OBSTETRIC COMPLICATIONS AS A RISK FACTOR FOR BIPOLAR AFFECTIVE DISORDER: COMPARISON WITH MATCHED NON- PSYCHIATRIC CONTROLS

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DEDICATION

To baby Sean McNeill who motivated me to finish this thesis so that I could spend all my spare time playing with him and watching him grow.

DECLARATION

All of the work presented in this thesis, including the statistical analysis, is directly attributable to the author. The systematic review presented in chapter two was adapted for publication by Prof. Jan Scott of the Institute of Psychiatry and is published in the British Journal of Psychiatry, 2006, 189 (1), 3-16.

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CHAPTER 1: EPIDEMIOLOGY AND AETIOLOGY OF BIPOLAR DISORDER

Chapter 2: SYSTEMATIC REVIEW OF STUDIES INVESTIGATING OBSTETRIC COMPLICATIONS AS A RISK FACTOR FOR BIPOLAR DISORDER.

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CHAPTER 5. DISCUSSION

Background

Family studies have consistently shown that the morbid risk of bipolar affective disorder (BP) in the relatives of BP probands is higher compared with that of the general population. However, concordance rates of less than 100% in identical twins indicate that in addition to genetic factors, environmental factors must contribute to the aetiology of BP. One environmental factor found to be associated with the subsequent development of several psychiatric illnesses is obstetric complications (OCs). A systematic review of OCs as a risk factor for the development of BP found that there was insufficient data to support the hypothesis that OCs are a risk factor for BP and thus more rigorous systematic studies with large enough sample sizes to avoid a type II error are required.

Aims

To determine whether OCs are more common in individuals with BP compared to matched non-psychiatric controls.

Hypotheses

1. More individuals with BP will have experienced OCs compared to matched controls.
2. Individuals with BP will have experienced a greater number of OCs compared to matched controls

Method

The methodology of this study involved linking the Scottish Morbidity Records (SMR) held at Information Statistics Division Scotland. The psychiatric inpatients register (SMR4) was used to identify all individuals born in Scotland between 1969 and 1974 who were subsequently admitted in Scotland with a diagnosis of BP. A link was established between this register and the maternity inpatient and day case register (SMR2) which provided all relevant obstetric information and a matched control for each for the BP probands. A case-control comparison was carried out for the prevalence of each pregnancy, labour, delivery and neonatal complication and the mean number of complications experienced in each period.

Results

A similar number of cases and controls had experienced OCs and the mean number of complications experienced by individuals in each group did not differ. A case control comparison of the individual obstetric events recorded on SMR2 however indicated that mothers of females with BP had significantly more previous pregnancies (1.8, sd 2.0 vs. 1.4, sd 1.5) and therefore a significantly higher parity (1.6, sd 1.9 vs. 1.2, sd 1.4) than mothers of controls. Further analysis of this variable indicated that the female offspring of mothers with a parity of three or more were at significantly increased risk of BP (OR 2.2, 95% CI 1.3-3.9). Furthermore the offspring of mothers who had had more than one x-ray during their pregnancy were at increased risk of BP (OR 4.2, 95% CI 1.2-14.7). Comparison of the mean birthweight of each diagnostic group indicated that the male probands were significantly smaller at birth (3282 grams vs. 3398 grams) however low birth weight (<2500 grams) did not significantly increase the risk of BP (OR 1.6, 95% CI 0.7-3.4).

Conclusion

This large prospective study failed to support the hypotheses that significantly more individuals with BP experienced OCs and that the mean number of OCs experienced by the individuals with BP was significantly greater.
The principal research implication of this study is the need for more systematic studies reporting on the frequency of specific OCs in addition to reporting the number of subjects in each group who experienced any definite OCs.

CHAPTER 1: EPIDEMIOLOGY AND AETIOLOGY OF BIPOLAR DISORDER

"Epidemiology is the study of the causes and distribution of an illness in order to permit a basic understanding. The basic principle of epidemiology involves observing, counting and comparing" (Tohen & Goodwin, 1995). This chapter will explore the epidemiology of bipolar affective disorder (BP), following these basic principles. The symptomatology of BP will be described and the incidence and prevalence rates explored with respect to demographic variables.

The main aim of this chapter is to establish the fact that although the morbid risk of BP in the relatives of BP probands is higher than that of the general population, concordance rates for BP in identical twins is less than 100%. Thus suggesting that in addition to genetic factors, environmental factors must contribute to the aetiology of BP. Obstetric complications are one environmental factor that have been found to be a risk factor for schizophrenia and several other diagnoses. This chapter will explore the idea that obstetric complications may be a risk factor for BP.

1. 1 EPIDEMIOLOGY OF BIPOLAR DISORDER

1.1.1 Diagnosis of Bipolar Disorder

Bipolar disorder, previously known as manic depression, is an affective mood disorder that is typically characterised by periods of euphoria or irritability and periods of depression. The diagnostic statistics manual (DSM IV) diagnostic criteria for hypomania, mania and depression are shown in appendix 1.

