and tired if possible – this proved challenging for those driving to the SGH, as babies tend to sleep during car journeys (Knickmeyer *et al.*, 2008). Upon arrival mother and baby were welcomed, and put at ease, while ensuring that necessary details, such as actual date of delivery (ADD), obstetric, postnatal and neonatal particulars and complications, birthweight, exact gestational age in days by EDD on the day of the scan, and information on baby's feeding and sleeping (to detect any significant features of neonatal adaptation syndrome) were collected and/or updated. Gestational age by EDD was calculated using the "Perfect

Wheel" app for iPhone, to ensure accuracy and consistency. Each baby was weighed, and his/her head circumference measured, before an MR checklist was completed for both neonate and mother (to allow her to enter the scan room allow with baby).

Participants were shown to the anaesthetic preparation room within the MR scanning suite, immediately opposite the scan room, and any questions answered. At this stage the lighting was dimmed, and babies were changed and swaddled. Mothers were advised in advance to bring clothing for them and baby appropriate for scanning, i.e. warm and without ferromagnetic fasteners, and suitable items were provided for babies where necessary. Foam ear plugs were cut to size and taped in position in babies' ears, and a pulse oximeter probe attached to a portable monitor was secured to one foot, before babies were fed and burped. Mothers who were bottle-feeding brought their own equipment, and a water bath was provided. A judgment was made in each case whether to allow babies to fall asleep in the preparation room, and then transfer to the scan room, or to be taken in to the scan room before sleep, as babies had to be secured in an adult head coil in the scanner by means of foam wedge supports, which frequently woke them up. Headphones through which white noise was played were fitted, and babies allowed a little time to settle in to a deep sleep before scanning started. Mothers were invited to remain in the scan room with their babies if they wished, with the option of observing through the viewing panel or enjoying a complementary beverage in the nearby canteen. The researcher remained with each baby throughout the scans, observing for any signs of distress, and monitoring heart rate and blood oxygen saturation. Scanning stopped immediately if babies moved or appeared distressed, and attempts made to resettle them. Scanning resumed if babies became and remained calm, but paused if distress was sustained, and mothers were asked to comfort babies initially in the scan room, and then in the preparation room if necessary. We reattempted scanning if babies settled once more, and mothers consented, but abandoned scanning if not.

Scanning protocol

Eight sequences were performed, as summarised in Table 7-2 (Appendix 13). As the imaging parameters prescribed had been carefully considered, to optimise comparisons between study groups by minimising the amount of variation and error in the subsequent measurements, strict instructions not to alter any settings were given to radiology staff, including not to copy slice thicknesses across different acquisitions.

Table 7-2 – Scanning sequences

Sequence	Purpose
Localiser 1	To establish subject position
Localiser 2	To correct more precisely for head position
3D IR-FSPGR	To acquire total cranium, including total brain volume, optimised to capture grey/white matter contrast
T2 measure (1, 2 and 3) (Dual TE, FSE-XL)	To compare T2 values in brain regions between the study groups
Asset calibration	To allow parallel imaging with the following DTI sequence, reducing acquisition time
DTI	To compare diffusion values in brain regions between the study groups
Dual echo T2 FSE-X	To measure volume of subcortical structures, including hippocampus and amygdala
MRS	To compare metabolite ratios in the cerebellum between the study groups

Two localising sequences were completed, to establish and correct for head position. A 3D sequence followed, corrected and "straightened" sagittally, axially and coronally with respect to the localising sequences, as for all

subsequent sequences. It acquired the whole head, including the skull. The 3D sequence was optimised for grey matter/white matter contrast, to allow comparison of averaged volumes/concentrations between study groups. The next sequence established T2 values in the brain regions of interest via the acquisition of multiple TE value images. Multiple acquisitions were required to cover the whole brain.

Thereafter, an axial asset calibration sequence allowed parallel imaging to be employed for the following DTI, significant reducing acquisition time. Subsequently, a dual echo T2 sequence focused on subcortical structures, acquiring coronal slices anteriorly to posteriorly from the rostral aspect of the amygdala to the tail of the hippocampus. An MRS sequence then captured metabolite ratios in the cerebellum. The full protocol with accompanying diagrams is shown in Appendix 13.

Imaging parameters were optimised for one month and four month scans, as per advice from Columbia (Appendices 14 and 15). If babies moved during image acquisition, this was detected either by the researcher in the scan room, or by the radiographers, who reviewed the images in real time to screen for any obviously suboptimal data.

We secured agreement from our Columbia colleagues that they would analyse the scanning data, due to their resources and expertise. All scans were also reviewed by a local consultant paediatric radiologist, to screen for any clinically concerning abnormalities.

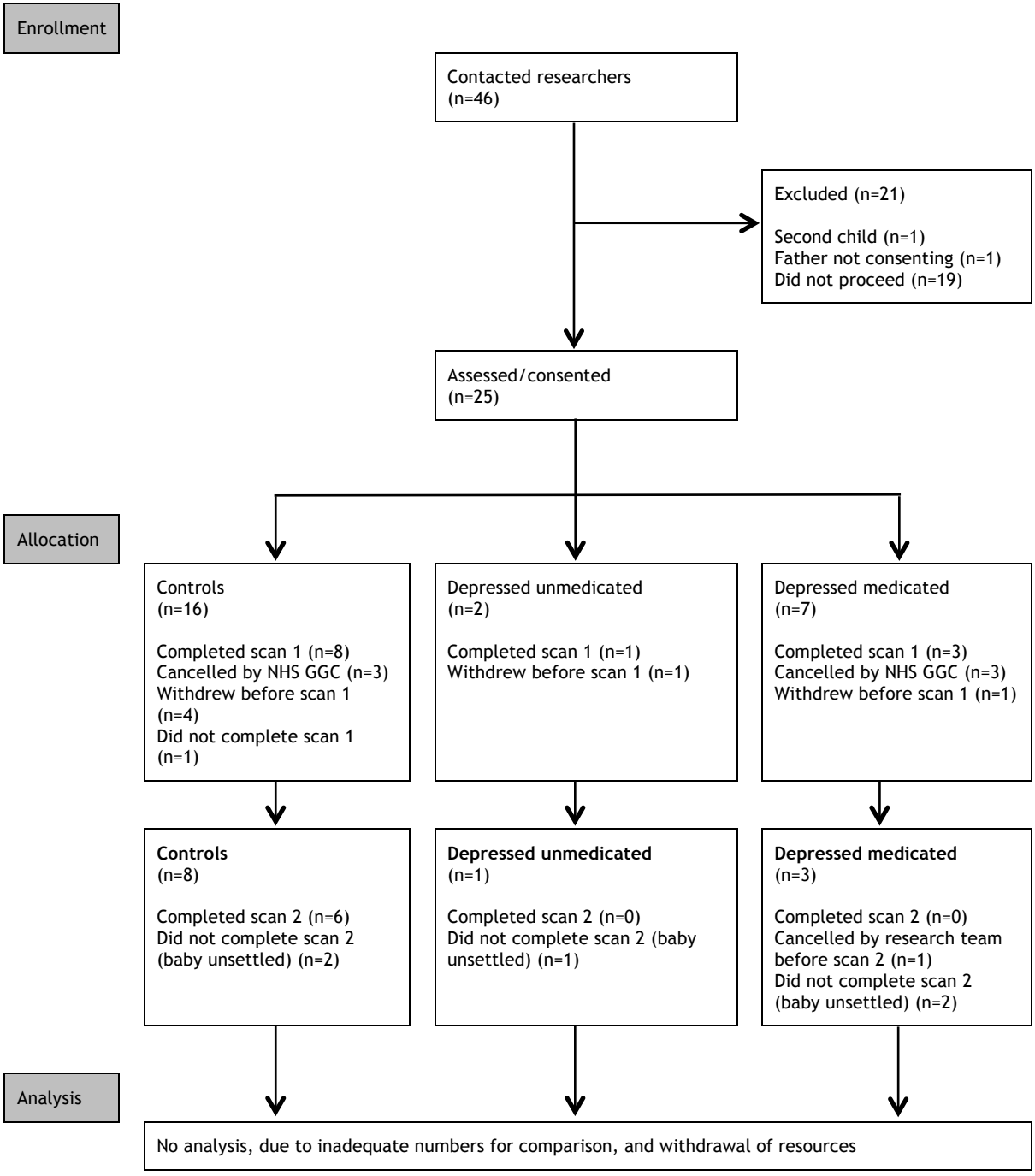
Project registration and approval

The scanning project was registered with NHS Greater Glasgow & Clyde Research & Development (NHS GGC, R&D), and ethical approval was obtained from the local Research Ethics Committee (REC) (Appendix 16). All amendments to the protocol were likewise reviewed and approved by the REC.

Forty-six women became known to the study between 13 July 2009 and 28 March 2012, two who contacted researchers by telephone, 41 via email, and three attending the PMHS, who consented to have their details passed on. Figure 7-1 depicts a CONSORT-style diagram to summarise the progress of the potential and actual participants through the phases of our study. The very first woman to make contact with the research team, by email, was excluded during the follow-up 'phone call as she was expecting her second child, but this exclusion criterion was quickly revised as discussed above. Of the 46 who became known to the research team, a few declined to proceed after initial telephone in discussion in response to their inquiry, but many simply did not respond to several attempts to contact them by 'phone, email, and/or post, including all those identified via the PMHS.

Although we had intended to recruit 10 women in each group, several factors beyond the research team's control conspired to end scanning in early 2012. Firstly, serious illness affected EJ's family in 2011, and he withdrew for nine months to support his wife through treatment. Secondly, in 2012 NHS GGC moved paediatric services from the SGH to the Royal Hospital for Sick Children, Yorkhill, meaning that we were no longer permitted to scan babies at the INS, despite considerable efforts to negotiate alternative arrangements. Thirdly, the Department of Neuroradiology acquired a new MRI scanner while the study was suspended, introducing another variable in comparing future scans with those already acquired. Fourthly, the head of department at the Columbia Sackler Institute moved to a new post in a different state, leading to the end of collaboration on this project, including our agreement regarding image analysis. These issues resulted in there being inadequate time for alternative arrangements to be made, and our pilot study was brought to a premature end, with insufficient data to allow meaningful comparison between groups, or to justify investment in analyses.

Figure 7-1 – CONSORT 2010-style flow diagram



Of the 46 women, 12 completed the one month scan, with six also completing the four month scan, all in the control group. One of those who made initial contact by 'phone did not proceed to assessment, and none of those contacted via the PMHS responded to invitations by 'phone or post. Otherwise, all completed all antenatal assessments, except HM015, for whom there was insufficient time to finish the SCID at the first meeting. As the "Columbia battery" of tests was used from HM001 through HM015, there were no ratings for antenatal anxiety or stress until HM016. Table 7-3 summarises the antenatal characteristics of the 12 mothers who attending for at least one scan. The median age was 33 (range 25-40). Eight of those undergoing scans were in the control group, with six being the first child – HM009 was expecting her second child, and HM014 had required treatment for an ectopic pregnancy the preceding year. HM015, the solitary depressed unmedicated participant, was rated as being severely depressed antenatally on the HRSD, although clinically she described herself as having felt better in the few weeks immediately prior to assessment. The second page of her BDI-II from the one month scan was missing, hence no score in Table 7-3.

HM015, the depressed unmedicated participant, attended for the one month scan, but not the scan at four months. Similarly, three depressed medicated subjects underwent the first but not the second scan – HM022 had been taking Citalopram 20mg since approximately two months before pregnancy, reduced to 10mg around 14 weeks, and increased back to 20mg daily at 18 weeks; HM030 had been taking Sertraline 200mg daily for some years prior to conceiving, and reduced to 100mg daily until delivering after discovering she was pregnant around six weeks gestation; and HM035 had been taking Fluoxetine 20mg daily for approximately 10 months before falling pregnant, and stopped between six and eight weeks' gestation. All eight of the controls attended for the one month scan, with six undergoing the four month scan, also – two were unable to complete the second scan, due to unsettled babies. Only one subject who attended for the one month scan (a control) was unable to complete, due to her baby being unsettled. Not all sequences were completed even in those attending for scans, due to a mixture of babies being unsettled and/or moving too much.

Table 7-3 – Antenatal maternal characteristics of those completing scans

							Antenatal			
ID	**Group**	**Age**	**Pregnancy**	**Child**	**EDD**	**ADD**	**Stage**	**Depression**	**Anxiety**	**Stress**
HM006	Control	33	1	1	24/02/10	20/02/10	113	Normal	-	-
HM009	Control	33	2	2	07/02/10	29/01/10	192	Normal	-	-
HM013	Control	34	1	1	16/05/10	21/05/10	173	Normal	-	-
HM014	Control	32	2[1]	1	19/04/10	14/04/10	193	Mild	-	-
HM015	Depressed	38	3	3	15/05/10	14/05/10	195	Severe	-	-
HM022	Medicated	27	1	1	28/09/10	22/09/10	185	Mild	Moderate	High
HM023	Control	39	1	1	06/11/10	21/10/10	179	Normal	Mild	Low
HM025	Control	30	1	1	22/02/11	09/03/11	183	Normal	Normal	Low
HM030	Medicated	32	4	4	04/04/11	27/03/11	217	Mild	Mild	Moderate
HM033	Control	33	1	1	02/07/11	27/06/11	181	Normal	Mild	Moderate
HM034	Control	25	1	1	08/07/11	11/07/11	180	Normal	Severe	Moderate
HM035	Medicated	40	1	1	25/07/11	21/07/11	163	Normal	Normal	Low

EDD = estimated delivery date by ultrasound scan; ADD = actual delivery date; Stage = gestation by EDD in days

[1] Previous ectopic pregnancy

Table 7-4 presents obstetric outcomes, indicating that all babies were born at term (defined as between 269 and 294 days gestation), and all were within normal birthweight range (2.5-4.5kg). Postnatal maternal outcomes are summarised in Table 7-5, revealing a trend towards improvement in severity ratings for those who scored as moderate or worse for depression, anxiety, or stress during pregnancy (particularly HM022 and HM034). Tables 7-6 and 7-7 show neonatal data for the one month and four month scans, respectively.

Usable images were generally acquired via the 3D MRI and the MRS sequence, e.g. Figure 7-2 and Figure 7-3, but there were technical difficulties with the DTI, although useable images were obtained, e.g. Figure 7-4. While some artefacts were clearly attributable to infants' movements, others were not as readily explained, and we were unable to resolve all difficulties, not least due to scanning and analysis not continuing as planned.

As most images were from healthy controls, comparative analyses were not possible.

Table 7-4 – Obstetric outcomes for those completing scans

ID	Group	Stage	Weight[1]	Centile[2]	Delivery	Obstetric complications
HM006	Control	276	3.97	93%	SVD[3]	None
HM009	Control	271	3.69	83%	SVD	None
HM013	Control	285	3.61	70%	Forceps	Breech presentation, external cephalic version, then forceps due to fetal heart rate slowing, then increasing
HM014	Control	275	3.36	60%	Elective section	Prolonged hypotension
HM015	Depressed	279	-	-	Elective section	Depressed until ~6 months, then recovered
HM022	Medicated	274	3.69	83%	SVD	Citalopram 20mg until 14 weeks, then 10mg until 18 weeks, then 20mg until delivery
HM023	Control	264	2.50	2%	Induced	Post-partum haemorrhage, neonatal jaundice, admitted to neonatal unit for ~36 hours
HM025	Control	295	3.88	85%	Induced, forceps	None
HM030	Medicated	272	3.15	425%	SVD	Sertraline 200mg until ~6 weeks, then 100mg thereafter
HM033	Control	275	3.49	70%	SVD	None
HM034	Control	283	4.05	95%	SVD	None
HM035	Medicated	276	3.54	74%	Elective section	Fluoxetine 20mg stopped between 6-8 weeks

Stage = gestation by EDD in days; [1] kilogrammes; [2] According to WHO charts; [3] SVD = spontaneous vaginal delivery

Table 7-5 – Postnatal maternal outcomes for those completing scans

		Scan 1				Scan 2			
ID	**Group**	**Stage**	**Depression**	**Anxiety**	**Stress**	**Stage**	**Depression**	**Anxiety**	**Stress**
HM006	Control	301	-	-	-	392	Normal	Normal	High
HM009	Control	304	-	-	-	395	Normal	Normal	Moderate
HM013	Control	318	Normal	Mild	High	395	Normal	Normal	High
HM014	Control	310	Normal	Normal	Moderate	394	Normal	Normal	Moderate
HM015	Depressed	305	-	Mild	High	Baby did not settle			
HM022	Medicated	309	Normal	Moderate	Moderate	Cancelled by research team (availability)			
HM023	Control	305	Normal	Normal	Moderate	389	Normal	Normal	Moderate
HM025	Control	309	Normal	Normal	Low	400	Normal	Normal	Low
HM030	Medicated	310	Mild	Mild	Moderate	Baby did not settle			
HM033	Control	312	Normal	Mild	Moderate	Baby did not settle			
HM034	Control	313	Normal	Normal	Low	Baby did not settle			
HM035	Medicated	310	Normal	Normal	Moderate	401	Normal	Normal	Moderate

Stage = gestation by EDD in days

Table 7-6 – Neonatal outcomes at one month

ID	Group	Stage	Weight[1]	Centile[2]	Head circumference[3]	Centile[2]
HM006	Control	301	4.25	60%	35.7	28%
HM009	Control	304	4.60	80%	35.5	22%
HM013	Control	318	4.54	61%	38.0	78%
HM014	Control	310	4.54	77%	37.0	70%
HM015	Depressed	305	-	-	35.5	22%
HM022	Medicated	309	4.55	77%	-	-
HM023	Control	305	4.05	28%	37.0	46%
HM025	Control	309	4.70	70%	38.5	88%
HM030	Medicated	310	-	-	-	-
HM033	Control	312	4.11	50%	37.5	83%
HM034	Control	313	4.28	62%	36.2	44%
HM035	Medicated	310	4.40	69%	37.0	70%

Stage = gestation by EDD in days; [1] kilogrammes; [2] According to WHO charts; [3] centimetres

Table 7-7 – Neonatal outcomes at four months

ID	Group	Stage	Weight[1]	Centile[2]	Head circumference[3]	Centile[2]
HM006	Control	392	6.00	29%	-	-
HM009	Control	395	7.00	75%	-	-
HM013	Control	395	6.40	21%	41.5	45%
HM014	Control	394	6.80	67%	-	-
HM015	Depressed	382	5.75	18%	-	-
HM022	Medicated	407	-	-	-	-
HM023	Control	389	5.87	6%	41	29%
HM025	Control	400	7.20	59%	42.3	71%
HM030	Medicated	394	5.50	10%	-	-
HM033	Control	396	5.70	16%	40.7	53%
HM034	Control	397	-	-	-	-
HM035	Medicated	401	6.50	53%	42	86%

Stage = gestation by EDD in days; [1] kilogrammes; [2] According to WHO charts; [3] centimetres