The diagnosis of BP has two subcategories. A diagnosis of bipolar I disorder (BPI) is given when one manic or mixed episode[1], with or without depression is experienced. A diagnosis of bipolar II disorder (BPII) is given when an episode of hypomania and depression, but not an episode of mania, is experienced. The preceding term "rapid cycling" applies where four or more mood episodes in one

year are experienced.

Symptoms

Manic states are characterised by the following symptoms; heightened mood, more and faster speech, quicker thought, quicker mental and physical activity and more energy (with a corresponding decreased need for sleep), irritability, perceptual acuteness, paranoia, heightened sexuality and impulsivity. By comparison, bipolar depression is characterised by a decrease in all aspects of emotion and behaviour including rate of thought, speech, energy, sexuality and ability to experience pleasure. Heightened irritability, anger, paranoia, emotional turbulence, suicidal behaviour and a diagnosis of anxiety are also common amongst individuals with bipolar depression. Individuals with BP can also experience psychosis. The psychotic symptoms are most likely to be delusions followed by hallucinations (Black & Nasrallah, 1989) and are most likely to occur during a manic episode (Rosen et al, 1983).

Comorbidity

Epidemiological studies have suggested that several psychiatric disorders co-occur with BP at higher rates than expected from chance alone; in Hungary 38% of individuals with BP have more than one DSM-III-R diagnosis (Szadoczky et al, 1998). Data from the epidemiological catchment area study (ECA) indicated that individuals with a lifetime history of BP were seven times more likely to have substance abuse, eighteen times more likely to have obsessive compulsive disorder (Boyd et al, 1984) and nineteen times more likely to have panic disorder (Chen & Dilsaver, 1996). Furthermore, Barbato and Hafner (1998) reported that 45% of individuals with BP have a comorbid personality disorder.

Prognosis for individuals with Bipolar Disorder

The DSM-IV estimates that approximately 90% of individuals with a manic episode will go on to have a future BP episode and Daniels et al (1998) found amongst 319 BP first admissions, 66% were admitted again in the following year. Individuals with BP may suffer from long-term neurocognitive impairment;

[1] A mixed episode is an episode in which the diagnoses of depression and mania are met simultaneously.

euthymic BP patients have shown impairment in verbal memory, frontal executive functioning, visiomotor speed, verbal fluency, new learning, sustained attention, reasoning and spatial orientation (Atre-Vaidya et al, 1998; Ferrier et al, 1999; van Gorp et al, 1998). Individuals with BP are more likely to be unemployed (Atkinson et al, 1997; Szadoczky et al, 1998) whilst those that are employed show significant work impairment and face social and economic disadvantages (Coryell et al, 1987). Thirty percent of BP patients cannot work and live independently. An additional 20% have varying degrees of reduced functioning (Tohen et al, 1990). Divorce and separation are three to six times higher than in the general population (Angst, 1998). Compared with 51% of the general population, 30% of individuals with BP have two or more children (Szadoczky et al, 1998). Compared with non-psychiatric controls, recovered BP patients have been reported as less emotionally strong, more introverted and more interpersonally dependent because of their illness (Hirschfeld et al, 1986).

1.1.2 Incidence of Bipolar Disorder

Boyd & Weissman (1982) reported that the annual incidence rate of BP varies from 9.2 to 15.2 per 10^5 males and 7.4 to 32.5 per 10^5 females. Data from several studies reporting the incidence of mania are presented in Table 1. The incidence of BPI or mania is estimated as equal to the incidence of BPII, therefore it is possible to double the figures reported in Table 1 to obtain a rough estimate of the incidence of BP in each location (Rasanen et al, 1998).

Table 1. Incidence of mania per 10^5 population

Study	Location	Male	Female	Total
Rasanen et al (1998)[1]	Finland	12.2	12.3	12.3
Der & Bebbington (1987)[1]	Camberwell, London	4.5	4.8	NK
Daly et al (1995)[2]	Dublin	4.1	4.9	4.8
Leff et al (1976)[2]	Aarhus , Denmark	3.1	2.0	2.6
Leff et al (1976)[2]	London	3.1	2.3	2.6

1figures from psychiatric registers thus includes only individuals hospitalised or treated

2 figures from a community sample NK denotes not known

1.1.3 Prevalence of Bipolar Disorder

According to the DSM-III-R, the lifetime prevalence of BP is approximately 1%. Table 2 presents data from the Cross National Collaborative group, which reported the results of several epidemiological studies (Weissman et al, 1996). All the studies presented in Table 2 used identical methodology; trained laypersons administered the third version of the Diagnostic Interview Schedule (DIS) to randomly selected household and institution samples. As shown, the lifetime prevalence rates of BP range from 0.3% in Taiwan to 1.5% in New Zealand, thus suggesting that the lifetime prevalence of BP is relatively consistent.