Figure 7-2 - 3D MR image from a 1 month scan

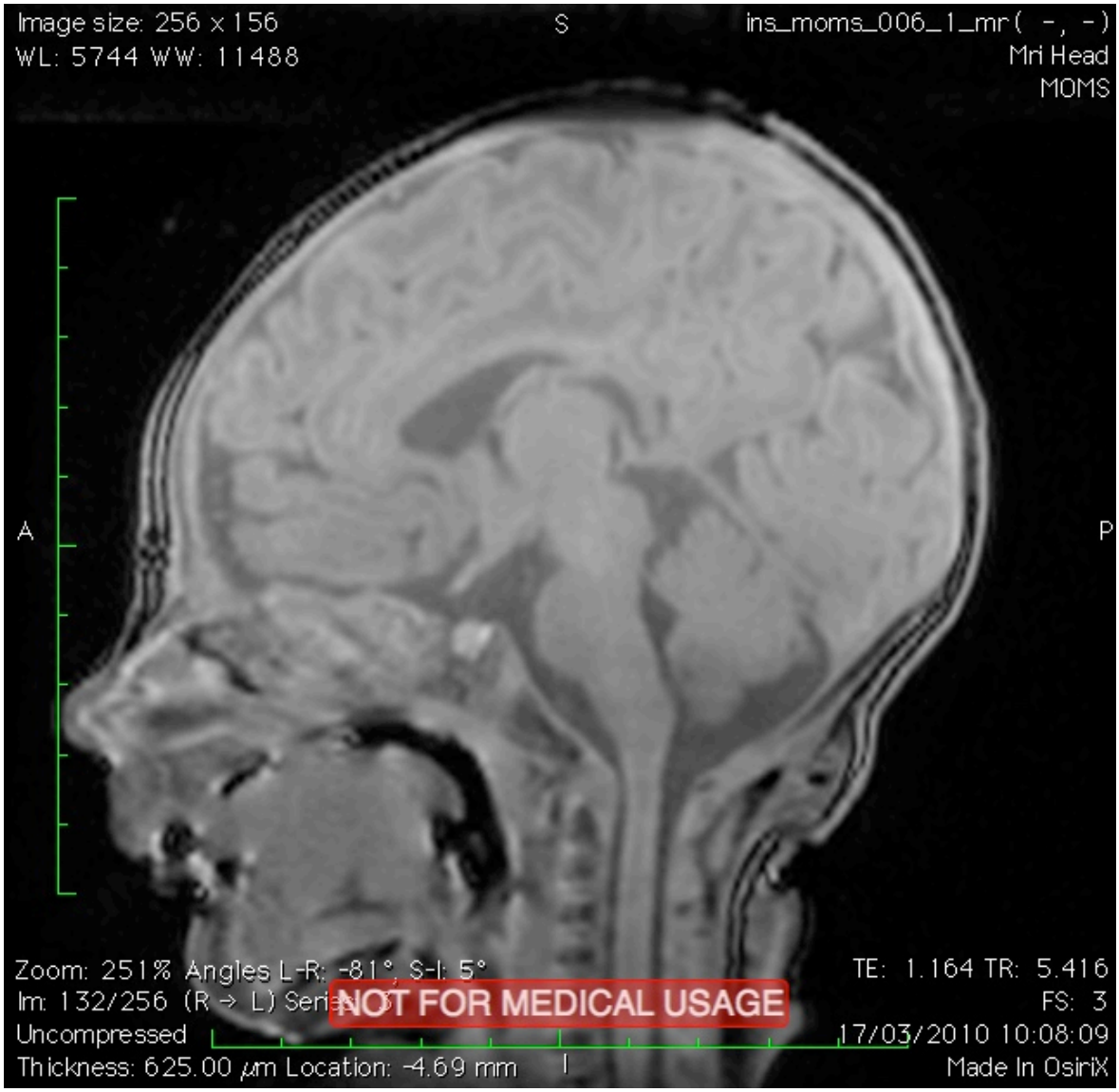
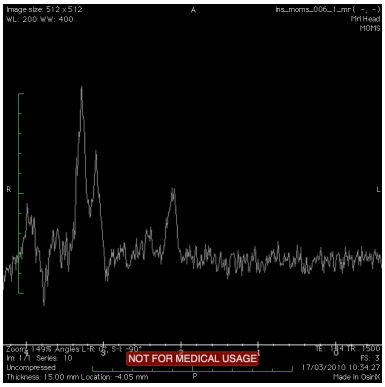
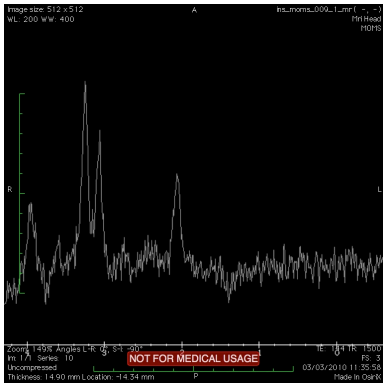


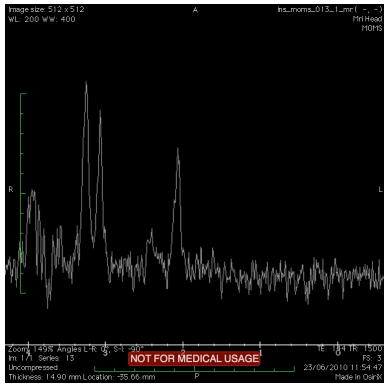
Figure 7-3 - MRS 1 month scans



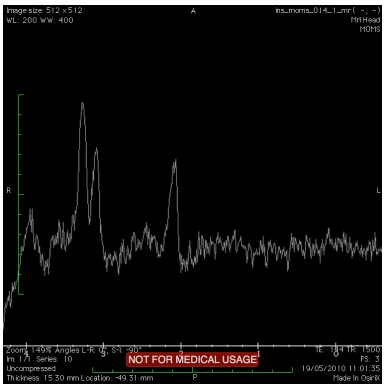
HM006 (control)



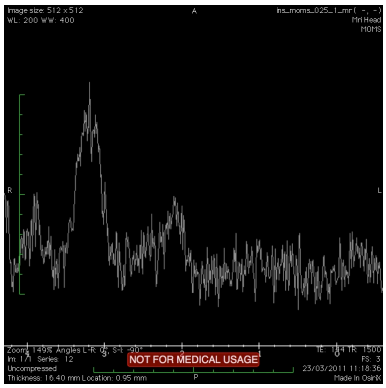
HM009 (control)



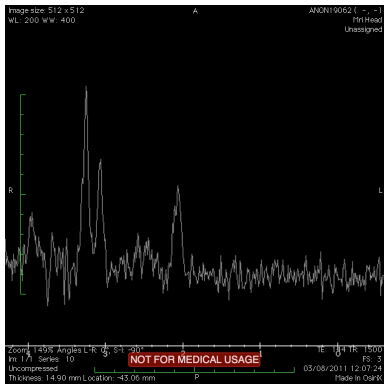
HM013 (control)



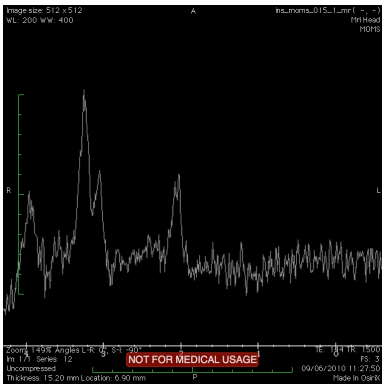
HM014 (control)



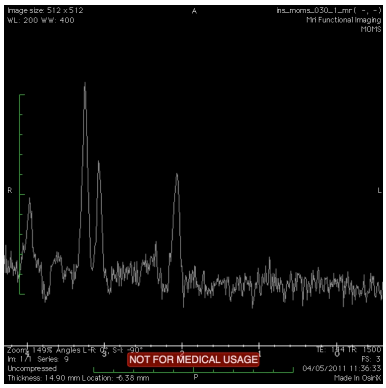
HM025 (control)



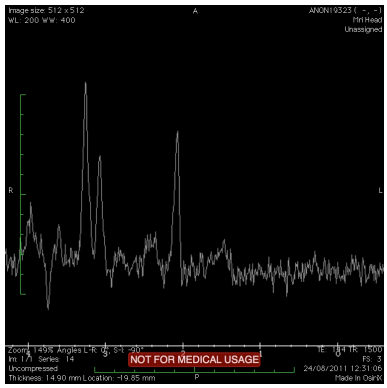
HM033 (control)



HM015 (depressed)

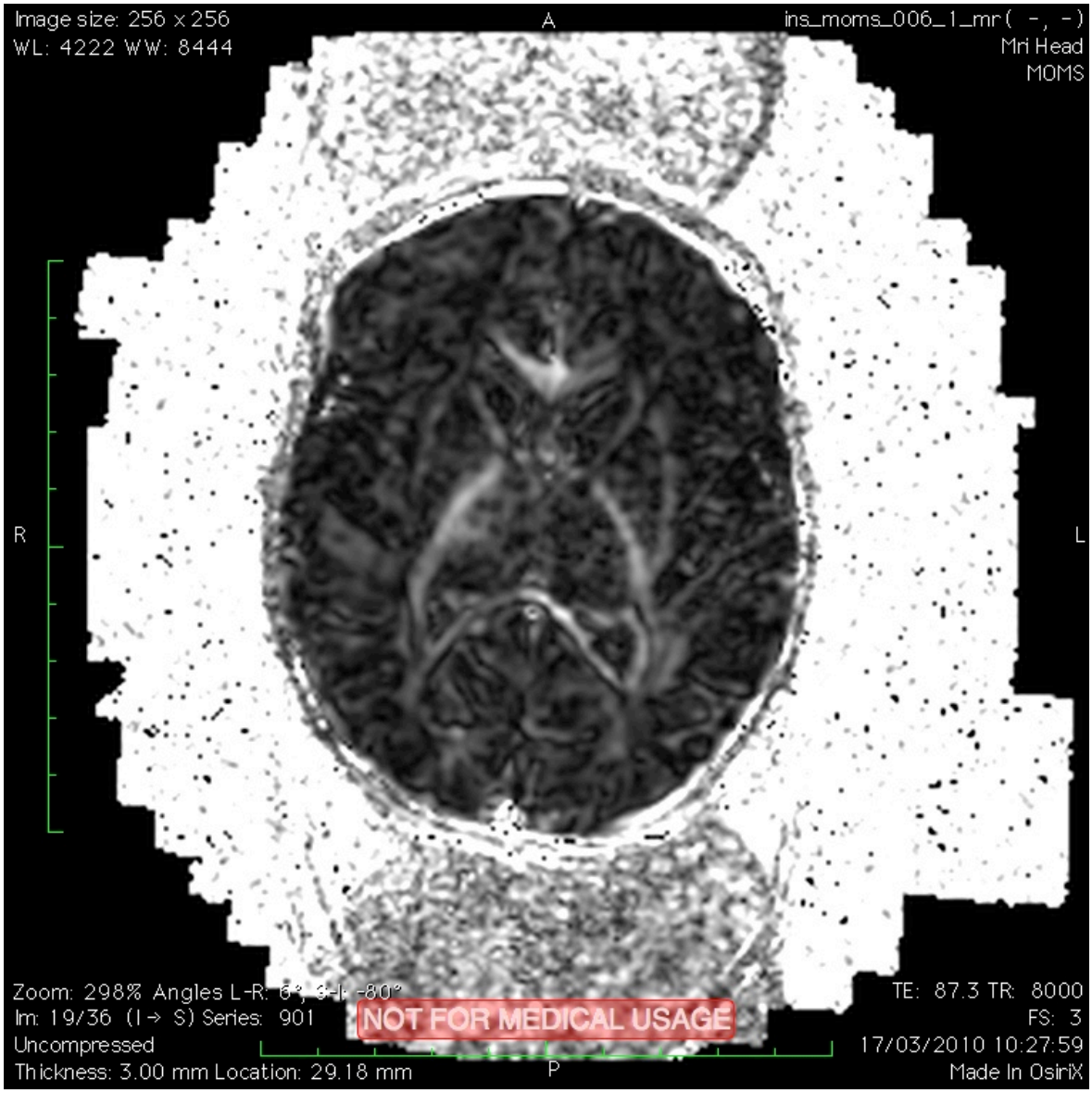


HM030 (medicated)



HM035 (medicated)

Figure 7-4 – DT image from a 1 month scan



Similar to Columbia, we encountered a number of challenges, leading to our intended pilot study recruiting insufficient numbers of women on antidepressants in the time available. Notwithstanding, we concluded that our recruitment strategy had been at least partially effective. Over a period of approximately 30 months, 46 women became known to the research team, with all but three alerted to our study via the information leaflet included in the Bounty pack. The other three attended the PMHS, and gave permission to their clinician for their contact details to be passed on, but none ultimately responded to invitations by 'phone and post to discuss participation with a researcher. A total of 25 women were assessed and consented, with the other 21 being filtered out without the need to meet in person, often following the 'phone conversation to discuss the study in more detail – thus, this appeared to be an effective strategy that saved time for both potential participants and researchers alike. There was a relatively high attrition rate, from the 46 who made contact, to the final six who completed the second scan, that was simply reflective of the difficulties inherent in conducting research of this nature.

Although subjects were recruited at a rate of almost one per month on average, the majority were controls, followed by mothers with depression on antidepressants, and then those with depression not treated pharmacologically, in a ratio of 16:7:2. We had anticipated that mothers on antidepressants would be the easiest to recruit, on account of both presumed anxiety over the potential adverse effects of antenatal exposure and attendance at the PMHS, but it was actually mothers with good health and uncomplicated pregnancies who demonstrated most interest. When asked informally about their reasons for contributing to the study, participants in the control group tended to cite an interest in what they perceived to be an exciting project, especially the prospect of seeing detailed images of their offspring's brains, in addition to an altruistic desire to contribute to research. Those affected by depression, whether medicated or not, focused more on the potential to find answers to concerns about the neurodevelopmental effects of fetal exposure to depression and its medical treatment, while acknowledging that they and their babies

would not benefit directly from this study. It was perhaps not surprising that the most difficult group to recruit were the depressed unmedicated women, both on account of their likely low motivation associated with their mental illness, and also possibly their perception that the study was about the effects of antenatal antidepressants, and not about the consequences of untreated depression, too.

The recruitment strategy could be improved through various amendments. Firstly, it is reasonable to assume more healthy controls could be recruited by including other nearby maternity units, potentially doubling or even tripling our rate of enrollment. Secondly, informing local GPs and psychiatrists about the study would significantly expand the population from which we could identify depressed mothers, and those prescribed antidepressants. Thirdly, rewording our printed material and web content to emphasise depression during pregnancy, whether treated medically or not, as the focus of study may attract those not taking antidepressants.

While we could not be certain why we were unable to recruit any subjects from the PMHS, our anticipated main source of depressed mothers, one possible explanation is that as the vast majority of the PMHS patients attend later in pregnancy, the clinicians may have perceived this to have excluded them from the study, especially as initially we aimed to identify potential participants "as early in pregnancy as possible". Although the lead psychiatrist in the PMHS was aware of our desire to be as inclusive as possible (and had in fact been the one who advised relaxing our exclusion criteria), he was not the only clinician seeing patients in the PMHS. The research team did visit the PMHS and updated the doctors and nurses due to recruitment being slow, but reviewing the details of recruitment from the PMHS would be a fourth option to improve a future study. However, our findings in the PMHS detailed in Chapter 3 also suggest that this cohort differs from the general maternity population in several ways, and an important conclusion is that looking to the PMHS as the only, or even the main, source of participants for a study such as ours is not warranted.

Fifthly, targeting relevant local audiences via social media and virtual groups, such as local users of www.netmums.com and www.mumfidential.com may also

be an effective way to boost numbers contributing. Moreover, although the printed information leaflets proved to be the most successful means of contacting potential participants, the Helping mums website was useful in establishing the kind of resource with which many people are familiar, and which allowed women to contact the research team in an easy, non-threatening manner, while also providing the means by which we were able to give additional information that could be easily updated, without the need to print thousands of new leaflets, and arranged physical distribution.

Another option to improve recruitment would be to consider offering attractive incentives like Columbia. However, this would bring its own challenges, such as securing a source of funding, and the ethical issues involved. As the UK healthcare and welfare provisions differ significantly from, and compare favourably to, those in the USA, we did not from the impression that offering incentives was either necessary nor desirable. Nevertheless, mother did express enthusiasm for receiving digital images and a print of their offspring's scans.

As presaged above, assessing those who continued to indicate interest following the initial 'phone discussion was associated with some challenges. In the early stages of the study in 2009 only one researcher was available to complete the assessments, and time for this was limited to Wednesday mornings. However, not all participants were free to meet at that time, and thus a degree of flexibility was required, particularly as we wished to make the process as easy as possible. Additionally, a suitable NHS venue was not always available, and therefore some women were seen at work or in a coffee shop. It quickly became clear that while the "Columbia battery" of assessments could be completed in around 60 to 90 minutes for healthy controls with uncomplicated histories, even two hours was insufficient to finish everything for those with less than straightforward backgrounds – this was most clearly the case for the depressed unmedicated mothers. Moreover, exploring sensitive personal information in a coffee shop, or taking up two hours of time for subjects at work or in a café was inappropriate, and thus we streamlined the assessments and rating scales as previously described, in addition to identifying a room both suitable and available at the INS, that also allowed a tour of the scanning suite.

Although initially we had planned to identify subjects as early in pregnancy as possible, and ideally not long after booking, and then to repeat assessment at around 24 weeks gestation to standardise findings to increase the validity of comparisons, this appeared to place an unnecessary burden on participants without clearly enhancing the quality of the data obtained. Similarly, when several women required assessment around the same time (as gestation dictated tight timescales), and scans had commenced (which were even more time-sensitive), it proved extremely challenging (and, on more than one occasion, impossible) for one researcher to do all the assessments, while supervising scans, too. Recruiting Higher Trainees in Psychiatry proved invaluable in this regard, allowing simultaneous assessment and/or scans, with them receiving useful research experience in return. Careful consideration was given to training and supervising these colleagues, and in general they did an excellent job, not least in looking after the participants. However, perhaps inevitably when several different researchers were assessing subjects and supervising scans, some data could not be found when analyses started (e.g. some maternal and neonatal measures in Tables 7-4, 7-5, 7-6, and 7-7.

Changing the rating scales to self-completed outcome measures saved time in assessments, and were also more practical to complete at the one month and four month scans – using the HRSD, CAPS, Stroop test and NART, as well as reviewing maternal, obstetric, and neonatal histories was not viable. A potentially desirable option for similar future studies would be the use of electronic self-completed measures at regular intervals throughout pregnancy, e.g. online, or via an app, with monthly prompts and automatic plotting, to allow further comparison of antenatal trends, and control (to a degree) for the confounding influences of severity of antenatal depressed mood, anxiety, and stress.

It proved relatively simple to assign the enrolled subjects to the relevant study group, but this would not necessarily always be the case. As our results, analyses, and conclusions would have been based on careful comparisons, it was necessary to ensure that our study groups represented the different parameters under study, while controlling for the many known and unknown confounders as

far as possible. For example, in order to accurately characterise any neurodevelopmental consequences of medicated and unmedicated antenatal maternal depression, one should ideally compare otherwise identical subjects who were either completely mentally and physically well and not on any medication; with those with depression of similar severity, duration, and subtype, but no other health problems or medication; with those on one specific type of antidepressant at the same dose throughout pregnancy, and no other medication or health problems other than depression. As highlighted above and discussed in Chapter 8, even SSRIs differ sufficiently in their pharmacokinetic and pharmacodynamics properties to necessitate studying each independently. Fluoxetine 20mg taken intermittently for the first six weeks of pregnancy for remitted mild reactive depression is not really equivalent to Sertraline 200mg taken daily throughout for severe endogenous depression with features that persist. Moreover, in order to adequately control for any effects of fetal exposure to mental illness, one would prefer to include only women whose depression had remitted. Enforcing these strict inclusion criteria would result in it taking significantly longer to recruit adequate numbers, even without controlling for factors such as parental age, ethnicity, parity, and genotype, obstetric complications, and fetal gender.

The time available to complete the study posed a challenge to completion, even without such restrictive measures. We had planned to use the four years available to the main researcher for a part-time Doctorate in Medicine, and ethical and R&D approval was in place before the MD was registered in October 2008. However, it took almost one year of preparatory work and waiting before the first potential participant made contact in July 2009, and the first scan did not take place until March 2010, due to the lag time between identifying a subject during pregnancy, and the final four month scan being completed. In a ideal case, we would identify the mother at around three months, meaning that it would take a total of 10 months to finish each subject. Recruiting at our rate of less than one per month would therefore take at least three and a half years to study the 30 participants we sought, assuming no complications and the correct ratio of subjects, suggesting that unless one could improve the rate of

recruitment of those with ideal characteristics, it would take several years to complete a study with 10 women in each study group.

However, less than three years after we recruited our first subject scanning was stopped by NHS GGC, in April 2012. This was due to a high level decision related to the reconfiguring of paediatric services in anticipation of the centralisation of hospital-based care at the new South Glasgow University Hospital (which opened in June 2015). Essentially, as clinical paediatric care at the SGH stopped between 2012 and 2015, the Department of Neuroradiology no longer performed neonatal scans, as there was no longer any provision for emergency life support for children who became unwell at the SGH. Although our project only included healthy babies, and we did not anticipate any becoming acutely unwell as a result of the MR scans, nevertheless we were not allowed to continue. It proved very difficult to identify exactly who had taken this decision, or if it could be amended for our study. This was a severe blow, and although we negotiated with the key stakeholders in radiology, radiography, and paediatrics, we had to stop scanning. The last four month scan had been completed in November 2011, as there had been a hiatus in recruitment for a few months, but we had managed to assess and consent a further six subjects, with their one month scans booked between April and September 2012 (three were healthy controls, two taking antidepressants, and one depressed unmedicated). The research team made significant efforts to negotiate with NHS GGC management via supportive consultant paediatric anaesthetists, and to demonstrate safe practice that would justify continuing the scans by completing training in paediatric immediate life support. However, we were unsuccessful.

This complication was compounded by the MR scanner used for the study being upgraded, meaning that even if we had been able to restart scanning, detailed comparisons of existing data with new images would be suboptimal. Moreover, the original arrangement for our imaging data to be analysed by Columbia, was negated due to their head of department relocating. In other words, numerous factors outwith our control or influence conspired to end scanning.

Notwithstanding, we were able to review our experiences, and reflect on other, theoretically resolvable challenges that should be addressed in advance of any future similar study. As access to the scanner was somewhat restrictive, this could be addressed by seeking additional ring-fenced research scanning time, funded via a grant. Acquiring equipment specifically intended for paediatric (and ideally neonatal) application, including MR head coil, and pulse oximeter probe would also be desirable. A full time research assistant, or part-time with administrative support, would be invaluable in keeping the project running smoothly at maximal efficiency, and local in-house image analysis would ensure greater control over this critical part of the research. Including a researcher with experience of image analysis, both manual and using automated voxel-based morphometry, although this approach has been criticized (Ashburner & Friston, 2000; Bookstein, 2001; Ashburner & Friston, 2001; Ashburner & Friston 2005).

In summary, therefore, we attempted an ambitious pilot project, to use neonatal MRI to characterise the early neurodevelopmental correlates of antenatal exposure to medicated and unmedicated depression in comparison with healthy controls. However, a number of potentially surmountable challenges were compounded by significant unforeseen obstacles, causing the study to end prematurely.

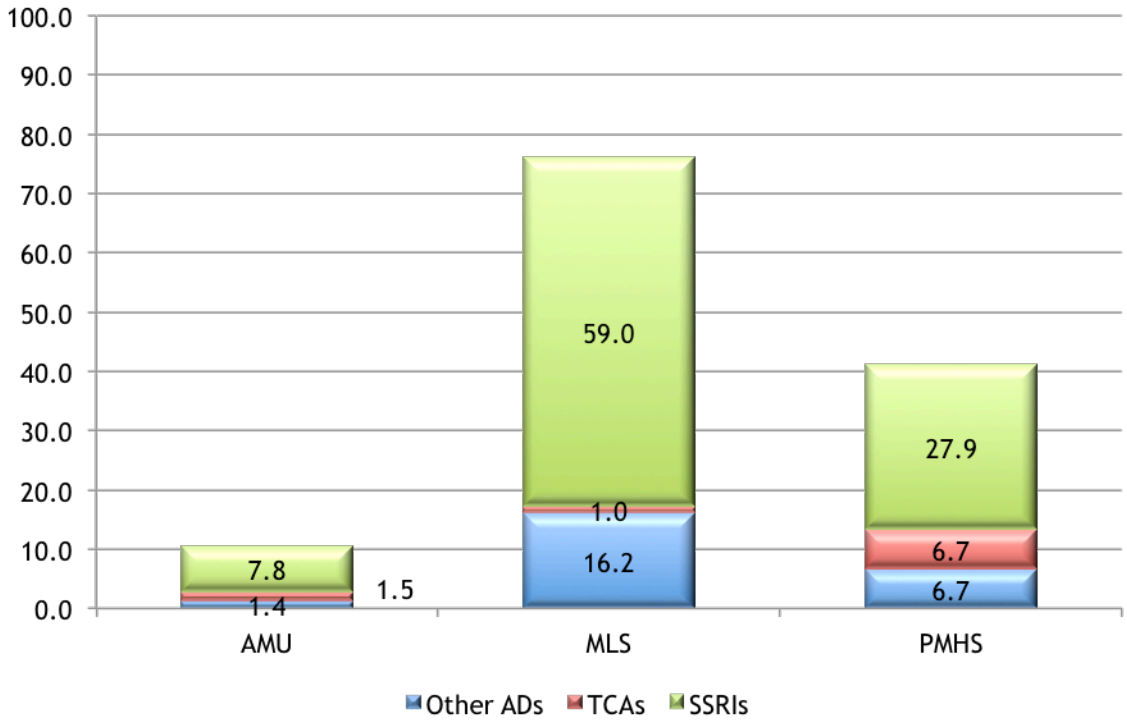
Chapter 8 – Synthesis, observations, and future research

Synthesis

The extent of antidepressant exposure during pregnancy in the samples from the three settings we analysed (the Ayrshire Maternity Unit [AMU]) general population, the Maternity Liaison Service [MLS] local specialist service, and the Glasgow Perinatal Mental Health Service [PMHS] regional specialist service) is presented in Figure 8-1. All values are expressed as percentages of the total sample size (875 from AMU, 105 for the MLS, and 627 for the PMHS), with figures for the AMU corrected forthwith following reanalysis by gestation as discussed in Chapter 5. (NB As per Margulis, Kang & Hammad [2014] [Figure 2-3], the total prevalence of exposure to any antidepressant was lower than the addition of SSRIs, TCAs, and other antidepressants, as some women in each sample were exposed to more than one type of antidepressant – the total percentages were 9.7% for AMU, 71.4% for the MLS, and 37.5% for the PMHS.)

Several observations can be made. Firstly, the proportion of pregnant women exposed to antidepressants in the AMU sample was higher than has been reported in the general British population. Petersen *et al*. (2011), Margulis, Kang and Hammad (2014) and Charlton *et al*. (2015) all reported overall prevalence of antidepressant prescribing as <6% antenatally. However, it should be reiterated that they all based their estimates on prescriptions issued during pregnancy, and did not include potential exposure to medication prescribed and taken periconception. Moreover, their values represent averaged prevalence over several years, during which time prescribing may have increased. Our figures were more up-to-date, included exposure even in early pregnancy, and accounted for all live/stillbirths, i.e. did not exclude participants on the basis of missing data before pregnancy.

Figure 8-1 – Prevalence of antidepressants in pregnancy



ADs = antidepressants; TCAs = tricyclics; SSRIs = selective serotonin reuptake inhibitors

Secondly, the overall proportion of women exposed to antidepressants in each setting varied significantly, with more attending the specialist services receiving medication. This was expected, although almost twice as many women seen via the MLS took medication as those in the PMHS. While this may appear counterintuitive, it is likely to be related to their respective remits – as per Tables 3-3 and 5-5 the PMHS provides care for more women with psychosis and bipolar disorders, and the MLS for a significantly greater proportion with affective and neurotic disorders, particularly depression. Moreover, the data for the PMHS spans 2002 to 2009, whereas the MLS data is for 2013.

Thirdly, as per the literature, the majority of antidepressant prescriptions during pregnancy were for SSRIs, regardless of setting (80.0%, 82.7%, and 74.5% in the AMU, MLS, and PMHS, respectively). There was a higher prevalence of TCAs in

the AMU sample compared with the MLS, but this is explainable on the basis that the majority of TCAs were "low dose" Amitriptyline, likely prescribed for non-psychiatric indications (Petersen *et al.*, 2011). A relatively higher proportion of PMHS attendees were prescribed TCAs, possibly reflecting higher levels of "treatment resistance" requiring alternatives to SSRIs, chronicity or comorbidity. The greater levels of "other" antidepressants seen in the MLS sample were due to SNRIs (5.7%, 6/105 - Venlafaxine and Duloxetine 2.9% each), Trazodone (5.7%, 6/105), and Mirtazapine (4.8%, 5/105).

Figure 8-2 presents the relative proportion of individual SSRIs taken by patients receiving monotherapy in each setting. The most obvious differences lie in the greater exposure to Sertraline and lesser exposure to Fluoxetine in the MLS, compared to both AMU and the PMHS, and the higher rates of Paroxetine prescribing in the PMHS. Following the US Food and Drug Administration's warning in 2005 about Paroxetine's potential for teratogenic effects (but not other SSRIs), prescribers moved away from using Paroxetine in pregnancy, and this increased proportion in the PMHS sample may simply represent a historical artifact (Stone *et al.*, 2009).

Figure 8-3 Illustrates timing of exposure to SSRI monotherapy, which was largely representative of other antidepressants. Again, themes and differences between the samples emerge. ~45% of the AMU and PMHS patients stopped in the first trimester, while this was true of only 16.6% of the MLS attendees. ~50% more women seen via the MLS were exposed to SSRIs throughout pregnancy than in the PMHS, and more than double the proportion in the AMU sample. ~20% of those seen via MLS or the PMHS commenced medication during the second and third trimesters, compared with 5% of the general population. A significant proportion of the AMU and MLS subjects followed a 'stop-start' pattern, but less so in the PMHS sample (possibly only an apparent difference due to simplification during documentation using the data collection forms). As discussed above, as most prescribing decisions are taken in the first trimester before being seen in the MLS or PMHs, whether made by patients or prescribers, these serve more as proxy markers for other factors, such as severity of illness, and relapse. For example, one might predict that relatively more women who stop in the first

Figure 8-2 – Exposure to individual SSRIs

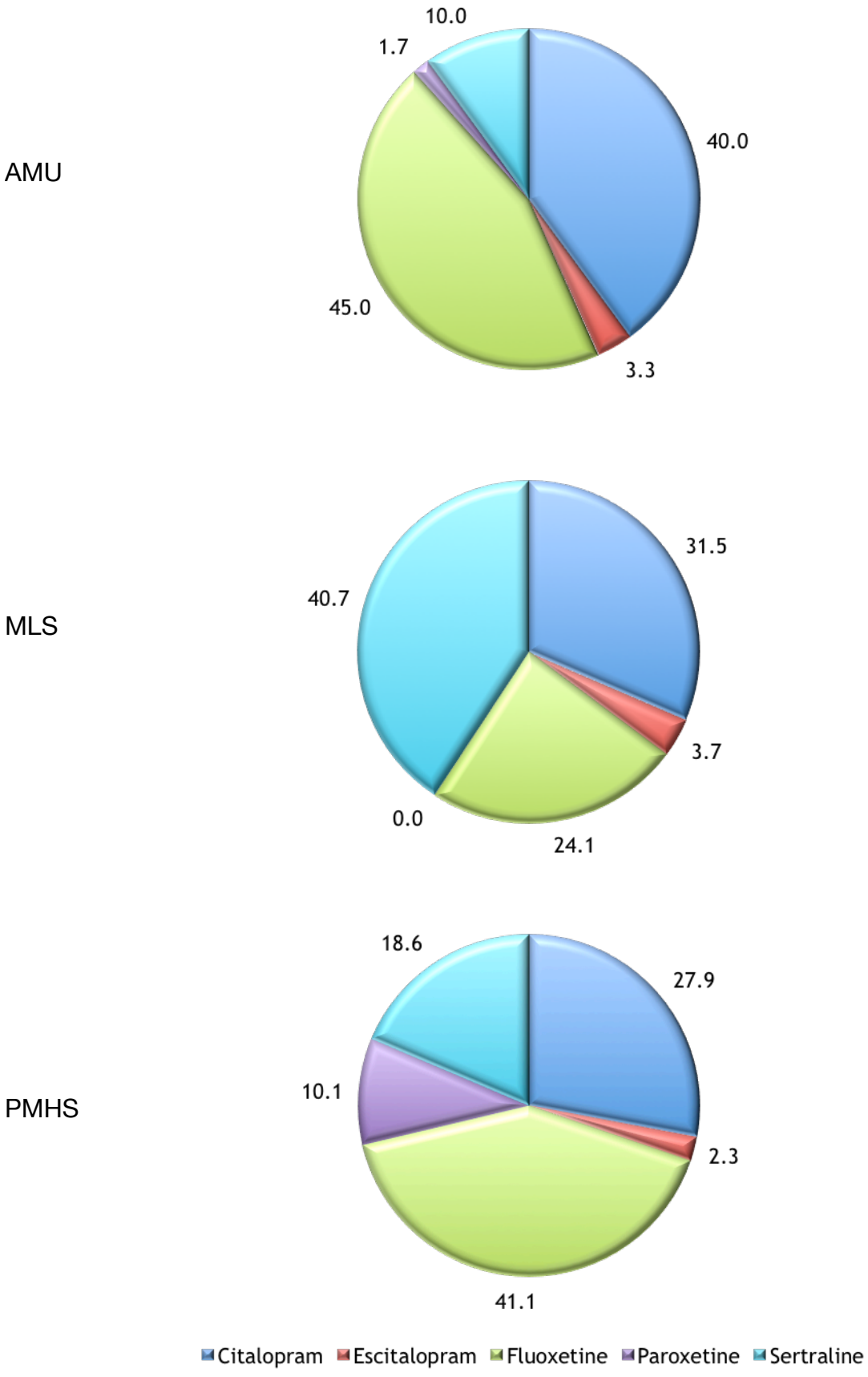
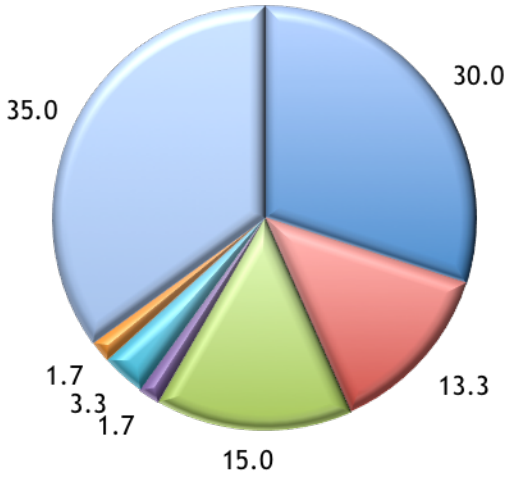
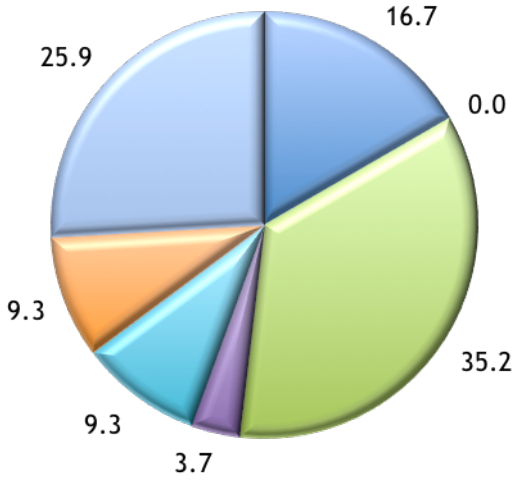


Figure 8-3 – Timing of exposure to SSRIs

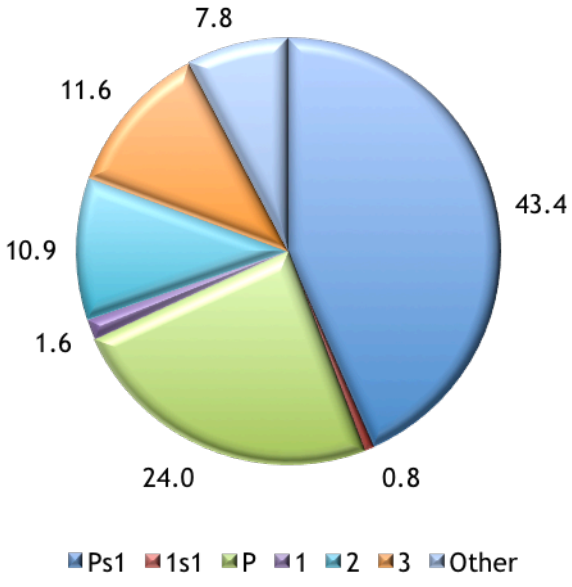
AMU



MLS



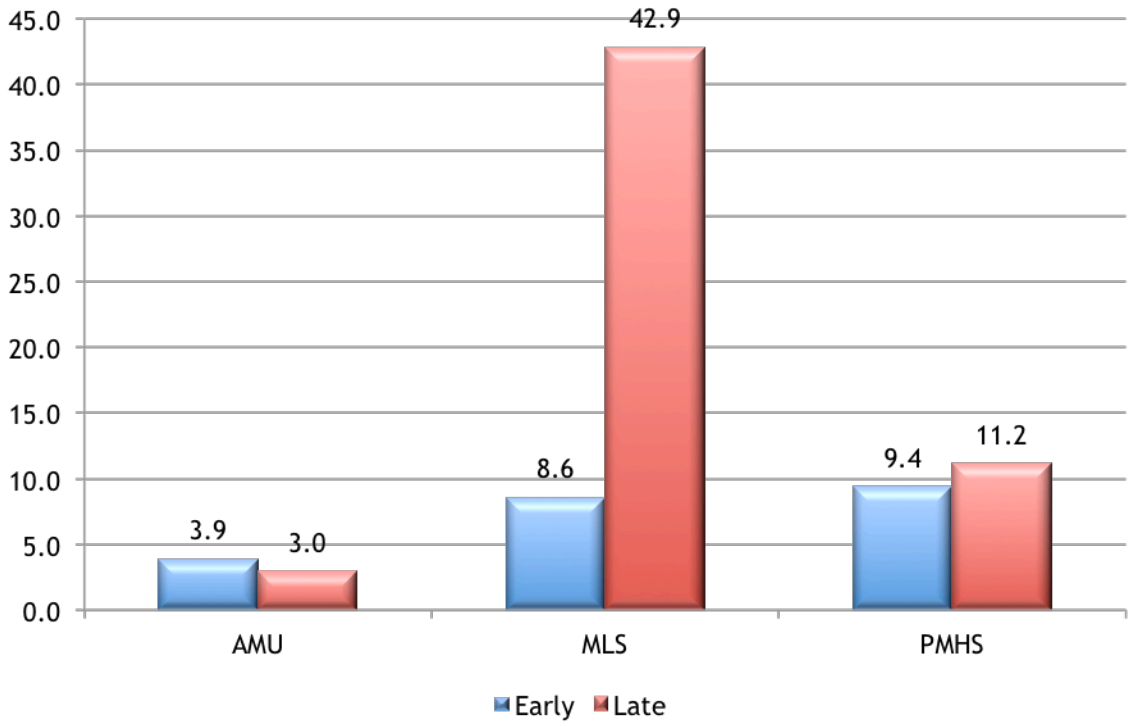
PMHS



trimester will be seen in a specialist service later in pregnancy, as they are at increased risk of relapse, and there may be uncertainty or concerns over restarting medication.

Equally, the higher proportion of women taking an SSRI throughout pregnancy seen in the MLS may reflect referrer-specific issues, e.g. a referral to the MLS from AMU due to concerns that medication is unnecessary as the patient appears well, when further assessment leads to the conclusion that her current good mental health is attributable to ongoing pharmacological intervention.

Figure 8-4 – Timing of exposure to SSRIs – early or late



Consistent with the above observations, third trimester ("late") exposure to SSRIs was less common than earlier exposure in the AMU sample, although not to the same extent as the literature pertaining to the UK, where reductions in

excess of 50% have been described (Figures 8-4 and 2-3) (Petersen *et al.*, 2011; Margulis, Kang & Hammad, 2014; Charlton *et al.*, 2015). Once more, the PMHS figures appeared intermediate between AMU and the MLS, most likely due to the diagnostic make-up of the sample.

A more detailed breakdown is given in Figure 8-5, where the percentage exposed in each trimester in each service is summarised (T1, T2, and T3, respectively). T0 represents those exposed at the time of conception, and is not comparable to other studies, which reported figures for prescriptions issued in the three or six months before pregnancy, and hence included those additional women who stop antidepressants prior to conceiving – this may explain the absence of significant reduction between T0 and T1 presented here (Figures 8-5 and 2-3). Notwithstanding, the trend seen in the AMU sample was similar to those reported, with almost a 50% reduction in exposure from T1 to T2, followed by a further reduction in T3. In contrast, however, there was a much smaller drop in exposure rate from T1 to T2 in MLS attendees, and an increase in T3. Once more, the figures for the PMHS sample were intermediate.