Table 2. Lifetime prevalence rates of bipolar disorder amongst individuals aged 18-64 years

Study	Location	% (sd)		
		Male	Female	Total
Robins & Regier (1991)[1]	United States	0.8 (0.1)	1.0 (0.2)	0.9 (0.1)
Orn et al (1988)	Edmonton, Alberta	0.7 (0.3)	0.5 (0.2)	0.6 (0.2)
Canino et al (1987)	Puerto Rico	0.8 (0.4)	0.5 (0.3)	0.6 (0.2)
Wittchen et al (1992)	Munich	NK	1.0 (0.7)	0.5 (0.4)
Hwu et al (1989)	Taiwan	0.3 (0.01)	0.3 (0.1)	0.3 (0.1)
Lee et al (1990a)	Korea	0.6 (0.2)	0.2 (0.1)	0.4 (0.1)
Wells et al (1989)	Christchurch, New Zealand	1.7 (0.6)	1.2 (0.5)	1.5 (0.4)

[1]Epidemiological Catchment Area study NK denotes not known

1.1.4 Age of onset Of Bipolar Disorder

Table 3 displays the results of several epidemiological studies reporting the age of onset of BP. It is possible the results differ greatly between studies because of the methodology. For example, studies defining onset as first hospitalisation will not report early episodes of hypomania. The results of Egeland et al (1987) reflect this point. When the authors defined age of onset as "first impairment associated with affective symptoms" and "first admission for BP" the age of onset reported was 15.5 years and 25.8 years respectively. Similarly, when Loranger & Levine (1978) defined age of onset as "first BP symptoms" the age of onset reported for males and females respectively was 33.0 and 31.6 years in comparison to 36.5 and 34.6 years when onset was defined as "first

hospitalisation for a BP episode."

Age of onset is important to the subsequent clinical course of BP. Early onset BP is characterised by a severe prognosis and more psychotic symptoms, especially delusions and ideas of reference (Ballenger et al, 1982; Rosen et al, 1983); analysis of the 53 psychotic subjects suggested a correlation of -0.42 between age of onset and psychosis[2] (Rosen et al, 1983). Early onset BP is also more commonly associated with a positive family history (Akiskal et al, 1985; Hays et al, 1998; Rice et al, 1987). By comparison, late onset BP is more commonly associated with an organic origin (Hays et al, 1998; Shulman & Post, 1980).

Table 3. Average age of onset of bipolar I disorder

Study	Location	Mean (sd or 95% CI)
Canino et al (1987)[1]	Puerto Rico	27.2 (3.4)
Lee et al (1990a)[1]	Korea	23.0 (2.4)
Wells et al (1989)[1]	Christchurch	18.2 (5.9)
Robins & Regier (1991)[1]	United States	18.1 (0.7)
Benazzi (1999)[1]	Italy	28.5 (14.2)
Bland et al (1988)[1]	Edmonton , Alberta	17.1 (1.1)
Hwu et al (1989)[1]	Taiwan	22.6 (1.9)
Szadoczky et al (1998)[1]	Hungary	19.9 (17.8-22.6)
Daly et al (1995)[2]	Dublin	28.8 (NK)
Leff et al (1976)[2]	London	32.2 (NK)

1 denotes first BP symptoms 2 denotes first admission for BP NK denotes not known

1.1.5 Demographics of Bipolar Disorder

Gender

The Epidemiological Catchment Area (ECA) study is one of the largest studies of the demographics of individuals with BP. Like the majority of studies the ECA found no significant gender difference in the lifetime prevalence of BP. Although men and women are equally likely to suffer BP, the course of the illness tends to differ. Women with bipolar disorder more likely to experience rapid cycling (Leibenluft, 1996), clinically significant depressive symptomatology, dysphoric as opposed to euphoric mania (Roy-Byrne et al,

[2] The results of this study must be interpreted with caution as 25 subjects met criterion for schizoaffective disorder or schizophrenia using the Schedule for Affective Disorders.

1985), an onset at ages 45-49 years (McElroy et al, 1992; Roy- Byrne et al, 1985) and are less likely to complete suicide possibly due a decreased comorbidity of alcohol dependence (Isometsa et al, 1995).

Social economic status

The ECA study found that social economic factors such as income, white-collar employment and years of education was not associated with the incidence and prevalence rates of BP in the Unites States (Weissman et al, 1991). However individuals who were homeless or who had been unemployed for 6 months or more in the last 5 years were at increased risk of BP, relative risk (RR) of 17.7[3] and odd ratio (OR) of 1.9 [3] respectively.

Ethnicity

The results of the ECA study were projected to provide national estimates of prevalence specifically adjusted to take into account the ethnicity of the United States (Regier & Kaelber, 1995). Therefore the findings of this study suggesting that no race difference exist in the prevalence of BP are considered reliable.

Marital status

The ECA study found a significantly increased prevalence of BP amongst individuals who were cohabiting, divorced, or who never married compared to individuals who were never divorced (Der & Bebbington, 1987; Szadoczky et al, 1998; Weissman et al, 1991).