These findings suggest that further research into exposures in specialist perinatal mental health settings may be a valuable complement to those based on data from the general population, both as an enriched source of exposures to illnesses, treatments, and confounders, and as a valuable aid to those making prescribing decision in such settings. This can be seen most clearly in our findings regarding outcomes. Expectant mothers and those caring for them need to know that babies born to those attending specialist psychiatric care may be at significantly increased risk of early morbidity of sufficient severity to warrant neonatal admission. Although admission rates appeared to be higher in those exposed to SSRIs in the AMU sample, the outcomes in the MLS sample pointed to illness severity being a more important predictor than exposure to medication. Rates of admission for different exposures in AMU and the MLS are shown in Figure 8-6.

Figure 8-5 – Timing of exposure to SSRIs by trimester

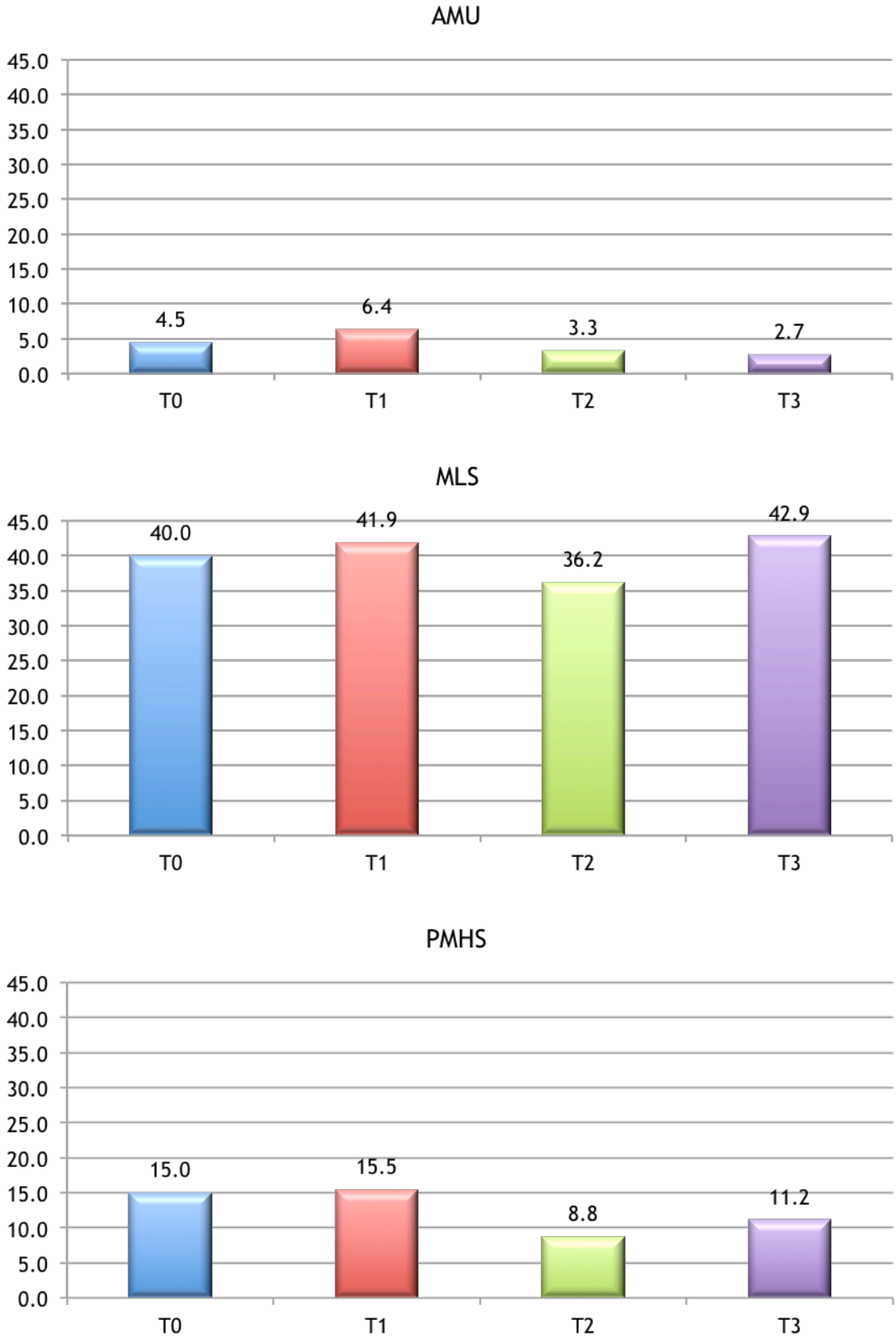
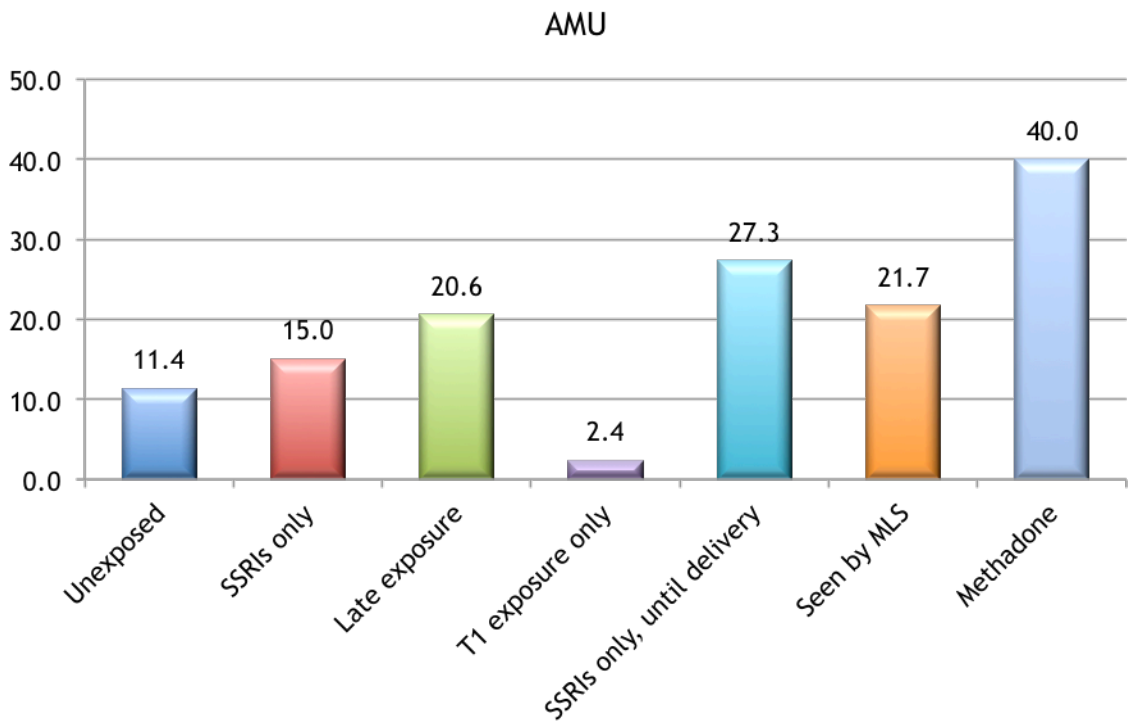
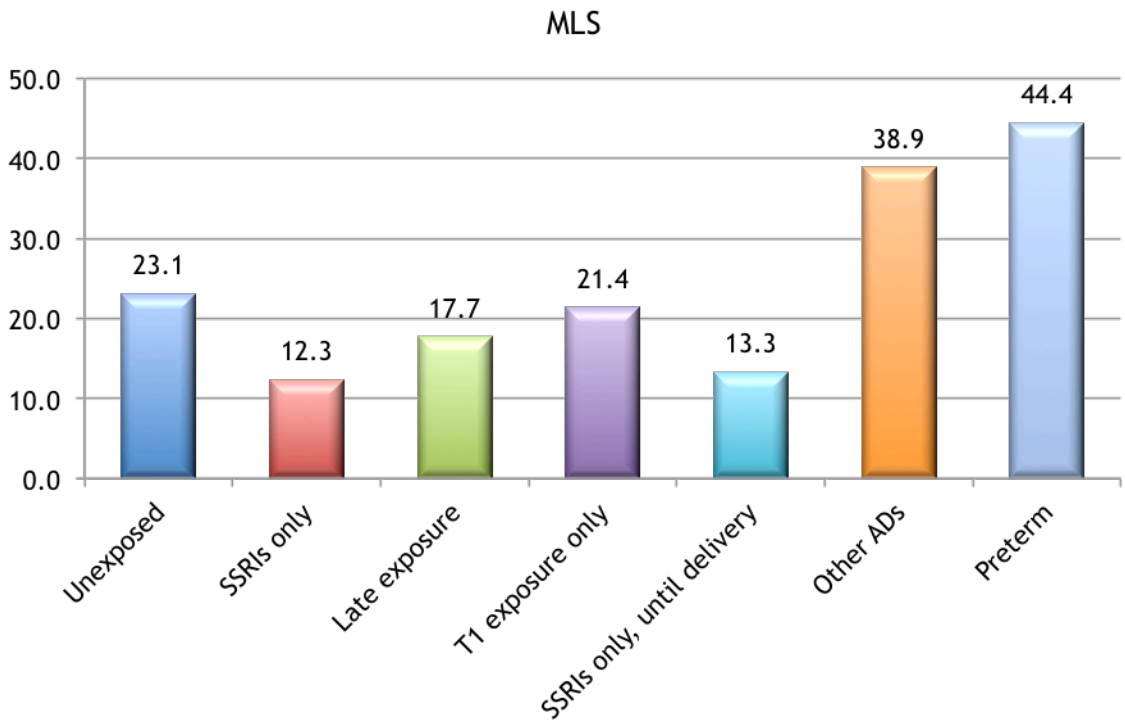


Figure 8-6 – Neonatal admission rates for select exposures





Additionally, the effects of depression severity and the moderating influence of antidepressants on gestation and birthweight merit further exploration, as although the associations we found between them and HADS-D and were statistically significant, it does not necessarily follow that they were clinically significant. Importantly, HADS-D did not predict admission, nor preterm delivery.

Observations

Perinatal depression, both antenatal and postnatal, remains an important clinical condition, with potentially far-reaching consequences for mothers and babies, in addition to the wider family, health services, and society in general. Optimal management necessitates relevant data, and this is still lacking in many areas. While a not insignificant amount is known about risk factors for and consequences of perinatal depression, we have less comprehensive knowledge about the advantages and disadvantages of antenatal antidepressants and, in the absence of adequate empirical data, current clinical practice and recommendations are largely based on extrapolation from findings of studies outwith pregnancy, retrospective observations, and expert consensus. We still are not absolutely certain how common depressive illness is during pregnancy, and foundational to the gaps in our knowledge in this specialist area are the intertwined issues of our lack of comprehension about the pathophysiologies of depression, our limitations in elucidating how antidepressants actually work, and our relative ignorance about the mechanisms underlying the intergenerational transmission of illness and risk. Most facts we do have are consistent with the overall positive zeitgeist with regards to the role of antenatal antidepressants, but there is still much to learn, and no place for complacency.

Notwithstanding, we can be confident that perinatal depression and related problems (including anxiety and stress) and their consequences are common and concerning, and that the therapeutic advantages of antidepressants appear to outweigh their risks for at least some expectant mothers and their offspring.

The account outlined above raises a number of important issues that suggest current and future priorities with regards to clinical care and research.

Clinical considerations

As discussed in Chapter 1, we do not know exactly how to conceptualise depression, nor even how to define clear and valid boundaries between normal depressive symptoms and a pathological state. It is unsurprising, therefore, that we are not clear about the prevalence of depression during pregnancy.

The validity, reliability, and utility of diagnosing depression

DSM is widely used in both clinical practice and research, and indeed, evidence-based recommendations about management are largely based on the outcomes of studies founded on DSM criteria. However, in addition to the limitations of DSM criteria in diagnosing major depression within and outwith pregnancy outlined in Chapter 1, when Regier *et al*. (2013) assessed the test-retest reliability of categorical diagnoses using DSM-5 operational criteria they concluded that the reliability of a diagnosis of major depressive disorder made by independent clinicians was "questionable", with a pooled intraclass kappa of 0.28 (0.20-0.35 95% confidence interval). (The individual kappas for the four different sites included were 0.13, 0.25, 0.27, and 0.42, i.e. three out of the four were categorised as "unacceptable" or "questionable".)

If DSM (or any other operational) criteria are neither valid nor reliable and cannot consistently discriminate between pathology and physiology, of what value are they? This is critical question to which there is no final answer. Parker (2000) critiques the unitarian conceptualisation of depression as being on a continuum, and the inadequacy of operational criteria in distinguishing between aetiologically distinct subtypes. Memorably, he compares classifying depression on the basis of symptoms to distinguishing between cars by using tyre size,

indicating that depressive symptoms shared between different underlying causes are a poor basis on which to judge severity of illness, or evaluate the effectiveness of different interventions. Parker uses the example of breathlessness, pointing out that we would not and should not measure the efficacy of a treatment that addresses only one underling cause, e.g. an antibiotic, in a heterogeneous sample made up of those with asthma, pulmonary embolus, and heart failure, in addition to pneumonia (Parker, 2009). In this context, counting symptoms to diagnose depression and/or rate its severity appears of limited relevance, despite being the approach adopted by both DSM-5 and ICD-10. Parker (2006) goes so far as to state that DSM and ICD-10 "have outlived their usefulness", with de Leon (2015) stating that DSM-III had "devastating consequences" that "put European psychiatry to sleep", and describing DSM-5 as a "dead end". However, Parker's views have been critiqued (and perhaps marginalised), with Goldney (2006) reaching more optimistic conclusions (Fahy, 2002).

Despite the limitations of operational criteria with regards to validity and reliability, Kendell and Jablensky (2003) contend that diagnoses do not have to be valid to be useful. We know that whatever depression criteria, structured clinical interviews, or rating scales are measuring, whether general distress, anxiety, or true depression, nevertheless they can be useful in identifying those at increased risk, and in monitoring response to treatment, as diagnoses and scores do correlate with outcomes. In other words, there is both validity and utility in our current clinical and research assessment tools, despite their shortcomings. It is noteworthy that Steer *et al*. (1992) reported that when they analysed Beck Depression Inventory scores as a continuous variable, they found that the risk of adverse outcomes (preterm deliveries, low birthweights, or small-for-gestational age babies) increased by "5-7% . . . for *each point* the BDI total score increased". This suggests that, in addition to using cut-off scores to determine "caseness", using continuous measures of depression/anxiety/distress, i.e. allostatic load, may be a clinically appropriate and relevant used of validated rating scales. Parker *et al*. (2015) call for this use of the EPDS, as highlighted in Chapter 1.

One final point regarding qualitative versus quantitative measures in evaluating depression is that, despite Parker's (2009) compelling argument that interventions for depression should be matched to the underlying pathology for maximum effect, nevertheless, studies continue to indicate that using depressive subtypes does not predict response to antidepressants, consistent with Kendell and Jablensky's (2003) observation that even the boundaries between psychiatric disorders are not well demarcated, and that variation in symptoms appears to be dimensional (Arnow *et al.*, 2015).

Screening for perinatal depression

Given the uncertainties pertaining to diagnosing whatever we think we mean by "depression", it is hardly surprising that some have questioned the validity of screening for a condition we cannot define. It is still unclear whether or not screening for depression is effective in improving outcomes in primary care (Thombs & Ziegelstein, 2014). Thombs *et al.* (2014) conducted a systematic review of perinatal depression screening and outcomes, and found only one eligible postnatal study, on which they opined that final conclusions should not be based, due to methodological limitations. Despite the challenges and uncertainties, Milgrom and Gemmill (2014) are more optimistic about screening for perinatal depression, given that it is "serious, prevalent, under-detected and treatable", and "a tolerable screening procedure of known accuracy is available".

Guidelines vary in their recommendations, while recognising the limitations of the current evidence. The American College of Obstetricians and Gynecologists (ACOG) recommend screening all women perinatally, while Australian guidelines recommend universal screening at least once both antenatally and postnatally – both countries recommend the use of a validated rating scale, with the Edinburgh Postnatal Depression Scale (EPDS) comparing favourably to alternatives (Austin *et al.*, 2011; ACOG, 2015). British guidelines also recommend antenatal and postnatal screening, with an emphasis on clinical

inquiry via psychosocial assessment and specific questions (essentially the PHQ-2), and to "consider using" rating scales (such as the EPDS) as "part of a subsequent assessment", "an aid to clinical monitoring" and "to facilitate discussion of emotional issues", rather than as the primary means of screening (NICE CG192, 2014; SIGN, 2012). Interestingly, although UK guidelines emphasise reliance on the PHQ-2, Austin *et al*. (2011) reported that the EPDS is superior. The different emphases appear related to the relative strengths and weaknesses of clinical inquiry and rating scales – neither is invulnerable to false positives or false negatives. The SIGN guidelines in particular take account of this, not least by emphasising the importance of a longitudinal perspective, whereby those who screen positive are followed up in two weeks to detect persisting symptoms (Matthey & Ross-Hamid, 2012; SIGN, 2012). It is noteworthy that Cameron, Lawton and Reid (2009) found that Scottish GPs (who were aware of the study) "rated depression" in 52% of patients who independently "screened positive" for "probable depression" (HADS ≥11), 24% of those with "possible depression" (HADS 8-10), and 8% of those with "no depression" (HADS <8), suggesting that GPs are circumspect in diagnosing depressive illness (and in prescribing antidepressants), placing symptoms and distress in clinical context.

Despite the lack of conclusive evidence, the available guidelines make sensible use of what we do know, and the emphases on awareness of risk factors and need for screening, shared documentation and management plans, prompt review of antenatal medication, and referral to specialist services where indicated, are welcome.

However, as evidenced by our findings that many women are exposed to antidepressants (and other psychotropics) periconception, and make decisions about continuing or stopping early in pregnancy, before/without the benefits of medical advice, guidelines also recognise the desirability of anticipating pregnancy. The recommendations by both SIGN (2012) and the updated NICE CG192 guidelines (2014) include that medication prescribed to those of "childbearing potential" should be accompanied by relevant information on risks and benefits, advice on contraception, and consideration of discontinuing if pregnancy is planned.

This direction is important, given that a significant proportion of pregnancies are unplanned and/or unintended. It has been reported that more than 50% of all pregnancies in the UK and the US are unplanned, with possibly even higher rates in women with mental illness (associated with increased adverse consequences), although research using different methodology and terminology suggests that the true figure lies somewhere between one in three, and one in six (Barkla *et al.*, 2000; O'Sullivan *et al.*, 2005; Lakha & Glasier, 2006; Wellings *et al.* 2013). However, it should be noted that rates appear to vary significantly between different age groups, with almost half of pregnancies in women aged 16-19 being described as unplanned, and clear differences between those terminating their pregnancies, and those continuing. For example, almost nine in ten of those undergoing abortion reported their pregnancies as unplanned, compared with less than one in ten of those proceeding to delivery. And more than one third of women completing pregnancy describe conceiving as unintended, although not necessarily unplanned. Falling pregnant is ultimately not entirely subject to human planning.

It follows, therefore, that all depressed women of childbearing potential should be treated with the same degree of vigilance, skill and tenacity as their expectant counterparts, as some may fall pregnant unexpectedly, and the stakes are high for mother and child. Indeed, in depressed women, unplanned pregnancy is a risk for unplanned antidepressant discontinuation, with consequent risk of relapse, and resumption of medication in more than 50% (Cohen *et al.*, 2006; Roca *et al.*, 2013). As in pregnancy clinicians are caring for two distinct patients with different needs and vulnerabilities, the fundamental and primary principle of western medicine, *primum non nocere* ("first do no harm"), reminds doctors that prescribing medication for pregnant women may be associated with a variety of significant risks to the developing fetus in both the short and longer term, including chronic disability (Herranz, 2002). Thalidomide remains a vivid illustration of the frightening potential for prescribers with good intentions to cause significant and extensive harm (Rasmussen, 2012).

Managing perinatal depression

A full review and discussion on the management of perinatal depression is beyond the scope of this thesis, and excellent evidence-based guidelines and reviews are available (SIGN, 2012; Howard *et al.*, 2014; NICE, 2014; Ray & Stowe, 2014; Taylor, Paton & Kapur, 2015; McAllister-Williams *et al.*, 2017). In the absence of evidence specific to antenatal medication, all concur that good practice during pregnancy is modeled on good practice outwith, in that one should prescribe when clinically indicated (in itself difficult to define), using the least number of drugs at their lowest effective doses, involving the patient and her family in the decisions, with a joint weighing of the potential benefits and risks of treating and not treating. While adverse outcomes have been reported to be associated with all currently available individual drugs and their classes, nevertheless (with the exception of Paroxetine, and occasionally Venlafaxine), no antidepressants are absolutely contraindicated or advised against, and SSRIs, TCAs, and SNRIs are recommended by the current NICE guidelines. Of course, choice of medication is specific to each individual, and balance is required – while no drug should be prescribed for longer than necessary, or at a higher dose than necessary, it is important that treatment is of adequate dose and duration, as being exposed to a medication at an inadequate dose or for too short a period merely increases risk rather than addressing it, and relapse following cessation of treatment is not uncommon (Weisskopf *et al.*, 2015).

Koren (2012) uses the title, "Depression in pregnancy: Time to stop terrifying pregnant women", to emphasise the importance of treating antenatal depression effectively. While there are known and unknown risks associated with antenatal antidepressants, it is not the case that we are complacently advocating the indiscriminate use of toxic placebos. Rather, we are thoughtfully recommending nuanced and individually-tailored effective evidence-based interventions to women suffering from significant illnesses that have the potential for both mortality and morbidity, in both mothers and babies, in the short and long term.

Of course, non-pharmacological interventions should also be considered as clinically indicated, and both psychosocial management and other physical

treatments have been discussed (Richards & Payne, 2013; Dennis, 2014; Stuart & Koleva, 2014; Kim *et al.*, 2015). Unfortunately, however, there is often even less evidence to guide decisions on these perinatally than there is for antidepressants.

Future research

In this thesis and series of related pilot studies we have reviewed the international literature and analysed local data, to ascertain both our current status and the future feasibility of research regarding the characteristics and consequences of antenatal exposure to SSRIs. We have noted the methodological, practical, and ethical challenges in studying this area; the complex interactions between antenatal antidepressants and the perinatal depression for which they are prescribed; the grievous issue of confounding; and the (often extensive) gaps in and uncertainty over our knowledge to date.

Our observations have highlighted both established facts, and outstanding questions that remain unanswered. Several future lines of inquiry suggest themselves, and have been identified numerous times by different authors. There is an ongoing pressing need to identify exactly what exposures, at what stages of pregnancy, are associated with what clinically relevant outcomes, and for whom.

In light of so many variables, and the relative frequency of different outcomes (some common, some rare), the ongoing use of large database linkage studies is appealing (Stewart, 2014). The advantages of "big data" are many, including the potential for large numbers to facilitate adequate statistical power, the inclusion of all subjects within a population, a longitudinal perspective across individuals' lives, and a relatively cost-effective and economic retrospective tool for addressing health-related queries.

However, there are also numerous disadvantages, as discussed throughout this thesis, and by Munk-Jørgensen *et al.* (2014) in general, and Grzeskowiak, Gilbert and Morrison (2013) regarding the use of administrative databases to explore perinatal exposures and outcomes in particular. These include (but are not necessarily limited to) biased, non-representative populations due to inclusion criteria and/or missing data; details of exposures and outcomes that are one or more steps removed from the clinical truth; a lack of explanatory power, in that only associations can be demonstrated, and not causality; a tendency towards finding statistical rather than clinical significance; and the inability to control for unknown confounders. Moreover, due to the sheer numbers involved, there is the risk of problematic heterogeneity, in that factors that should be assessed independently are often lumped together. All must be carefully considered and addressed in future research.

Some of these issues are illustrated clearly by antenatal antidepressants. In the order of disadvantages given above, many of the studies referenced above have been based on skewed populations (e.g. insurance-related, or live births only), and have excluded any for whom not all data was available (sometime >50% of the original sample); have identified medication prescribed/dispensed/paid for rather than medication actually taken; have focused on exposure to medication in isolation from exposure to the condition for which it was prescribed; have highlighted 'cardiac abnormalities' as an adverse outcome, regardless of how clinically significant; and have not taken into account other known contributors to the risks under study, including psychosocial stress.

One major problem is the lack of precision with regards to both exposures and outcomes. Antidepressants are not a homogeneous group, with congruent effects (Ciraulo, Shader & Greenblatt, 2011). For example, SSRIs alone vary considerably pharmacokinetically, pharmacodynamically, and pharmacogenetically, are known to cross the placenta to different degrees, and are not necessarily equally efficacious, with a complex interaction with serotonin transporter genotype (Hendrick *et al.*, 2003; Serretti & Artioloi, 2004; Serretti *et al.*, 2007; Cipriani *et al.*, 2009; Kato & Serretti, 2010; Ababneh, Ritchie & Webster, 2012; Altieri *et al.*, 2014). Similarly, as discussed in Chapters 4 and 6, different risks may be

associated with different SSRIs, but grouping together heterogeneous outcomes such as "major malformations" may mask some true associations, e.g. the Reefhuis/Bérard discrepancy (Reefhuis *et al.*, 2015; Bérard, Zhao and Sheehy, 2015).

Several factors must be considered when addressing/avoiding these issues. Not necessarily in order of importance, these include collecting data prospectively and longitudinally, in inclusive and representative samples of sufficient size, with an adequate level of detail and accuracy, for specific exposures and specific short term and long term outcomes, that can be analysed statistically.

The preferred approach is to use prospective rather than retrospective data, and to collect all information desired for analysis on an intentional basis. This observation was presaged almost 40 years ago by Doering and Stewart (1978), and reiterated by Wisner *et al.* (2009), specifically with regards to evaluating outcomes associated with individual SSRIs. It ensures that all necessary data is available in a format that can be accessed and used, however, demands proactive intentionality, time, resources, and funding. Both the administrative databases synthesised by ISD, and the data collection forms used in the PMHS and the MLS can serve as a convenient source of prospectively gathered data, collected on a routine basis. However, the data collection forms and their associated processes would require revision to render them less open to idiosyncratic and subtotal completion and ambiguity, to ensure that they are always filled for each patient, and updated at each contact.

This segues into a related issue – the data must be longitudinal. While cross-sectional studies can provide a snapshot in time, it is clear that antenatal exposures are dynamic, and fluctuate unpredictably in individuals throughout pregnancy. This was illustrated by our findings regarding prescribing changes during pregnancy, and one of the motivators underlying the studies by Petersen *et al.* (2011), Margulis, Kang and Hammad (2014) and Charlton *et al.* (2015). However, it is not only drugs that change during pregnancy. Illnesses vary, too, as does objective and subjective stress (Matthey & Ross-Hamid, 2012; Parker *et al.*, 2015). As severity of illness may be even more predictive of adverse

outcomes than exposure to medication, it is desirable if not necessary that the longitudinal courses of exposure to both illness severity and stress, and also known confounders such as comorbid medical conditions and associated medication, and other psychoactive substances such as alcohol, tobacco and non-prescription drugs, are estimated. As many of these details are not captured by administrative databases, there remains a need for planned prospective, longitudinal, observational data collection, ideally in clinical settings such as the PMHS and the MLS.

While ISD can provide data representative of the whole population, and thus contribute to inferences relevant to all, including background baseline norms, there are some advantages in closer scrutiny of the different populations seen by the PMHS and the MLS. These include smaller numbers at increased risk of both exposures and adverse outcomes, as well as the potential to collate more relevant data from the detailed and comprehensive assessments carried out by the respective specialist teams. Moreover, longitudinal information on illness, stress, and medication, as well as known confounders is routinely documented. Organising and structuring the documentation to facilitate easier retrospective analysis, while dovetailing with any mandatory local templates, and avoiding unnecessary duplication, would be a route to achieving a powerful valuable repository of knowledge. Databases from the PMHS and the MLS would have the potential to provide knowledge directly applicable to the patients seen, e.g. increased neonatal admission rates, and the likely impact of associated medication.

As well as having access to sufficient details in larger enough and representative samples, data would of course have to be accurate. This may entail utilising more than one source of information, e.g. combining local details from forms, letters, and electronic records such as Eclipse, FACE, SAMS, and BadgerNet, with centralized ISD figures, to permit verification. This would have the advantages of allowing clinicians to compare their findings with what official sources indicate, and give an estimate of issues such as adherence over time.

Such data linkage and cross-checking, while time-consuming, would foster confidence in the level of detail achieved for statistical analysis. While it would not allow access to information such as maternal and fetal genotype, nor the exact level of fetal exposure to drugs, nevertheless, it would permit better confirmation of whether drugs prescribed and dispensed were actually, at what doses, when, and how consistently. Estimates of adherence during pregnancy are generally fairly high (although findings and conclusions are affected by a variety of methodological issues, such as non-representative populations, e.g. >80% reporting a planned pregnancy), but some studies suggest that up to half of pregnant women prescribed psychotropics may not take medication as prescribed, especially those with more severe depressive symptoms (Bosman *et al.*, 2014; Lupattelli *et al.*, 2015). Critically, it would also be possible to establish exact gestation at each data timepoint, a necessary prerequisite to define exposure type, but one that is challenging to achieve retrospectively from large databases (Margulis *et al.*, 2015). While some have simply assumed a uniform duration for all pregnancies, it is clear that the majority of pregnancies will not last exactly 280 days, and this can lead to inaccuracies in defining exposure, as discussed and illustrated in our AMU sample, affecting 25% of those for whom actual gestational age at birth could be calculated (Chapters 4 and 5).

As noted above, future research also needs to use specific exposures and outcomes, as it cannot be assumed that even the same antidepressant, at the same dose, for the same duration, and for the same indication, will be associated with the same outcome(s) in different women. Moreover, as many of the existing studies simply report categorical outcomes for group exposures, it is critical that these are teased apart. For example, despite the methodological robustness of Oberlander *et al's* 2008 study, it is imperative to note that almost 40% of the women in their sample were exposed to Paroxetine, indicating that their findings and conclusions are not necessarily relevant to patients attending the MLS now, when Paroxetine is scarcely used.

Another challenge in observational studies of perinatal exposures and outcomes is that many are either very common or extremely rare, and therefore large numbers are required to establish statistically significant relationships. While

this is true in the general population, the enriched samples in the PMHS and the MLS afford opportunities to explore more specific and exaggerated exposures and outcomes, while accounting for known confounders to some extent, using appropriate multivariate analyses.

One final factor of note is that while short term health outcomes have been relatively straightforward to study, longer term consequences, and particularly non-health outcomes, may be less specific and/or easy to establish, e.g. suicide, criminality, academic/vocational achievement, fertility, etc.

Comprehensive exploration of these factors requires follow-up over decades, and extensive linkage across "electronic patient records and other population-based datasets", e.g. social, criminal justice, and educational databases, with all the associated practical and ethical challenges. The Farr Institute @ Scotland (www.farrinstitute.org, formerly the Scottish Health Informatics Programme) has the potential to contribute to this aspiration, although it is yet early in its inception (Pavis & Morris, 2015).

Future research proposals

In light of this several future directions for research emerge.

Firstly, scanning. Despite the barriers we experienced in completing our pilot, we noted with interest that Dr Michael Craig, Senior Lecturer in Reproductive and Developmental Psychiatry at Kings College London, received funding to conduct a similar MR study based on virtually identical hypotheses; that prenatal depression is a risk factor for structural and functional abnormalities in limbic brain regions (Craig, 2015). Collaboration and sharing our experience may prove fruitful.

Secondly, it appears wise to repeat and extend our retrospective analyses in the MLS, by including more patients over several years to confirm our findings,

further refining our methodology, and exploring reasons for admissions to the NNU in more detail.

Thirdly, it would be relevant to characterise reasons for admission to the NNU in the general population, both to provide a context in which to place the MLS findings, and to fill the gap in the literature – we were unable to find a recent paper addressing this.

However, it must be acknowledged that these plans cannot address one of the most important questions; what are the long term consequences of exposure to antenatal depression and/or antenatal antidepressants?

While the gold standard would be to undertake a prospective cohort study, this would be costly in terms of years, resources, and finances. A more efficient option would be to mine the ALSPAC data.

The Avon Longitudinal Study of Parents and Children (ALSPAC, www.bristol.ac.uk/alspac/) began in the early 1990s, and has collected a wide range of health, social, and other data for over 14,000 mothers and their children since. It is "the most detailed study of its kind in the world", with over 1000 academic publications, and we have confirmed that it would be possible to access their dataset retrospectively to establish details of antenatal depression and medication, and maternal and child outcomes, in addition to key known confounders (Appendix 17). Although at one point we considered incorporating ALSPAC data into our research, we were advised that this proposal would merit a doctoral project in its own right. We will prepare the groundwork for this, and apply for funding, in anticipation of identifying a suitable researcher.

However, our aspiration is to set up a prospective cohort study, initially within the MLS, and thereafter in the AMU. The ultimate goal is a Scotland- or UK-wide register of antenatal exposure to depression and antidepressants, modeled on the successful UK Epilepsy and Pregnancy register, which has yielded valuable information on the risks of antenatal anticonvulsants (www.epilepsyandpregnancy.co.uk/home.htm). This will involve reviewing the

processes surrounding the assessment and review of patients attending the MLS, and revising the data collection form to ensure that all relevant details are captured in an unambiguous way. Moreover, to prevent forms from being left uncompleted or incomplete, we are considering the possibility of devising a bespoke perinatal assessment template, thus ensuring both that clinical assessment and documentation are comprehensive, and that all details relevant to our research questions are collected and updated at each contact. In addition to this being a paper proforma, it is possible that an electronic FACE template could be produced, which would facilitate efficient automated data extraction into an Excel® spreadsheet for ease of analysis. This would allow data linkage via CHIs.

Making prospective data collection part of routine clinical practice within the MLS can be justified on the grounds of providing and evidencing excellent care, and will provide an accurate and accessible resource for answering some key research questions. In particular, establishing the practice of regular and routine self-rating of symptoms via validated rating scales may inform management through monitoring illness severity and response to treatment, and facilitate timely decisions about interventions. Although well-established in clinical psychology, the use of mood diaries in unipolar depression to monitor response to medication has not been well-studied. Notwithstanding, there is significant face validity in employing rating scales as an adjunct to clinical assessment, and some hold that involving patients in their own care is empowering, and likely to lead to better outcomes (Bauer *et al.*, 2006). Therefore, asking the MLS patients to complete a mood rating scale every two or four weeks would help to establish data on the longitudinal course of their symptoms in relationship to treatment, and provide sufficient detail to allow a more nuanced analysis of the relationships between illness, treatment, and outcomes.

Diagnosing depression is difficult, as it defies decisive definition. However, as numerous studies indicate that whatever "depression" rating scales are measuring antenatally, it correlates with perinatal outcomes, we propose that alongside 'care as usual' in the MLS, with clinical diagnoses and treatment decisions, one or more outcome measures be routinely employed (Steer *et al.*,

1992). Ideally, in addition to being valid, these should be both brief and patient-completed. While evidence exists to support the use of most available rating scales outwith pregnancy, Ji *et al's* (2011) findings indicate that interpretation must be intelligent, and Parker *et al*. (2015) advise against imposing cut-off points on continuous measures. Scores derived from rating scales should therefore be analysed as a continuous predictor variable, rather than categorical. Although the PHQ-2 (Patient Health Questionnaire-2, the two questions recommended by NICE and coded on Eclipse) and the EPDS are perhaps the most sensitive screening tools for antenatal depression, it is not clear which rating scales are best for gauging severity and/or most sensitive to change in response to medication (Austin *et al.*, 2011). Therefore, we propose a systematic review of studies on depression rating scales in pregnancy, with particular reference to their properties in rating severity and sensitivity to change. Meantime, continuing to use the HADS appears reasonable.

Measuring depression and describing medication in detail during pregnancy, and linking with obstetric and paediatric outcomes, will help to establish a potentially fruitful research culture and effort within the MLS, enhancing clinical care. However, the patients attending the MLS are not representative of the general population. (They are, of course, representative of pregnant women with depression and/or prescribed antidepressants requiring psychiatric care.) As not all mums-to-be exposed to depression or antidepressants in Ayrshire are referred to or seen via the MLS, it is important to consider what further research would be desirable and feasible within AMU, with the potential for extension to the rest of Scotland and the UK once methodology, infrastructure, and funding are established. This is where our proposal regarding an Ayrshire Register of Depression and Antidepressants in Pregnancy is relevant, and again, this will involve a considerable investment of time, money, and resources. It is therefore best taken forward by a dedicated and appropriately funded research team, rather than relying on full time clinicians, although the lessons learned from and experience with the MLS research will provide a key foundation. Following the completion of our current programme of research, we plan to work towards such an undertaking in Ayrshire

Until then, as per guidelines, we recommend that all women booking at AMU are screened for depressive symptoms using the PHQ-2 (or the EPDS), and that any for whom there are concerns, and/or any on antidepressants, are referred to or discussed with the MLS.

Conclusions

This thesis describes the background to, findings of, and conclusions from a series of pilot studies exploring the characteristics and consequences of antenatal exposure to SSRIs, and related factors. Chapter 1 provides an overview of some key issues pertaining to perinatal depression. Chapter 2 gives Chapter 3 outlines the characteristics of antenatal psychiatric medication in a regional specialist mental health service, with Chapter 4 describing complementary findings in general and local specialist settings. Chapter 5 highlights certain outcomes associated with exposure to antenatal depression and antidepressants, and Chapter 6 discusses key methodological issues in using "big data" to investigate perinatal outcomes and exposures. Chapter 7 presents challenges in neuroimaging structural sequelae in infants exposed *in utero*. This chapter provides a synthetic summary of key findings, and proposals for future research.

Antenatal depressive symptoms and illness are common, as are antenatal antidepressants, taken by nearly one in 10 pregnant women in the local Scottish population. Exposure to either depression or antidepressants is associated with diverse adverse outcomes for mothers and babies, but much remains unknown, particularly the long term sequelae. While current clinical guidelines provide apposite and sage recommendations on the basis of the available evidence, further research is needed to confirm detailed characteristics of both antenatal depression and antidepressants, and their consequences. The retrospective interrogation of population-based datasets has hitherto yielded much illumination, yet there remains a significant need for more comprehensive, detailed, and accurate information on which to base the information available to pregnant women, and the care they receive. Intentional prospective longitudinal

clinical data collection has an important role to play in ensuring that we continue to help mothers, while caring for their babies.