Urbanicity

Kessler et al (1997) found that a diagnosis of BP was positively related to urbanicity. The results of the ECA study support this finding (Weissman et al, 1991). For example, in St. Louis the one-year prevalence of BP was three times higher in urban areas compared with rural areas (1.5 vs. 0.5, adjusted OR 2.25 [3], $p<0.001$). In Durham the OR for urban area vs. rural areas was 3.78 [3] ($p<0.05$). Similar, but non-significant, results were found in Ontario where the 1 year prevalence of mania amongst urban dwellers was 0.6% in comparison to 0.4%

[3] 95% CI were not available

amongst rural dwellers (Parikh et al, 1996).

1.2 GENETIC VULNERABILITY TO BIPOLAR DISORDER

Family studies have consistently shown that the morbid risk (adjusted prevalence) of BP in the relatives of BP probands is higher compared with those of the general population. The morbid risk of BP in individuals with a family history of BP ranges from 2.9 – 14.5% (Table 4) by comparison the estimated morbid risk of BP in individuals with no family history of BP is 0.3% (Tsuang et al, 1980).

Table 4. Morbid risk of bipolar disorder in the relatives of bipolar disorder probands

Study BP probands	Number of relatives at risk (age corrected)	morbid risk of BP (%)
Taylor et al (1980)	600	4.8
Baron et al (1982)	135	14.5
Gershon et al (1982)	598	8.0
Coryell et al (1984)	389	7.0
Fieve et al (1984)	1309	2.9
Tsuang et al (1985)	608	3.9
Angst (1986)	1441	5.6
Rice et al (1987)	838	10.6

The findings of several twin studies suggest increased concordance rates in identical twins compared to fraternal twins (Table 5). By pooling the data from these studies Craddock & Jones (1999) estimated that the concordance rates in identical twins was 50% (95% CI 40%- 60%).

In summary family and twin studies provide extensive and consistent evidence supporting the existence of a genetic vulnerability for BP; i.e. the relatives of BP probands are more at risk of developing BP than the relatives of control subjects. However, concordance rates of less than 100% in identical twins indicates that in addition to genetic factors environmental factors must contribute to the aetiology of BP.

Table 5. Concordance rates for bipolar disorder in twins.

Study	Sample	Identical twins	Fraternal twins
Kringlen (1967)	Norway twin and psychosis register. 6 identical twin pairs	67%	-
Allen et al (1974)	USA veteran twins register. 5 identical and 15 fraternal twin pairs	20%	0%
Bertelsen et al (1977)	Denmark twin and psychiatric registers. 34 identical and 37 fraternal twin pairs	62%	8%
Torgersen (1986)	Norway twin register. 4 identical and 6 fraternal twin pairs	75%	0%
Kendler et al (1993)	Sweden twin and psychiatric registers. 13 identical and 22 fraternal twin pairs	39%	5%
Cardno et al (1999)	UK psychiatric hospital twin register. 22 identical and 27 fraternal twin pairs	36%	7%

From Craddock & Jones (1999): systematic review of all published studies of genetic risk and BP

1.3 SCHIZOPHRENIA

Table 6 summarises the key features of schizophrenia as detailed in the DSM-IV. Schizophrenia and BP are distinguishable from each other by (1) the degree and persistence of the mood disorder, (2) the fact that mania generally includes activation and increase in goal directed activity and schizophrenia does not and (3) by the relationship of the psychotic symptoms to the mood state e.g. in BP, psychotic symptoms occur only during a mood episode whereas in schizophrenia the mood symptoms have a duration that is brief in comparison to duration of psychotic features. Furthermore, schizophrenia is viewed as a more severe illness than BP possibly because the developmental and neurological impairment is more marked in individuals with schizophrenia and individuals with schizophrenia have a worse long-term outcome (Marneros et al, 1990).

Table 6. Key features of schizophrenia

Psychotic symptoms: at least 2 present for at least 1 month
Disorganised speech (incoherence, evidence of thought disorder)
Disorganised or catatonic behaviour
Negative symptoms e.g. affective flattening, lack of motivation
Impairment in social or occupational functioning
Duration of the illness of at least 6 months
Symptoms not primarily due to mood disorder or schizoaffective disorder
Symptoms not due to a medical, neurological or substance induced disorder.

Despite these differences BP and schizophrenia share may similarities. For example the impulsive manic behaviour of the BP patient is often similar to the schizophrenic patient who is experiencing bizarre or paranoid delusions. Elevated rates of schizophrenia have been reported in the relatives of individuals with BP in comparison to the relatives of non-psychiatric controls (Angst & Scharfetter, 1985; Kendler et al, 1985; Taylor et al, 1993). Schizophrenia and BP share similar developmental abnormalities, including delayed motor and language milestones, educational problems and neurological signs such as poor co-ordination and both result in neurological dysfunction such as reduced

intelligence and memory defects (Maneros et al, 1990). Previous research has also suggested similar brain pathology in BP and schizophrenia as BP and schizophrenia have been found to share similar structural brain abnormalities. These include, lateral and third ventricle enlargement, cortical sulcal and fissure widening, and cerebellar atrophy (Nasrallah, 1991), reductions in dendritic spine density (Rosoklija et al, 2000) neuronal size, (Rajkowska et al, 1999; Cotter et al 2001) and synaptic proteins (Eastwood & Harrison, 2001) and glial cell deficit (Rajkowska et al, 1999). Furthermore ventricular dilation and reduced hippocampal and frontal brain volumes seen in schizophrenia are also present to a lesser degree in individuals with BP (McCarley et al, 1999).