Appendix 1 – Systematic review search strategy

Database	Strategy	Date searched	Results
Medline & Embase (SSRIs)	Database: Ovid MEDLINE(R) 1946 to Present with Daily Update, Embase <1974 to 2016 October 07> Search Strategy: --- 1 "selective serotonin reuptake inhibitors".mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw, fs] (15258) 2 "Serotonin and Noradrenaline Reuptake Inhibitors"/ (4622) 3 Serotonin Uptake Inhibitors/ (58591) 4 serotonin noradrenalin reuptake inhibitor/ (4539) 5 serotonin uptake inhibitors/ (58591) 6 citalopram/ or fluoxetine/ (63464) 7 Fluvoxamine/ (13908) 8 Paroxetine/ (28850) 9 Sertraline/ (25059) 10 (citalopram or cipramil).ti,ab. (10018) 11 (dapoxetine or prilegy).ti,ab. (412) 12 (escitalopram or cipralex).ti,ab. (4800) 13 (fluoxetine or prozac or oxactin).ti,ab. (23682) 14 (fluvoxamine or faverin).ti,ab. (5440) 15 (paroxetine or seroxat).ti,ab. (11525) 16 (sertraline or lustral).ti,ab. (8668) 17 ssri.ti,ab. (12886) 18 sri.ti,ab. (14001) 19 ssris.ti,ab. (14044) 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (145561) 21 pregnan*.ti,ab. (911901) 22 exp Pregnancy/ (1514688) 23 Pregnant Women/ (59352) 24 exp pregnancy/ (1514688) 25 pregnant woman/ (74025) 26 womb.ti,ab. (1518) 27 fetal.ti,ab. (456149) 28 exp Fetus/ (341613) 29 fetus/ (267489) 30 foetal.ti,ab. (34371) 31 Prenatal Exposure Delayed Effects/ (41776) 32 prenatal exposure/ (44025) 33 ant*natal.ti,ab. (61688) 34 per*natal.ti,ab. (130630) 35 pr*natal.ti,ab. (166818) 36 "in utero".mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw, fs] (52142) 37 intr*uterine.ti,ab. (100138) 38 fetus.ti,ab. (125716) 39 foetus.ti,ab. (13488) 40 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (2143160) 41 exp Great Britain/ (335856) 42 (national health service* or nhs*).ti,ab,in. (300770) 43 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (50100) 44 (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in. (4035796) 45 (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or	10/10/16	485

	ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in. (2847979) 46 (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in. (112223) 47 (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in. (402187) 48 (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in. (51324) 49 or/41-48 (4882671) 50 (exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp great britain/ or europe/) (5137913) 51 49 not 50 (4614740) 52 United Kingdom/ (609021) 53 (national health service* or nhs*).ti,ab,in,ad. (347509) 54 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (50100) 55 (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in,ad. (4087026) 56 (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad. (2865308) 57 (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad. (112799) 58 (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad. (404171) 59 (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad. (51518) 60 or/52-59 (5007306) 61 (exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (united kingdom/ or europe/) (3589895) 62 60 not 61 (4787301) 63 51 or 62 (4842059)		

	64 20 and 40 and 63 (637) 65 remove duplicates from 64 (538) 66 limit 65 to english language (525) 67 limit 66 to human (485) 68 limit 67 to humans (485)		
Cochrane (SSRIs)	ID Search Hits #1 "selective serotonin reuptake inhibitors":ti,ab,kw (Word variations have been searched) 1566 #2 MeSH descriptor: [Serotonin and Noradrenaline Reuptake Inhibitors] explode all trees 1 #3 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees 2660 #4 MeSH descriptor: [Fluvoxamine] explode all trees 371 #5 MeSH descriptor: [Paroxetine] explode all trees 827 #6 MeSH descriptor: [Sertraline] explode all trees 721 #7 (citalopram or cipramil):ti,ab 1035 #8 (dapoxetine or prilegy):ti,ab 48 #9 escitalopram or cipralex:ti,ab,kw (Word variations have been searched) 958 #10 (fluoxetine or Prozac or oxactin):ti,ab 2420 #11 (fluvoxamine or faverin):ti,ab 676 #12 (paroxetine or seroxat):ti,ab 1834 #13 (sertraline or lustral):ti,ab 1482 #14 ssri:ti,ab 1157 #15 sri:ti,ab 370 #16 ssris:ti,ab 837 #17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 9375 #18 pregnan*:ti,ab 21005 #19 MeSH descriptor: [Pregnancy] explode all trees 6437 #20 MeSH descriptor: [Pregnant Women] explode all trees 131 #21 womb:ti,ab 174 #22 (fetal or foetal):ti,ab 5427 #23 MeSH descriptor: [Fetus] explode all trees 1657 #24 MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees 301 #25 ant*natal:ti,ab 2131 #26 per*natal:ti,ab 2642 #27 pr*natal:ti,ab 1973 #28 intr*uterine:ti,ab,kw (Word variations have been searched) 3009 #29 pr*natal:ti,ab 1973 #30 (fetus or foetus):ti,ab 1300 #31 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 30290 #32 #17 and #31 53 #33 MeSH descriptor: [Great Britain] explode all trees 6368 #34 (uk or gb or nhs):ti,ab,pt 11279 #35 "national health service" 2519 #36 (England or Scotland or Ireland or wales):ti,ab,pt 4917 #37 #33 or #34 or #35 or #36 20928 #38 #32 and #37 3	10/10/16	3
Web of Science (SSRIs)	# 10 **99** #8 AND #4 **Refined by:** **COUNTRIES/TERRITORIES:** (IRELAND OR SCOTLAND OR ENGLAND OR WALES) *Timespan=All years* *Search language=Auto* Select to combine sets. Select to delete this set. # 9 **1,529** #8 AND #4 *Timespan=All years* *Search language=Auto* Select to combine sets. Select to delete this set. # 8 **386,258** #7 OR #6 OR #5 *Timespan=All years* *Search language=Auto* Select to combine sets. Select to delete this set. # 7 **13,790** **TOPIC:** ("in utero") *Timespan=All years* *Search language=Auto* Select to combine sets. Select to delete this set.	11/10/16	99

	# 6 **118,986** **TOPIC:** (pr*natal or ant*natal or per*natal or intr*uterine) *Timespan=All years* *Search language=Auto* — Select to combine sets. Select to delete this set. # 5 **351,576** **TOPIC:** (pregnan* or womb or fetal or foetal or fetus or foetus) *Timespan=All years* *Search language=Auto* — Select to combine sets. Select to delete this set. # 4 **35,426** #3 OR #2 OR #1 *Timespan=All years* *Search language=Auto* — Select to combine sets. Select to delete this set. # 3 **19,938** **TOPIC:** (citalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or cipramil or dapoxetine or prilegy or escitalopram or cipralex or prozac or oxactin or faverin or seroxat or lustral) *Timespan=All years* *Search language=Auto* — Select to combine sets. Select to delete this set. # 2 **116** **TOPIC:** ("serotonin and noradrenaline reuptake inhibitors") *Timespan=All years* *Search language=Auto* — Select to combine sets. Select to delete this set. # 1 **22,088** **TOPIC:** ("selective serotonin reuptake inhibitors") ***OR*** **TOPIC:** ("serotonin uptake inhibitors") ***OR*** **TOPIC:** (SSRIs or SRI or SSRI) *Timespan=All years* *Search language=Auto*		
TRIP (SSRIs)	("selective serotonin reuptake inhibitors" or "serotonin uptake inhibitors" or citalopram or cipramil or dapoxetine or prilegy or escitalopram or cipralex or fluoxetine or prozac or oxactin or fluvoxamine or faverin or paroxetine or seroxat or sertraline or lustral or ssri or ssris or sri) AND (pregnan* or womb or fetal or foetal or fetus or foetus or prenatal or antenatal or perinatal or "in utero" or intrauterine) AND (uk or "united kingdom" or gb or "great britain" or england or scotland or ireland or wales)	11/10/2016	366 (0 selected)
Opengrey (SSRIs)	("selective serotonin reuptake inhibitors" OR "serotonin uptake inhibitors" OR citalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR cipramil OR dapoxetine OR prilegy OR escitalopram OR cipralex OR prozac OR oxactin OR faverin OR seroxat OR sertraline OR lustral OR ssri OR sri OR ssris) AND (pregnan* OR womb OR fetal OR foetal OR fetus OR foetus OR prenatal OR antenatal OR perinatal OR "in utero" OR intrauterine) AND (uk OR gb OR "united kingdom" OR "great britain" OR scotland OR engalnd OR ireland OR wales)	11/10/2016	3 (0 selected)
PROSPERO (SSRIs)	#1"selective serotonin reuptake inhibitors" or "serotonin uptake inhibitors" 38 #2MeSH DESCRIPTOR Serotonin Uptake Inhibitors EXPLODE ALL TREES 15 #3MeSH DESCRIPTOR Serotonin and Noradrenaline Reuptake Inhibitors EXPLODE ALL TREES 1 #4citalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or cipramil or dapoxetine or prilegy or escitalopram or cipralex or prozac or oxactin or faverin or seroxat or sertraline or lustral 59	11/10/2016	23

	#5ssri or ssris or sri 146 #6#5 OR #4 OR #3 OR #2 OR #1 182 #7pregnan* 1793 #8MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES 882 #9MeSH DESCRIPTOR Pregnant Women EXPLODE ALL TREES 9 #10womb or fetal or foetal or fetus or foetus 528 #11ant*natal or per*natal or pr*natal or intr*uterine 718 #12"in utero" 55 #13#12 OR #11 OR #10 OR #9 OR #8 OR #7 2125 #14#6 AND #13 23		

Appendix 2 – PMHS data collection form

GLASGOW PERINATAL SERVICE - PATIENT INFORMATION FORM

Affix label here

Name: _____ Date seen: _____

D.O.B: _____ Maternity Hospital: _____

Hosp No: _____ Consultant Obstetrician: _____

Source of referral
☐ GP ☐ Maternity Service
☐ Health Visitor ☐ Social Work
☐ Primary Care MH Team ☐ General Psychiatric Service
☐ Other, please specify _____

Where seen
☐ OPD ☐ Ante/postnatal ward
☐ Home ☐ Other

Pregnant?
☐ Yes *If yes*: **E.D.D.** _____
☐ No **Intending to breast feed?** ☐ Yes ☐ No

Child less than 1 year old?
☐ Yes *If yes*: **D.O.B.** _____
☐ No **Breast feeding?** ☐ Yes ☐ No

Previous ante/post natal psychiatric contact? ☐ Yes ☐ No

Previous ante/post natal GP contact for psychological treatment? ☐ Yes ☐ No

Previous non-pregnancy related psychiatric contact? ☐ Yes ☐ No

Smoking usual: _____ during preg./breastfeeding: _____

Alcohol use (units/week) usual: _____ during preg./breastfeeding: _____

Drug use usual: _____ during preg./breastfeeding: _____

Other professionals involved in care
Community Midwife: _____
Health Visitor: _____
Social Work: _____
Other: _____

ICD10 diagnosis - initial assessment
F ☐☐.☐☐☐ (main) _____
F ☐☐.☐☐☐ (add.) _____

ICD10 diagnosis- discharge
F ☐☐.☐☐☐ (main) _____
F ☐☐.☐☐☐ (add.) _____

NB: Please complete medication record (overleaf) for early pregnancy, initial and each subsequent visit

GLASGOW PERINATAL SERVICE - INITIAL & FOLLOW-UP VISIT PATIENT MEDICATION FORM

Date	Pregnant Y/N	***Breast Feeding*** Y/N	***Medication 1*** (total daily dose)	Medication 2 (total daily dose)	***Medication 3*** (total daily dose)	***Medication 4*** (total daily dose)
Conception/ early preg.						
If medication stopped during pregnancy – when? (weeks)						
Initial visit						
Infant outcome – neonatal						
Infant outcome – 3-6 month						

Please record all medications (not only psychotropic) and total daily dose

Appendix 3 – Psychotropics

BNF Section	Category	Class	Drug	Dose range (daily)[1]
4.2.1 and 4.2.2	Antipsychotics	Typical	Benperidol	0.25-1.5mg
		Typical	Chlorpromazine	75-1000mg
		Typical	Flupentixol	1-18mg
		Typical	Haloperidol	1-30mg
		Typical	Levomepromazine	25-1000mg
		Typical	Pericyazine	75-300mg
		Typical	Perphenazine	12-24mg
		Typical	Pimozide	2-20mg
		Typical	Prochlorperazine	15-100mg
		Typical	Promazine	400-800mg
		Typical	Sulpiride	400-2400mg
		Typical	Trifluoperazine	10-15mg
		Typical	Zuclopenthixol	20-150mg
		Atypical	Amisulpride	400-1200mg
		Atypical	Aripiprazole	10-30mg
		Atypical	Clozapine	200-900mg
		Atypical	Olanzapine	10-20mg
		Atypical	Palperidone	3-12mg
		Atypical	Quetiapine	300-800mg
		Atypical	Risperidone	2-16mg
4.2.3 (see also 4.8.1)	Mood stabilisers	-	Carbamazepine	200-2000mg
		-	Valproate	600-2500mg
		-	Lithium	As per serum level
4.3	Antidepressants	TCA	Amitriptyline	10-200mg
		TCA	Clomipramine	10-250mg
		TCA	Dosulepin	75-225mg
		TCA	Doxepin	75-300mg
		TCA	Imipramine	75-300mg
		TCA	Lofepramine	140-210mg
		TCA	Nortriptyline	10-150mg
		TCA	Trimipramine	50-300mg
		TCA-related	Mianserin	30-90mg
		TCA-related	Trazodone	150-600mg
		MAOi	Phenelzine	45-90mg
		MAOi	Isocarboxazid	30-60mg
		MAOi	Tranylcypromine	20-30mg
		RIMA	Moclobemide	300-600mg
		SSRI	Citalopram	10-40mg
		SSRI	Escitalopram	5-20mg
		SSRI	Fluoxetine	20-60mg
		SSRI	Fluvoxamne	50-300mg
		SSRI	Paroxetine	10-60mg
		SSRI	Sertraline	50-200mg
		SNRI	Duloxetine	60-120mg
		NaSSA	Mirtazapine	15-45mg
		NARI	Reboxetine	8-12mg
		SNRI	Venlafaxine	75-375mg
4.8.1	Antiepileptics	-	Lamotrigine	100-500mg

[1] oral doses licensed in adults, for various indications including psychotic, affective and neurotic disorders

Appendix 4 – MLS data collection form

Demographic details

Research identifier	DOB
Postcode	Ethnic background

Personal and Family Psychiatric History

ICD-10 Diagnoses		Family Psychiatric History – including partner
Age at first onset illness		
Total no. Past Psych admissions	Of these No. admissions within 6 months postnatal	Index pregnancy admissions Prenatal Postnatal

Obstetric details

LMP	EDD by scan	Booking BMI	Booking Date
Gestation at Psych contact		Parity	
Obstetric complications (past and current)		Past medical history with dates	
Obstetrician/Midwife/Hospital			

Alcohol, Nicotine and Substance Use

	Before conception	Periconception	During Pregnancy	Potnatal
Alcohol				
Smoking				
Recreational drugs/ 'Legal Highs' /OTC Medicines				

Periconception, Pre and Postnatal Pharmacological Management

Drug	Dose	Frequency	Date started	Date stopped/changed & Reason for change

Delivery, Neonatal and Postnatal details

Date delivery	Gestation at delivery			Sex
Mode delivery	Birth weight (kg)			
Delivery complications	Birth length (cm)			
	If on Psychotropics during pregnancy attach copy of withdrawal scoring sheet			
Postpartum complications	APGAR	1min	5min	10min
	Breastfeeding dates			

Maternal Mental State

Timing of review	Mental State (well/ exacerbation/ ICD-10 relapse/admission, state rating scale score)
Date	
Date	
Date	
Date	

Appendix 5 – Defining the trimesters of pregnancy

The trimesters of pregnancy have no agreed definition, and are used for convenience to stage a continuous process. Apart from the brain, organs are largely complete by the end of the first trimester, with growth and maturation characterising the second and third trimesters. Pregnancy is defined as lasting 280 days (normal range 260-294) from the first day of the last menstrual period, and we took the timing of the trimesters to be as follows:

Days	Weeks	Trimester
1-7	1	1
8-14	2	1
15-21	3	1
22-28	4	1
29-35	5	1
36-42	6	1
43-49	7	1
50-56	8	1
57-63	9	1
64-70	10	1
71-77	11	1
78-84	12	1
85-91	13	1
92-98	14	2
99-105	15	2
106-112	16	2
113-119	17	2
120-126	18	2
127-133	19	2
134-140	20	2
141-147	21	2
148-154	22	2
155-161	23	2
162-168	24	2
169-175	25	2
176-182	26	2
183-189	27	3
190-196	28	3
197-203	29	3
204-210	30	3
211-217	31	3
218-224	32	3
225-231	33	3
232-238	34	3
239-245	35	3
246-252	36	3
253-259	37	3
260-266	38	3
267-273	39	3
274-280	40	3
281-287	41	3
288-294	42	3

Appendix 6 - Information leaflet

New baby on the way?

Congratulations!

Can you help with an important study to benefit mothers & babies?

We'd like to hear from you if you have taken an **antidepressant**, or had **clinical depression** at any point during pregnancy

To find out more, contact **Dr Everett Julyan**

- info@helpingmums.org.uk
- www.helpingmums.org.uk
- call/text 07985 956997

What is the research?

We are looking for any effects of antidepressants on baby development. We need help from mums-to-be who are keeping well, as well as those who are clinically depressed, and those taking antidepressants.

Around 1 in 10 women become ill with depression during pregnancy. Sometimes they need to take an antidepressant medicine. We know that antidepressants can really help mums-to-be, but we want to make sure that they are safe for their baby.

We will give babies in our study a check-up with an MRI scan to see how their brains are developing.

What does it involve?

1. Speaking to a researcher about your health during pregnancy. This usually takes no more than 1 hour.
2. Speaking to a researcher again 1 month and 4 months after your baby is born. Baby will have an MRI scan at these times, too. The whole thing is likely to take 2-3 hours.

Other things you may be wondering about:

- MRI scans are safe for babies
- There is no anaesthetic
- Transport will be provided if you need it
- You can withdraw from the study at any time
- The study has ethical approval
- There are no drug companies involved

Everett will be really happy to tell you more about the project and to answer your questions. Please do get in touch or speak to your midwife.

Version 1
1 October 2009

Helping mums, caring for babies

Information

about the MRI scan

Please read carefully

Version 1 - 1 October 2009

Where to come

- Institute of Neurological Sciences, Zone 3, Southern General Hospital (see accompanying map on page 5).
- Turn right after entering the building, and enter the Department of Neuroradiology (next to Aroma coffee).
- Call/text Everett on 07985 956997 or ask at the reception desk - I'll be expecting you.

When to come

- Please try to come around 9:30am.
- Let me know if you need transport.
- If you need a parking space, please call/text Everett on 07985-956997 when you arrive.

What to bring

- Please bring a swaddling blanket.
- MRI uses magnets, so baby's clothes musn't have any metal poppers or fasteners.
- We will provide clean clothes and blankets if you don't have anything suitable.
- Please bring nappies and wipes.
- If baby is bottle-fed, please bring a feed with you.
- As the scan room can feel cool, please bring a cardigan or jumper for yourself.
- You may want to bring something to read during the scan.

Feeding and sleeping

- It's great if baby can come to the scan hungry and tired!
- Then baby can feed and go to sleep.
- This is because we need baby to stay still during the scan to get the best pictures we can.
- So please try to keep baby awake when coming to the scan.
- If baby sleeps on the way to hospital, we might not be able to do the scan.
- If baby wants fed before coming to the Southern, please try to give a half feed, saving the rest for just before the scan.

What actually happens?

- We'll meet you, and go to a room next to the MRI scanner.
- We'll check that it's OK to do the scan.
- We'll give baby a check-up, by asking about feeding and sleeping, and by measuring head circumference.
- Baby's nappy and clothes can be changed (if necessary).
- We'll use ear pads and a hat for baby, to keep him/her warm and to keep things quiet for sleeping.
- Baby can then be swaddled and fed.
- When baby is sleeping, he/she can go in the MRI scanner.
- The scan will take around 45 minutes to 1 hour to complete, and we may have to pause or stop if baby moves.
- During the scan you can stay in the room with baby or be nearby while speaking to one of us.
- We will keep a close eye on baby during the scan to make sure that everything is OK, including heart rate.
- It's natural to feel a bit anxious during the first scan.
- If you have any questions at any time, just ask.
- After the scan we will send the data to one of our specialist colleagues for checking.

Information about MRI scans

- MRI stands for Magnetic Resonance Imaging.
- MRI produces images of the inside of the body without using X-rays.
- It works by using a strong magnet, radio waves and a computer.
- You will be asked to complete a safety checklist for baby.
- You will be asked to complete the safety checklist, too.

Please note that the department does not have childminding facilities

Contact details

Web www.helpingmums.org.uk

Email info@helpingmums.org.uk

Tel 07985-956997

Institute of Health & Wellbeing
College of Medical, Veterinary & Life Sciences
University of Glasgow
Sackler Institute of Psychobiological Research
Southern General Hospital
Glasgow G41 5TF

in association with

Version 1 - 1 October 2009

Appendix 8 – Information sheet

MRI STUDIES OF INFANTS EXPOSED PRENATALLY TO DEPRESSION AND ANTIDEPRESSANTS

INFORMATION SHEET Version 4 20/04/09

We are asking you to help with research that is being carried out by the University of Glasgow and NHS Greater Glasgow & Clyde. The research project aims to explore whether there are any effects of depression and antidepressant medication on the developing brain and on behaviour in babies.

What we are asking you to do

We would like to review your clinical records, carry out a clinical interview, **measure your baby's heart rate** and do some psychological tests during your pregnancy. Once baby is born we would like to carry out a brain scan on your baby at aged 1 month and again at 4 months. The type of brain scan is MRI.

In order to decide whether or not you wish to enroll yourself and your child, you should know about the risks and benefits of participating. This information sheet provides the essential details about this project. If you would like to know more, a member of the research team will also discuss the project with you and answer any of your questions about the project. This discussion will go over all aspects of the study, including its purpose, its procedures, any risks of participating, the potential benefits of participating. Once you understand the study, you will be asked if you are willing to enrol yourself and the baby in the study. If so, you will be asked to sign a consent form.

Alternatives to Participation

You do not need to participate in this research. The information gathered in this study is for research purposes and is not intended to guide the care for you or the infant.

Description of Procedures

The study will be conducted following your antenatal visit and at the Southern General Hospital in Glasgow (or other location suitable to you). There is no treatment involved for you or the baby. Information is being collected for research purposes only.
The project is a 2-year study.

1) Clinical information, gathered through personal interviews, will address your medical, emotional, and medication-use history.
2) Physical examination, neurological evaluation, and MRI scan of the baby 1 month and 4 months after birth.
3) Standardized developmental and psychological tests will be administered to you and your baby at each visit. We will also observe your baby's behaviours.

1. Your Clinical Interviews, Baby's Heart Rate & Psychological Tests
This set of interviews generally takes no more than 2 hours. Questions will be asked about your medical and emotional history, family life, support systems, relationships, parenting beliefs and practices, and history of medication use. In addition, we are requesting permission to review the clinical and hospital charts for you and the baby.
We would also like to measure baby's heart rate. This will be done using a non-invasive monitor (Monica AN24), consisting of a unit the size of an MP3 player worn around your neck with 5 leads attached to your tummy. This can be done while the other assessments are being made.

2. The Baby's MRI Scan

At aged 1 month, the baby will receive a physical, neurological, and behavioural examination that will take about 40 minutes. At a time that is convenient for you and the baby, you and the baby will be escorted to the MRI scanner. A member of the research team will explain the MRI procedure in detail before the scan and will be present throughout the entire scan. A paediatrician will also be present with the baby throughout the entire scan.

The baby's breathing and heart rate will be monitored throughout the scan. This is done to ensure the complete safety of the baby during the scan, and not because the scan will affect the baby's heart or breathing in any way. We will also give the baby earplugs as well as earmuffs to help dampen the sound of the scanner and be sure that the baby can sleep soundly through the scan. You will then feed and swaddle the baby, and together with the study team, we will move the baby while sleeping into the scanner.

For the MRI scan, the baby will lie on a padded table that moves into a doughnut-shaped magnet. The baby is unlikely to feel any discomfort at all during the scan, although the machine can be noisy during the scan. The noises are usually knocking or buzzing sounds, which the ear muffs will help to dampen for the baby. This knocking is the magnet taking pictures. We will give you ear plugs to block out most of the noise as well. You, the technologist operating the scanner, and the paediatrician will be able to see the baby during the scan, and we will all be able to hear if the baby wakes up and cries. You may stay in the room with the baby during the entire scan, which will take approximately 60 minutes once the scan begins. If you decide that you do not want to be in the room during the scan, you are welcome to bring a friend or family member to sit in the room with the baby.

Within 1 month of the MRI scan, the scan will receive a clinical reading and any significant results will be shared with you and a physician of your choice.

For the second scan, we will contact you when baby is just about to turn 4 months.

Scanning the baby twice will allow us to see the growth and development of the baby's brain as it changes during the first year of life. The procedure for the rescan will be exactly the same as that of the first scan. The second scan will take approximately 60 minutes. You can be with the baby in the scan room.

Risks and Inconveniences

Clinical Interviews & Examinations: The risks of the interviews (for you), neuropsychological testing (for you and the child), and physical examinations (for the baby) are few. These procedures do take time to complete, so we have built in short breaks to minimize fatigue. You can stop at any time, and we can offer the sessions in 2 appointments if you so desire. You do not have to answer all questions if they make you uncomfortable.

MRI: The long-term effects of being placed in a magnet of this strength (3 Tesla) are unknown, but you should be aware that there have been no reports of any ill long-term effects caused by magnets of the same or even higher strength. Except for people who have some types of metallic implants, we know of no health hazard from the MRI scan. The scan can be noisy, and so we will provide ear plugs and ear muffs for your baby to reduce that noise level. If he or she cries, the scan will be interrupted and the baby will be attended to immediately. You and the study team, or a person of your choice will remain with the baby throughout the entire scan to ensure optimal comfort. The additional scan does not put the baby at greater risk. The risk is the same as with the first MRI scan.

Benefits

The MRI pictures, clinical interviews, physical examinations, and neuropsychological tests are unlikely to be of direct benefit to you or the child. While MRI scans are sometimes done for clinical purposes, the kind of MRI scan you will have as part of this study is for research purposes only. Nevertheless, these scans will be checked by a consultant radiologist and if any clinically significant findings happen to be detected on the MRI scan, or if we detect clinically significant findings on the neuropsychological tests or clinical interviews regarding you or the child's psychological well-being, we will provide you with that information and appropriate referrals will be made for treatment. Finally, the findings of this study could add to our understanding of the effects that exposure to illness or medication during pregnancy has on brain development, and this knowledge could one day benefit other children in similar situations.

Confidentiality

Information obtained in this study, as well as information from the baby's hospital chart review, is strictly confidential unless the law requires disclosure. You will be assigned a research number, rather than your name, which will be recorded on data we collect about you and the baby. All of this data will be secured under lock and key. Your name will not be used in the reporting of information in publications or conference presentations.

Research Standards and Rights of Participants

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, neither you nor the child will lose any benefits to which you are otherwise entitled. A decision not to participate will not effect the treatment of you or the child in any way. Should you wish to consult an independent doctor further about this study.

Dr Michael Smith would be available at: Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE. Telephone 0141 884 5122

Appendix 9 - Assessment proforma

Helping mums, caring for babies

Personal details			
Date		Assessment	
Name		Code	
Address		DOB/CHI	
		Tel	
		Mobile	
Postcode		Email	
Employment		Marital status	
GP		Religion	
Referred by			
Pregnancy details			
EDD by scan		Current gestation	
Planned pregnancy		Breastfeeding plans	
Obstetrician		Midwife	
Hospital		Antenatal clinic	
Issues			
Current health			
Past medical history			

Past psychiatric history

Medication				
Drug	**Dose (mg)**	**Frequency**	**Commenced**	**Withdrawn**

Alcohol & substances			
Before conception	Periconception	During pregnancy	Postnatal

Family history

Appendix 10 - Assessment checklist

Helping mums, caring for babies

Checklist

Code

Visit	1	2	3	4
EDD				
Date (aim)				
Date (actual)				
Gestation (aim)	10-16	24-28	44	56
Gestation (actual)				
Consent				
Assessment				
SCID				
HRSD				
CAPS				
Stroop				
NART				
MRI				
DTI				
MRS				
fMRI				
Depressed during pregnancy?			When/how long?	
On SSRIs during pregnancy?			When/how long?	
Past history of depression?			No. of episodes	

Notes

Appendix 11 - Revised assessment checklist

Helping mums, caring for babies

Checklist

Code

Visit	1	2	3	4
EDD				
Date (aim)				
Date (actual)				
Gestation (aim)	10-16	24-28	44	56
Gestation (actual)				
Consent				
Assessment				
SCID				
BDI				
BAI				
LES				
fHR/fHRV				
MRI				
DTI				
MRS				
fMRI				
Depressed during pregnancy?			When/how long?	
On SSRIs during pregnancy?			When/how long?	
Past history of depression?			No. of episodes	

Notes

Appendix 12 - Visit to the Sackler Institute, Columbia University, New York, USA

Professor Jonathan Cavanagh (JC), Dr John McLean (JMcL), and Dr Everett Julyan (EJ) visited the Sackler Institute, Columbia University, New York, in September 2009, spending time with various collaborators over a three day period. Although we planned to observe a scan from start until finish, this proved impossible as the scanner was "down" pending maintenance. We were advised that we should expect this to be a common problem in Glasgow.

Despite this, it had been arranged that a participant would attend with her baby, and go through the entire process without scanning actually taking place, so that we could understand each stage. We learned that women were recruited via the New York-Presbyterian Hospital (NYPH), a university teaching hospital ranked among the top 10 hospitals in the USA (US News and World Report, 2015 http://health.usnews.com). It is affiliated with two Ivy League medical schools, Columbia and Cornell, and has over 2,400 beds, dispersed between a number of sites, including the Morgan Stanley Children's Hospital (MGCH), where the scanning took place. The MGCH serves a wide metropolitan area in Manhattan, including the deprived area of Harlem, from which many scanning subjects were recruited, especially those using prescribed and non-prescribed opiates during pregnancy.

MSCH obstetricians, midwives and paediatricians were involved in identifying potential participants antenatally, and women were offered an incentive of vouchers for baby products worth $100 to take part in the study. A battery of maternal assessments and rating scales were completed at least once during pregnancy, including a standard psychiatric history, the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I/NP), the Hamilton Rating Scale for Depression (HRSD), the Clinician-Administered PTSD Scale for DSM-IV (CAPS), the Stroop Test, and the National Adult Reading Test (NART).

Women were invited to attend with their babies between 43 and 46 weeks gestational age by scan, and to present at the research location between 9am and 10am. As neonates spend most of their time sleeping, punctuated by short periods of feeding and activity, women were advised to bring their babies hungry and tired, by keeping their babies awake from the time they woke up in the morning until arriving at the scanning suite, and unfed for at least 3 hours, with the expectation and intention that they would then be ready to feed, and then more likely to sleep during the scan. Our colleagues had one full time researcher dedicated to looking after the mothers and babies, in addition to support from radiographers, radiologists, physicists, paediatricians, other research staff, and administrative infrastructure. Moreover, they had daily access to a MRI scanner dedicated solely to research.

Prior to scanning, each mother was interviewed to update the assessments and rating scales, with a specific emphasis on prescribed and other drugs, and maternal mood, alongside general questions about her baby's health, development, feeding and sleeping. The infant's weight was noted, and both mother and baby had an MRI checklist completed, to ensure safety, with all ferromagnetic materials being removed at that point (mothers were encouraged to enter the scan room, and even stay with their little one throughout the scan if they wished). Babies had their diapers changed, were tightly swaddled, and had ear protectors fitted. They were then fed by breast or bottle, winded, and allowed to fall asleep, before being carried into the scan room and placed on the MR bed.

When the scanner was functional, various scan sequences to establish positioning, total brain volume, regional volumes, white matter integrity, and cell metabolism were completed, lasting 45-60 minutes. We were advised to expect babies to wake up frequently during the scans, particularly when moving from one sequence to another (heralded by periods of sudden silence, then a sudden change in noise pattern, often associated with a startle response from the babies). Our colleagues explained that they often set aside a whole day for each scan, and recommended that we plan for the same, including that we

retain the option to invite each mother back the following day if the scans had not been completed successfully.

JMcL then spent time with the physicists, clarifying their scanning protocols, and learning from their experiences of unsuccessful scans, technical challenges, and how to overcome these, while EJ practiced his swaddling technique under supervision. EJ was advised to "look after" the mothers and babies well, and to seek to be reassuring throughout the day of the scans, as most mothers would be anxious to some degree. It was thought particularly important to leave plenty of time for the scans, as working under the pressure of time would not be conducive to avoiding anxiety, and in particular to allow sufficient time to repeat sequences several times. There was also extensive discussion about the differences between the Columbia research, and that to which we were aspiring in Glasgow, and caution advised about the likely success of our endeavours, due to the significant disparity in resources. Our New York colleagues were uncertain about our ability to complete the proposed scanning, as EJ as the main researcher would be attempting the study in only 4 hours per week (Wednesdays 9am to 1pm) as part of "Supporting Professional Activities" time in his job plan as a fulltime NHS Consultant Psychiatrist, without dedicated research or administrative support. Similarly, JMcL would be the only physicist involved, and although we had input from colleagues in radiography, radiology, and midwifery, our resources were significantly less than those of our Columbia collaborators. Moreover, the MRI scanner we planned to use was an NHS unit, used for clinical healthcare in addition to research, and there would be no option to scan outwith the allotted slot, nor invite participants back the following day. Furthermore, we were advised to source accommodation and storage, for assessments, preparation, and equipment, as it was not clear if these would be available in Glasgow.

We discussed the best stage at which to scan, and were advised that as early as possible between 43 and 46 weeks gestational age by antenatal ultrasound scan was advisable, as this would allow us to compare findings between the USA and the UK, in addition to this being a stage at which babies were as likely as any to sleep throughout the scans. As babies tend to sleep in 40-45 minutes cycles we

learned that it was advisable to keep the combined scan sequences below this target duration, and/or to allow adequate time for breaks, and that we should be ready to start scanning as soon as the baby was soundly asleep. It was recommended that we change each baby before feeding, to avoid subsequent nappy changes waking him/her up, and to swaddle and secure ear protectors before feeding for the same reason. We were also advised to ask mothers to bring a cardigan for themselves in case they wanted to stay in the scan room throughout, as the ambient temperature is low due to the cryogenic agents used to optimise superconduction of the electromagnetic coils.

As any results and conclusions would be based on comparative findings between our three proposed study groups, we were also advised to scan each baby twice, to allow comparison of developmental trajectories, i.e. growth differences between each group. This would allow not only a snapshot of structural, tract and spectroscopy parameters in each group of subjects at one month, but also relative changes between each group, in addition to within each subject. We were recommended to consider rescanning at four months postnatally, ~56 weeks gestational age, as after this time contrast and discrimination are diminished in T1-weighted scans due to changes in the developing brain parenchyma, and also as infants become increasingly less likely to complete MR scans without anaesthesia beyond this age.

Other recommendations included obtaining paediatric advice and support, especially with regards to monitoring babies while in the MR scanner, via electrocardiography, oximetry, and temperature checking using neonate-appropriate equipment. Clinically competent staff should also be on hand, in case of unforeseen events or emergencies. To put mothers at ease we were advised to give as much detailed and specific information in advance as possible, including exactly what should/would happen on the day of the scan, including exactly who would be there, and also a tour of the scanning suite during antenatal assessment. We would need access to a suitable room in which to assess mums-to-be, as well as a space to use to prepare for the scans. MR-safe equipment would need to be provided (vests without metal fasteners, clothes, hats, blankets, and nappies), and wipes, bottle warmers, and beverages

available for mums, too. We would also require secure clean storage for our apparatus, and means of laundering and sterilising paraphernalia.

We were encouraged to consider what incentives we could offer potential participants, e.g. free samples or vouchers for baby items, or a print of one of the scans, and to think about what prospective follow-up we should put in place, to monitor long term clinically relevant outcomes. We were advised to review scans immediately, while mother and baby were still present, to ensure adequate scan data acquisition. Other suggestions included incorporating measures of antenatal and postnatal distress, via maternal rating scales and fetal/neonatal heart rate variability and salivary/urinary cortisol, and even maternal/fetal genotyping via cord blood, to take account of SERT and BDNF polymorphisms known to influence neurodevelopment.

We were advised to be alert to child abuse issues, e.g. shaken baby syndrome, and to ensure that all scans would be reviewed by an appropriately experienced radiologist, with a clear plan in place to manage any incidental pathological findings. In view of our limited resources, we were encouraged to think about involving others on a voluntary basis, e.g. undergraduate medical and intercalating students for audits, and postgraduate trainees in psychiatry, psychology, paediatric, obstetrics & gynaecology, and/or radiology to assist in maternal assessments and supervising scans.

Above all, we were advised to standardise all measures as much as possible, without sacrificing patient participation or data acquisition, e.g. completing rating scales and scans in all subjects at comparable time points.

After returning to Glasgow, we met with the Glasgow PMHS lead psychiatrist, to discuss the way forward. As per the advice received, we developed our hypotheses and aims as detailed above.

Appendix 13 – Scanning protocol

On the MRI select Babies 1 Month or Babies 4 Month protocol depending on the age of the infant.

NB: Please note, the imaging parameters prescribed for all the following imaging sequences described have been carefully considered and should not be changed. This is to facilitate the optimum comparison between study groups by minimising the amount of variation and error in the subsequent measurements that will be made. Similarly, one should follow this imaging protocol such that images are planned consistently throughout the study.

NB: Copy Rx may be used throughout to replicate slice orientations only. I.e. do not copy slice thicknesses etc across different acquisitions.

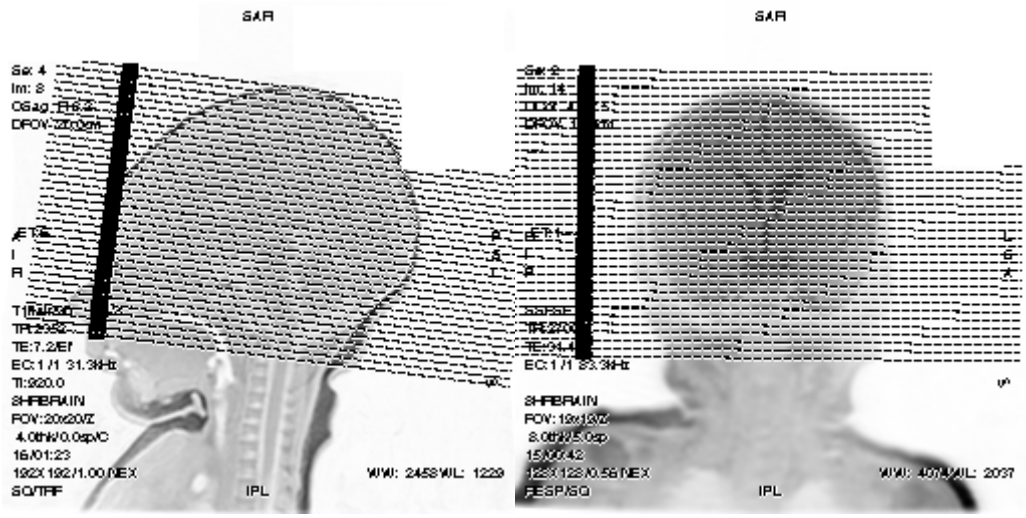
Localiser 1: Use the longer (42s), quieter localiser

Localiser 2: Re-run the longer (42s), quieter localiser correcting for baby head position

Sequence: 3D IR-FSPGR

Plan: This axial oblique acquisition should be planned with respect to the AC-PC points on the sagittal localiser image. The planned acquisition should also be corrected on the coronal localiser (relative to temporal horns), and axial localiser (relative to inter-hemisphere boundary) planes such that it is 'straight'. The acquisition should include the whole head, i.e. include skull as well as brain. Care must be taken to avoid image wrap.

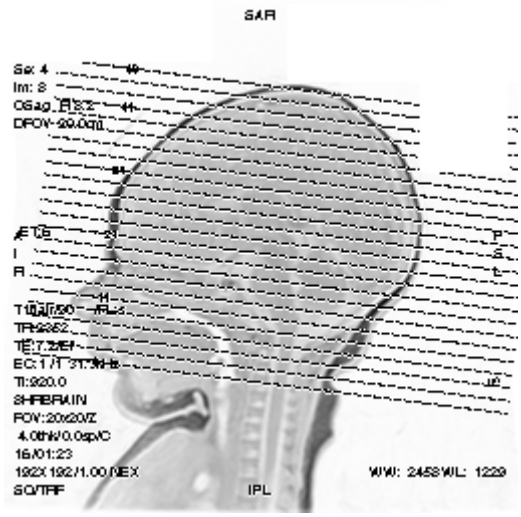
Purpose: This 3D acquisition has been prescribed to optimise the grey matter/ white matter contrast (GM/WM), hence the longer than normal (adult) inversion time for this neonatal study. The 3D acquisition will be used to create group averaged template neonatal images which will allow GM and WM volumes and concentrations to be compared across study groups.