Obstetric complications and schizophrenia

The most extensively studied environmental antecedent of schizophrenia is obstetric complications (OCs). The term obstetric complication refers to 'the broad class of somatic deviations from an expected, normal course of events and offspring development during pregnancy, labour-delivery, and the early neonatal period' (McNeil, 1987).

A meta-analysis of studies investigating the association between schizophrenia and a history of OCs reported that the odds ratio of the effect of exposure to any obstetric complication (during pregnancy, labour delivery or the neonatal period) on the subsequent development of schizophrenia was 2.0 (95% CI 1.6-2.4) (Geddes et al, 1999).

More recently, researchers have focused on determining exactly which particular obstetric complication is associated with schizophrenia. Examples of the specific OCs that have been found to be significantly associated with schizophrenia are listed in table 7[4]. In a meta analytic review of prospective population-based studies investigating OCs and schizophrenia (including all studies listed in table 7), Cannon et al (2002) reported that the following specific OCs were significantly associated with schizophrenia: diabetes (OR 7.7, 95% CI 1.37-43.9); birth weight <2000g (OR 3.9, 95% CI 1.4-10.8); bleeding in pregnancy

[4] Specific OC reported limited to those recorded on the SMR 2 database. SMR2 is the database which provided birth information for the subjects in this study.

(OR 1.7, 95% CI 1.1-2.52); emergency caesarean section (OR 3.2, 95% CI 1.04-7.5); congenital malformations (OR 2.3, 95% CI 1.2-4.6); uterine atony (OR 2.3, 95% CI 1.5-3.5); threatened premature delivery (OR 2.0, 95% CI 0.8-4.9) and asphyxia (OR 1.7, 95% CI 1.15-2.6).

Table 7: Specific obstetric complications significantly associated with schizophrenia

Author	Obstetric complication	OR (95% CI)
Sacker et al (1995)	Rhesus negative mother	1.8 (1.4-6.4)
	Parity >2	2.4 (1.3-4.3)
	Bleeding in pregnancy	3.0 (1.4-6.4)
	BW< 2500g	3.9 (1.9-8.1)
Jones et al (1998)	BW ≤2500g	2.4 (1.0-5.6)
	BW ≤2500g & GA ≤37 weeks	3.5 (1.3-3.6)
Hultman et al (1999)	Bleeding during pregnancy	3.5 (1.2-10.3)
	Parity> 4 (males only)	3.6 (1.6-7.8)
Dalman et al (1999)	Pre-eclampsia	2.5 (1.7-4.5)
	Vacuum extraction	1.7 (1.1-2.6)
	Parity =1	1.3 (1.0-1.6)
	Bleeding during pregnancy	2.0 (1.0-4.2)
	GA<32 weeks	2.7 (1.0-7.0)
	BW<2500g (males)	2.2 (1.1-4.1)
	BW <1500g (females)	6.0 (1.7-21.4)
Byrne et al (2000)	C-section	4.0 (1.1-22.1)
Kendell et al (1996)	Pre-eclampsia	9.0 (1.25-395)
	Non-spontaneous delivery	3.5 (1.1-14.6)
Geddes et al (1999)[1]	Premature rupture of membranes	3.11 (1.39-7.0)
	Forceps delivery	1.47 (0.99-2.2)
Kendell et al (2000)	Labour >12 hours	-[2]

[1] Meta-analysis of 12 studies [2] OR not documented in research paper.

1.4 WHY MIGHT OBSTETRIC COMPLICATIONS BE A RISK FACTOR FOR THE DEVELOPMENT OF BIPOLAR DISORDER?

The following sections will explore some of the models regarding the development of BP. The first of these suggests that "stressors"[5] occurring during fetal life can permanently change the endocrine system's future response to "stress" such that an individual becomes more susceptible to the environmental

[5] In this section, the terms "stress" or "stressor" refers to anything that disrupts physiological balance. The term "stress-response" refers to the body's adaptation designed to re-establish the balance.

variables that trigger mental illness. The second suggests that BP is associated with structural brain abnormalities caused by insults occurring during the developmental period. The third model discussed suggests that BP is associated with a chemical imbalance in the central nervous system.

All of these theories suggest that BP is associated with brain changes. In each section, the author will explore how OCs may be associated with these changes and thus be a risk factor for the development of BP.