Sequence: T2 measures (1, 2 and 3) (Dual TE, FSE-XL)

Plan: This axial oblique acquisition should be planned with respect to the AC-PC points on the sagittal localiser image. The planned acquisition should also be corrected on the coronal localiser (relative to temporal horns), and axial localiser (relative to inter-hemisphere boundary) planes such that it is 'straight'. These scans are relatively short, but multiple acquisitions will necessary to cover the whole brain. NB: maximise number of slices per acquisition number (~ 6 slices x 4 acquisitions to cover whole head)

Purpose: T2 values change rapidly in early life. We aim to compare T2 values in different regions of the brain across the three groups in this study (normal, depressed/ unmedicated, depressed/medicated). To obtain T2 values, multiple TE value images are acquired.



Asset Calibration:

Plan: This must be planned as a straight axial acquisition and cover the entire field of view

Purpose: Acquiring the asset image enables parallel imaging to be used with the subsequent DTI acquisition. This results in the DTI acquisition being significantly less time to acquire.

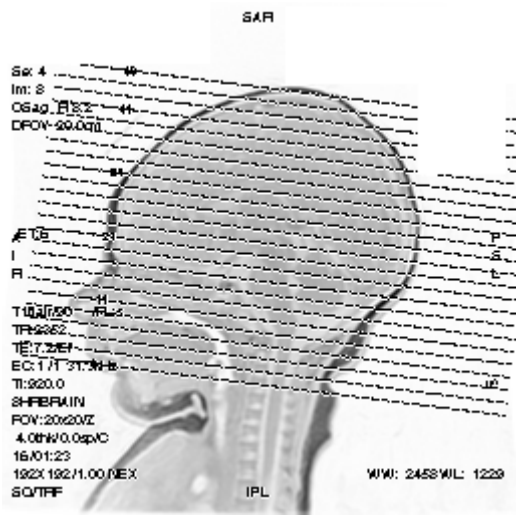
Sequence: DTI (Single shot, DW-EPI, b = 600, 3 x b0 acquisitions, 11 diffusion directions)

Plan: This axial oblique acquisition should be planned with respect to the AC-PC points on the sagittal localiser image. The planned acquisition should also be corrected on the coronal localiser (relative to temporal horns), and axial localiser (relative to inter-hemisphere boundary) planes such that it is 'straight'.

NB: Following 'Save series' and 'Download', the transmitter gain (TG) must be amended. Run 'Manual prescan' the TG is likely to be around 160, this should be set to 85, modify the value and then let manual prescan continue to run for a few seconds, then click 'apply'.

Run the Scan

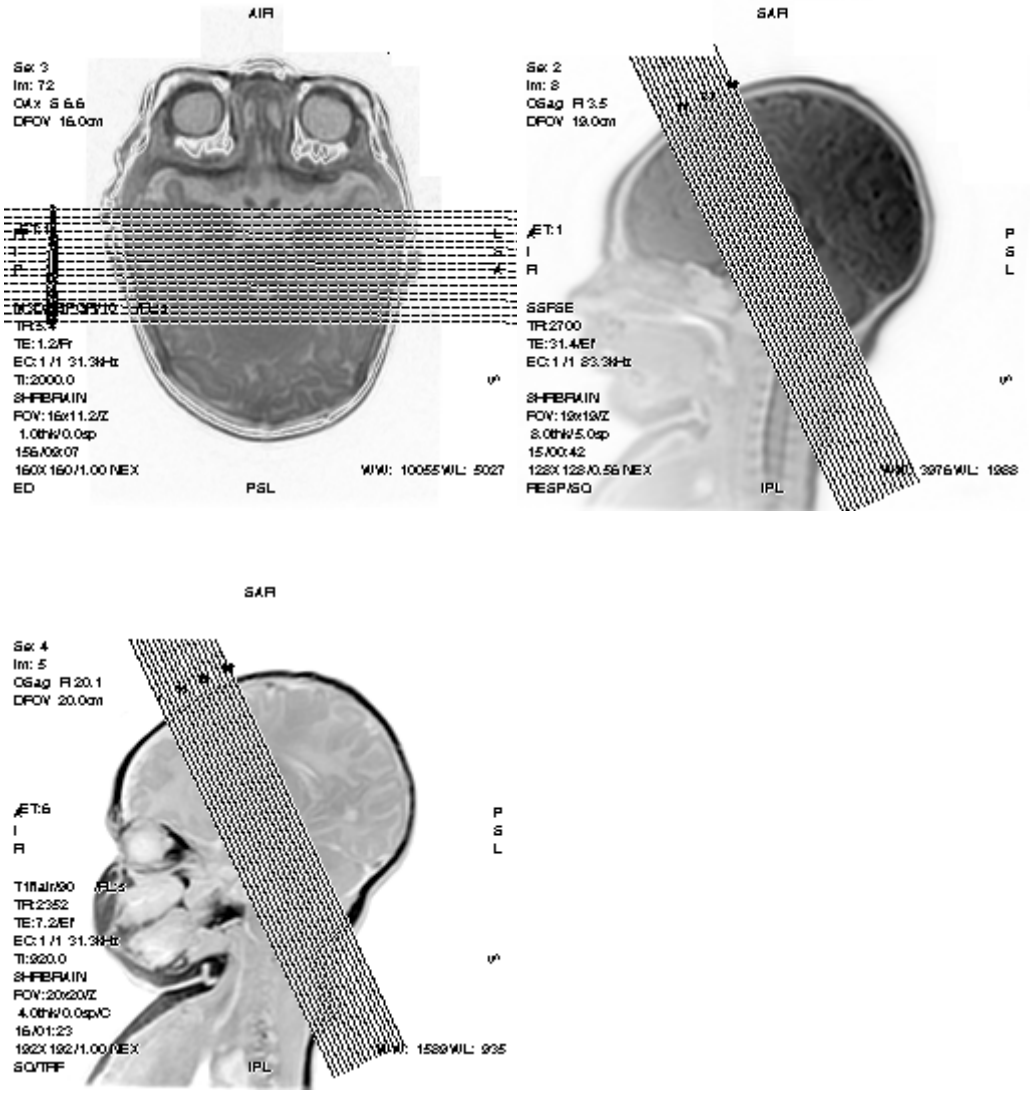
Purpose: Brain diffusion values change rapidly in early life. We aim to compare diffusion values in different regions of the brain across the three groups in this study.



Sequence: Dual echo T2 FSE-XL (For mid-brain structure volume measurements)

Plan: This coronal acquisition should be planned perpendicular to the hippocampus. The slices should cover anterior to posteriorly the amygdala to the tail of the hippocampus.

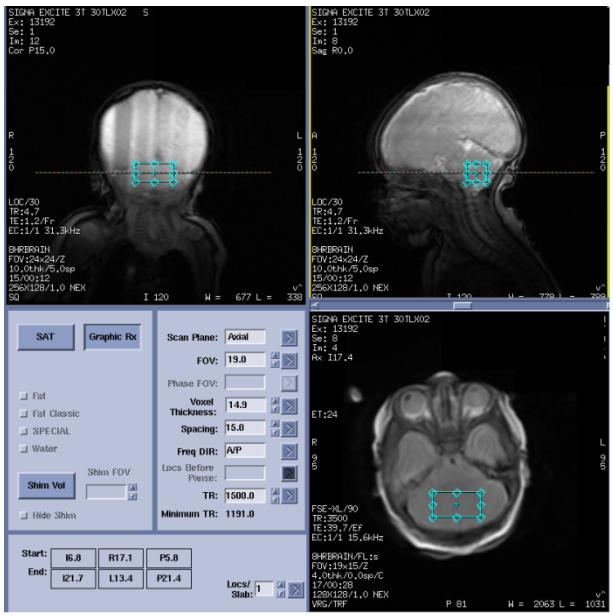
Purpose: The coronal acquisition will allow mid-brain structures such as the amygdala and hippocampus to be measured such that the size of these structures can be compared between the three groups in the study.



Sequence: MRS (Magnetic Resonance Spectroscopy)

Plan: The 3cm (R/L) x 1cm (A/P) x 2cm (S/I) single voxel should be placed within the white matter of the cerebellum, centred on the inter-hemispheric boundary. Plan on the T1 3D, T2 FSE and/or localiser images, use 2 or 3 planes. Save a screenshot of the voxel position (Go to image browser screen > right click on background > service tools > command line > type gimp).

Purpose: We aim to compare metabolite ratios in the cerebellum, a key area in brain development, between the three groups in this study.


SIGNA EXCITE 3T 30TLX02
Ex: 13192
Se: 1
Im: 12
Cor P15.0
LOC/30
TR:4.7
TE:1.2/Fr
EC:1/1 31.3kHz
8HRBRAIN
FOV:24x24/Z
10.0Hk/5.0sp
15/00:12
256X128/1.0 NEX
SIGNA EXCITE 3T 30TLX02
Ex: 13192
Se: 1
Im: 8
Sag R0.0
LOC/30
TR:4.7
TE:1.2/Fr
EC:1/1 31.3kHz
8HRBRAIN
FOV:24x24/Z
10.0Hk/5.0sp
15/00:12
256X128/1.0 NEX
SAT
Graphic Rx
Fat
Fat Classic
SPECIAL
Water
Shim Vol
Shim FOV
Hide Shim
Scan Plane: Axial
FOV: 19.0
Phase FOV:
Voxel Thickness: 14.9
Spacing: 15.0
Freq DIR: A/P
Locs Before Pause:
TR: 1500.0
Minimum TR: 1191.0
Start: I6.8 R17.1 P5.8
End: I21.7 L13.4 P21.4
Locs/ Slab: 1
SIGNA EXCITE 3T 30TLX02
Ex: 13192
Se: 8
Im: 4
Ax I17.4
ET:24
FSE-XL/90
TR:3500
TE:39.7/Ef
EC:1/1 15.6kHz
8HRBRAIN/FL:s
FOV:19x15/Z
4.0Hk/0.0sp/C
17/00:28
128X128/1.0 NEX
VRG/TRF

Appendix 14 – Parameters for one month scans

Scan	*Seq.*	*Orient.*	*TE/ TE2 eff*	*TR*	*TI*	*Phase FOV*	*Slice Thick*	*Slice Gap*	*Matrix*	*FOV*	*Flip Angle*	*options*	*NEX*	*Freq Dir*	*B/W*	*ETL*	*Slices & Acq's*	*EPI vols*	*Duration*
Localiser		3-plane																	~12s
Localiser		3-plane																	~40s
3D T1	IR-FSPGR	Obl-Ax	Min 1.2	5.5	2000	0.7	1.0	0	160 x 160	16	10	SCIC ON, IRP, EDR, FAST	1	A/P	31.25	-	~ 150		9:03
T2 measure 1	Dual TE FSE-XL	AC-PC Axial	105/ 245	3500	-	0.7	5	0	128 X 128	19	-	SCIC ON, EDR	1	A/P	15.63	32	12 & 3		1:25
T2 measure 2	Dual TE FSE-XL	AC-PC Axial	35/ 210	3500	-	0.7	5	0	128 X 128	19	-	SCIC ON, EDR	1	A/P	15.63	32	12 & 3		1:25
Asset	Calibration		2.1/ 1	3.8	-	-	8	0	48					A/P	31.12	39			6S
DTI (NY)	DW-EPI	AC-PC	Min	8000	-	1	3	0	128 x 128	19	-	b = 600, directions = 11	1	R/L	62.5		34	~700	4mins
MRS Plan	FSE-XL	Axial	4.2	3500	-	0.7	4	0	128 x 128	19	-	SCIC: On	1	A/P	31.25	24	17		
MRS	PRESS	Axial	144	1500	-	-	-	-	1 x 1	-	-	128 averages	8	-	-	-	-	-	2mins:12
T2 measure 3	Dual TE FSE-XL	AC-PC Axial	140/ 270	3500	-	0.7	5	0	128 X 128	19	-	SCIC ON, EDR	1	A/P	15.63	32	12 & 3		1:25
T2 FSE	Dual TE	Coronal -Obl	60/ 160	4000	-	0.7	2	0	192 x 192	19	-	EDR	2	S/I	16.63	?	?	-	4mins:8s
T1 FLAIR	-	AC-PC	Min	22000	960	0.75	5	0	128 x 128	19	-	1	1	A/P	31.25	8	25		2mins:02
Resting fMRI	GRE-EPI	AC-PC	30	2200	-	0.75	5	0	64 x 64	19	90			R/L			100	200	3mins:48s

Appendix 15 – Parameters for four month scans

Scan	*Seq.*	*Orient.*	*TE/ TE2 eff*	*TR*	*TI*	*Phase FOV*	*Slice Thick*	*Slice Gap*	*Matrix*	*FOV*	*Flip Angle*	*options*	*NEX*	*Freq Dir*	*B/W*	*ETL*	*Slices & Acq's*	*EPI vols*	*Duration*
Localiser		3-plane																	~12s
Localiser		3-plane																	~40s
3D T1	IR-FSPGR	Obl-Ax	Min 1.2	5.5	2000	0.7	1.0	0	160 x 160	16	10	SCIC ON, IRP, EDR, FAST	1	A/P	31.25	-	~ 150		9:03
T2 measure 1	Dual TE FSE-XL	AC-PC Axial	105/ 245	3500	-	0.7	5	0	128 X 128	19	-	SCIC ON, EDR	1	A/P	15.63	32	12 & 3		1:25
T2 measure 2	Dual TE FSE-XL	AC-PC Axial	35/ 210	3500	-	0.7	5	0	128 X 128	19	-	SCIC ON, EDR	1	A/P	15.63	32	12 & 3		1:25
Asset	Calibration		2.1/ 1	3.8	-	-	8	0	48					A/P	31.12	39			6S
DTI (NY)	DW-EPI	AC-PC	Min	8000	-	1	3	0	128 x 128	19	-	b = 600, directions = 11	1	R/L	62.5		34	~700	4mins
MRS Plan	FSE-XL	Axial	4.2	3500	-	0.7	4	0	128 x 128	19	-	SCIC: On	1	A/P	31.25	24	17		
MRS	PRESS	Axial	144	1500	-	-	-	-	1 x 1	-	-	128 averages	8	-	-	-	-	-	2mins:12
T2 measure 3	Dual TE FSE-XL	AC-PC Axial	140/ 270	3500	-	0.7	5	0	128 X 128	19	-	SCIC ON, EDR	1	A/P	15.63	32	12 & 3		1:25
T2 FSE	Dual TE	Coronal -Obl	60/ 160	4000	-	0.7	2	0	192 x 192	19	-	EDR	2	S/I	16.63	?	?	-	4mins:8s
T1 FLAIR	-	AC-PC	Min	22000	960	0.75	5	0	128 x 128	19	-	1	1	A/P	31.25	8	25		2mins:02
Resting fMRI	GRE-EPI	AC-PC	30	2200	-	0.75	5	0	64 x 64	19	90			R/L			100	200	3mins:48s

Appendix 16 – Ethical approval

Research Ethics
Primary Care, Community & Mental Health REC
R&D Directorate
1st Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Dr Jonathan Cavanagh
Senior Lecturer in Psychiatry
University of Glasgow
5th Floor Institute of Neurological Sciences
Southern General Hospital
Old Govan Road
Glasgow G51 4TF

Date 8th August 2008
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 2811
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Dr Cavanagh

Full title of study: **MRI Studies of infants exposed prenatally to depression and anti-depressants**
REC reference number: **07/S0701/163**

Thank you for your letter of 23 July 2008, responding to the Committee's request for further information on the above research and submitting revised documentation, subject to the conditions specified below.

The further information together with the expert opinion letter was considered at the meeting of the Committee held on 07 August 2008. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Glasgow & Clyde Primary Care, Community & Mental Health

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/S0701/163	**Issue number:**	0	**Date of issue:**	08 August 2008
Chief Investigator:	Dr Jonathan Cavanagh*				
Full title of study:	MRI Studies of infants exposed prenatally to depression and anti-depressants				

This study was given a favourable ethical opinion by Glasgow & Clyde Primary Care, Community & Mental Health on 07 August 2008. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes (1)*
Dr Jonathan Cavanagh		Southern General Hospital.	Glasgow & Clyde Primary Care, Community & Mental Health	08/08/2008	

Approved by the Chair on behalf of the REC:

..... Liz Jamieson ..... (Signature of Chair/Co-ordinator)

(delete as applicable)

..... LIZ JAMIESON ..... (Name)

Appendix 17 – Email correspondence re: ALSPAC

From: Kate Northstone <Kate.Northstone@bristol.ac.uk>
Subject: Fwd: FW: Informal enquiry - ALSPAC data on long term consequence of antenatal antidepressants
Date: 26 February 2013 20:51:49 GMT
To: everett@julyan.co.uk
Reply-To: Kate.Northstone@bristol.ac.uk

Dear Everett,

Further to the message below: Yes, it is most likely that this project would be feasible. To be sure and to obtain formal approval you need to complete a proposal form (http://www.bristol.ac.uk/alspac/researchers/data-access/) and submit to alspac-exec@bristol.ac.uk. We have a standard access fee, which is currently £702. THe medication data may be tricky in that it is highly identifiable in it's raw state (from text responses to Qs) and additional work will be required to identify the exact drugs that you would require and to create relevant indicator variables - additional informaiton would be provide on this if your project was approved. A standard data request takes two weeks from the time that a 'clean' request is made to the team.

Kind regards
Kate

Dr Kate Northstone
Senior Research Fellow

ALSPAC (Children of the 90s)
School of Social and Community Medicine
University of Bristol
Oakfield House
Oakfield Grove
Bristol
BS8 2BN

Tel: +44 (0) 117 3310040
Fax: +44 (0) 117 3310080
Follow us on Twitter @CO90s

From: T Everett Julyan [mailto:everett@julyan.co.uk]
Sent: 26 February 2013 12:40
To: alspac-exec@bristol.ac.uk
Subject: Informal enquiry - ALSPAC data on long term consequence of antenatal antidepressants

Dear Sir/Madam

I wish to make an informal enquiry re: accessing the ALSPAC data to determine the long term consequences of antenatal exposure to antidepressants. I am a consultant psychiatrist in Ayrshire, Scotland, with a research interest in the neurodevelopmental effects of psychotropics. I am currently working towards an MD via the University of Glasgow, and am considering accessing ALSPAC data as part of this.

I wish to acquire data on the parameters below, and have gleaned from your website that much of this is likely to be available. I would be happy to 'phone to discuss this enquiry further, but wonder:

1. Is this feasible?
2. How much would it cost?
3. What would be the timescale(s) involved?

Thank you.
Everett Julyan

Parameters

Mother
General
- Age
- Socioeconomic status
- Parity
- Depression/anxiety during pregnancy (timing, severity, self-reported or clinician-diagnosed?)
- Psychotropic medication during pregnancy (what, dose, timing, self-reported or confirmed from records)
- Other medication during pregnancy
- Substances/alcohol during pregnancy (what, dose, timing)
- Postnatal depression
- Breastfeeding +/- psychotropic medication

Obstetric
- Antenatal issues - infections, bleeding, other significant complications
- Labour complications - length, PROM, streptococcal infection, pyrexia
- Haemorrhage (antenatal, pre/intra/post-partum)
- Delayed discharge

Child
Neonatal
- APGARs, birth weight, gestational age, pulmonary hypertension, adaptation syndrome (abnormal sleep or feeding, irritability)
- Major congenital malformations
- Other/minor congenital malformations
- Admission to SCBU/NICU

Childhood
- Medical history (significant childhood illnesses, depression, anxiety, contact with mental health services, other referrals to secondary care or hospital

admissions)
Forensic issues (criminal charges)
Substance misuse
Educational outcomes (SATS, GCSEs/A levels, further/higher education, qualifications)
Vocational (employment/unemployment post-education)
Relationships (any consistent/pervasive difficulties)
Social functioning

_____

Dr T Everett Julyan
Consultant Psychiatrist

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