1.4.1 Stress- Diathesis Model Of Bipolar Disorder

The stress- diathesis model proposes that BP develops through a complex interaction of hereditary variables and environmental variables. This complex interaction of nature and nurture affects not only the development of BP but also its clinical course. This model proposes that environmental variables do not cause BP but rather they act as a trigger for the onset of the illness in individuals who are already vulnerable due to hereditary variables. The severity of the environmental variable required to precipitate an episode varies from one person to another; an individual with a low vulnerability (low diathesis) will require more environmental trauma than an individual with high vulnerability (high diathesis). The environmental variables that can release a BP episode include disturbing life events (Ambelas, 1987; Kennedy et al, 1983), the disruption of circadian rhythms (Wehr & Goodwin, 1983) and physical trauma.

This section will explore the theory that stressors occurring during fetal life (known as prenatal stress) can alter the set-point of the hypothalamic-pituitary-adrenal (HPA) axis through prenatal programming. Consequently, future stressors will result in an exaggerated and prolonged stress-response. Several areas of research suggesting that an altered HPA axis is associated with a diagnosis of BP are present. Furthermore suggestions as to how OCs may be associated with changes in the set-point of the HPA axis are explored. The author aims to link this back to the stress-diathesis model of BP by suggesting that an individual with an overactive HPA axis is more sensitive to the environmental variables that trigger BP.

Endocrine and neural systems response to stress

The diagram 1 represents the endocrine and neural systems response to stress i.e. the stress-response. The stress-response is non-specific. Different stressors will result in the same endocrine and neural reaction because regardless of the stressor they all throw the body out of homeostasis and the task of re-establishing the balance is the same.

Diagram 1. The Stress-Response

As shown above stress is perceived by the brain resulting in the release of the hormone corticotropin-releasing hormone (CRH) from the hypothalamus in the base of the brain. CRH then stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH)[5], which in turn stimulates the adrenal gland to release glucocorticoid. Glucocorticoid is a steroid hormone that comes in a number of different forms. In humans and primates the dominant form is cortisol (also known as hydrocortisone), whereas in rodents the dominant form is corticosterone. Other hormones are also secreted in the stress-response. These include β-Endorphin secreted from the pituitary gland, which regulates pain perception and reproductive physiology during the stress-response; prolactin which also effects reproductive physiology and vasopressin (also known as diuretic hormone) involved in the regulation of renal function and water volume. The autonomous nervous system is also involved in the stress-response. The sympathetic nervous system is activated to mobilise the body's resources and releases epinephrine (EPI) and norepinephrine (NE). The parasympathetic nervous system, which is primarily involved in the process of maintenance, is inhibited during the stress-response. In short, the stress-response involves mobilising energy and delivering it to where it is needed through the sympathetic nervous system whilst curtailing non-essential physiological process through the parasympathetic nervous system. Once a stressor is terminated it is important that the stress-response is also terminated. Activity within the HPA axis is regulated by a negative feedback loop whereby the end products of the axis, circulating glucocorticoid, feedback to the pituitary and specific brain regions to inhibit the release of ACTH from the anterior pituitary.

What is prenatal programming?

"Programming" describes the process whereby the central nervous system (CNS) is permanently altered by a stimulus or insult occurring at a sensitive or critical period of development. The human CNS is more susceptible to programming during periods of rapid growth. It has been calculated that the fertilised human ovum goes through 42 cycles of cell division before birth and just 5 cycles thereafter (Barker, 1998) and therefore widely accepted that the CNS is most

[5]ACTH is also known as adrenocorticotropin, corticotrophin, and corticotropic hormone

susceptible to programming during fetal life. As a result, prenatal stress can permanently alter the programming of the endocrine system.

How does prenatal stress alter the programming of the HPA axis?

Prenatal stress alters the HPA axis in two possible ways. Firstly, glucocorticoid circulates best when bound to a protein. This role is served mostly by corticosteriod-binding globulin (CBG). Typically, 95% of the glucocorticoid is bound to CBG. It is the unbound 5% that is biologically active and involved in the negative feedback loop. Prenatal stress increases CBG in females, but not in males, by 50%. Control animals and prenatally stressed animals have the same basal (resting non-stressed) corticosterone levels but the increase in CBG in the prenatally stressed animal results in less unbound glucocorticoid (Kanitz et al, 2003). Secondly central corticosteriod receptors form a crucial part of the negative feedback loop. Type I or mineral corticoid receptors (MRs) are involved in the control of basal HPA activity whilst type II or glucocorticoid receptors (GRs) are important for mediating the stress-response via negative feedback control. The balance of the MRs and GRs is of critical importance to the programming of the HPA axis as adrenal corticoids act on these specific receptors in the brain and pituitary to inhibit the release of CRH and ACTH. It has been shown that prenatal stress decreases the number of these receptors (Kanitz et al, 2003).

As a result of these permanent changes prenatal stress can cause deregulation of the HPA axis. Prenatal stress weakens the resting state HPA negative feedback loop thus prenatally stressed animals show higher resting levels of ACTH and corticosterone compared with controls (Takahashi et al, 1990; Takahashi et al, 1991). Secondly as the negative feedback loop is essential to terminating the stress-response, following a stressor the prenatally stressed animal will have a heightened and more enduring stress-response. For example prenatally stressed rats have shown greater and more prolonged secretion of corticosterone following exposure to novel environments, tailshock, restraint and saline injection (Henry et al, 1994; McCormick et al, 1995; Weinstock et al, 1992). Exposing pregnant monkeys to an unpredicted noise during mid- to late gestation

resulted in the offspring having raised basal cortisol levels and a raised ACTH response during the stress-response (Clarke et al, 1994). Prenatally stressed rats also show abnormal adaptation to novelty environments in that they continue to release high amount of corticosterone even after repeated exposure to the same environment (Fride et al, 1986).

In short prenatal stress can alter the programming or "set-point" of the endocrine system such that there is an altered, usually exaggerated, stress-response.

Deregulation of the HPA axis and the development of Bipolar disorder

Although a full review of this area is beyond the scope of this thesis there are several areas of research supporting the hypothesis that an altered HPA axis is involved in the development of psychiatric illness and in particular BP.

Firstly, elevated levels of stress hormones have been found in individuals with a variety of psychiatric diagnoses. Elevated levels of CRH have been reported in individual with depression and individuals with anorexia nervosa (Levitt et al, 1996; Plotsky et al, 1995). Patients with schizophrenia have been found to have an exaggerated ACTH response to stress exposure (Elman et al, 1998). Elevated free cortisol levels have been reported in individuals with depression (Holsboer, 1995; Schmider et al, 1995) and individuals with mania (Schmider et al, 1995) compared with controls.

Secondly in healthy individuals the release of ACTH and cortisol can be suppressed for approximately 24 hours by a single oral dose of 1 to 2 mg of dexamethasone (DEX), which is a synthetic glucocorticoid. A number of individuals with BP do not show normal suppression of cortisol secretion after administration of DEX (table 8).

Table 8: Frequency of DEX non-suppression in individuals with a diagnosis of bipolar disorder

Author	Subjects	BP mania	BP mixed episode
Hwu & Lin (1990)	21	19%	-
Kiriike et al (1988)	9	44%	-
Hunt et al (1989)	19	45%	-
Stokes et al (1984)	16	50%	71%
Evans & Nemeroff (1983)	Mania n=3 Mixed n=7	70%	100%
Krishnan et al (1983)	10	-	100%
Schmider et al (1995)	11	55%	-
Cassidy et al (1998)	Mania n=37 Mixed n=7	43%	86%

The combined dexamethasone suppression and corticotropin releasing hormone (DEX/CRH) test shows a higher sensitivity (90%) than the DEX test alone (20-50%). The CRH/DEX test works in the following way. Circulating cortisol will suppress release of ACTH after CRH challenge. It would therefore be expected that administration of DEX followed by administration of CRH the next day would result in a suppression of ACTH release. Normal controls do show ACTH and cortisol response to CRH that decreases gradually with increased DEX administration (Holsboer, 1995). However several studies have shown that individuals with BP do not show normal suppression after DEX followed by CRH administration. For example Schmider et al (1995) reported significantly higher levels of ACTH and cortisol after DEX/CRH administration in individuals with mania (ACTH = 2.9pmol/L; cortisol= 127.6nmol/L) in comparison to controls (ACTH=1.2pmol/L; cortisol=20.4nmol/L). In a comparison of 16 individuals with BP depression, 24 individuals with unipolar depression and 20 non psychiatric controls, Rybakowski & Twardowska (1999) found that significantly more BP subjects (56%) had cortisol concentrations over 50μg/l, indicating non-suppression, 16 hours after DEX intake in comparison to individuals with depression (0%) and the controls (5%).

Thirdly, behaviour of prenatally stressed animals also suggests that deregulation of the endocrine system may be involved in the development of psychiatric illness. Adult prenatally stressed animals differ from control animals in their behavioural response to threat; they are more fearful and show more behavioural

suppression in the face of novelty, hyperanxiety in unfamiliar intimidating situations and in general display an inability to cope in aversive and intimidating situations. The characteristics of depression in human subjects include reduced interest in other people or surroundings, inability to feel joy or pleasure and a decrease in appetite and libido. Although depression cannot be diagnosed in animals, animals that have been exposed to prenatal stress show behaviours that have been interpreted as depressive symptomatology. For example consumption of sweet substances such as saccharin, which has no nutrition value, is believed to represent a pleasurable activity in animals (Katz, 1982). A reduction in saccharin consumption in adult rats can be induced by a mild stressor and restored by antidepressants (Moreau et al, 1994). Thus suggesting that decreased sweet consumption is a depressive-like behaviour in animals. Compared with control female rats, prenatally stressed female rats show decreased saccharin intake (Keshet & Weinstock, 1995). Furthermore, in animals exogenous CRH leads to reduced food intake and sleep disturbance both of which are symptoms of depression (Plotsky et al, 1995)

Finally, symptom remission is often associated with normalisation or at least improvement in the regulation of the endocrine system. For example Schmider et al (1995) found that the ACTH levels decreased in manic patients between an acute episode (2.9pmol/L) and remission (2.3pmol/L) but were still significantly higher that that obtained from non-psychiatric controls.

In conclusion, considerable research has shown that deregulation of the endocrine system, in particular over activity of the HPA axis, is associated with psychiatric illness. An overactive HPA axis causes an individual to have an exaggerated and prolonged stress-response. With respect to the stress-diathesis model of BP, in such individuals less traumatic life events or physical traumas will trigger an episode of BP and therefore, such an individual would be are more at risk of BP.

How might obstetric complications be related to the deregulation of the HPA axis?

How is prenatal stress related to obstetric complications? Firstly, OCs themselves could be considered prenatal stress if they were fetal insults which caused permanent changes in the stress response. If OCs are considered prenatal stressors then an individual who experiences OCs will have an exaggerated and prolonged reaction to stress. In accordance with the stress-diathesis model this individual will be at increased risk of a bipolar episode even if they have very little genetic vulnerability (low diathesis) as their endocrine system will over react to environmental variables which would usually cause little anxiety.

Secondly OCs themselves may not be directly associated with BP but rather associated with prenatal stress which in turn is associated with BP. There are several ways in which the stress reponse may increase the likelyhood of OCs. Firstly during the stress response the immune system is suppressed and therefore the fetus may be increasingly exposed to infection and disease and more damaging effects from an infection if one occurs. Secondly, prenatal stress can cause depression of fetal blood pressure and oxygenation resulting in an increased risk of fetal asphyxia. Several studies have suggested an association between prenatal stress and OCs. For example in a prospective study of 90 pregnant women, Wadhwa et al (1993) found that independent of obstetric risk, each unit increase of anxiety[6] in the prenatal period was significantly associated with a 55gram decrease in infant birth weight and with a 32% increase in the relative risk of low birth weight (<2500grams). Furthermore, each unit increase in prenatal pregnancy-specific anxiety[6] was significantly associated with a 3-day decrease in gestation. In a study of more than 2500 pregnancies in the USA Weinstock (2001) found that maternal anxiety[6] measured at the start of the third trimester was associated with preterm delivery and low birth weight after adjustment for maternal demographic factors. These finding are supported by several carefully controlled prospective and retrospective studies showing that

[6] In this context, the term "anxiety" does not refer to a diagnosis of anxiety but rather psychological stress. The term stress is not used to avoid confusion with the previous use of the term "stress" to refer to anything that disrupts physiological balance.

adverse life events during pregnancy and / or self- reported anxiety[6] are associated with preterm delivery and low birth weight for gestation age (Hedegaard et al, 1993; Multale et al, 1991; Steer et al, 1992; Zambrana et al, 1999). Furthermore prenatal measures of anxiety[6] have been associated with lower Apgar scores at one and five minutes (Pagel et al, 1990).

Therefore there may be two pathways that lead to the relationship between OCs, prenatal stress and bipolar disorder. Firstly OCs are prenatal stressors which deregulate the HPA axis resulting in an exaggerated stress-response and therefore a greater risk of a bipolar episode being triggered. Secondly, prenatal stress increases the risk of several OCs and thus OCs are a common factor between prenatal stress and bipolar disorder.

1.4.2 Neurodevelopmental hypothesis of bipolar disorder

The neurodevelopmental hypothesis proposes that an early insult to the developing brain could result in brain changes that are fixed, non-progressive and lie dormant until they manifest as mental illness in adolescence or early adulthood.

The most consistent structural abnormality found amongst individuals with BP has been the presence of ventriculomegaly (an abnormally expanded state of the ventricle) and T_2 hyperintensities.

Ventricular Abnormalities

In a comprehensive review of neuroimaging studies of BP, Strakowski et al (2000) concluded that lateral ventriculomegaly occurs commonly in individuals with BP. The findings of the studies reviewed are presented in Table 9. All the studies used MRI, with the exception of the authors in italics who used CT scans.

T_2 Hyperintensities

MRI provides sharp resolution of brain images and therefore allows researchers to detect small changes in water content as areas of increased signal intensity (hyperintensities) when using T_2 weighted images. Several studies have shown that individuals with BP exhibit higher rates of MRI T_2 signal hyperintensities compared to healthy matched controls (Table 10). Altshuler et al (1995) combined the data from eight studies comparing the prevalence of T_2 hyperintensities in BP subjects and controls and reported that the OR for the presence of any T_2 hyperintensity in the BP subjects (n=198) compared to controls subjects (n=307) was 3.3 (95% CI 1.9-5.6).

Table 9. Ventricular abnormalities found in individuals with bipolar disorder compared to healthy control subjects. Adapted from Strakowski et al (2000)

Study	Ventricles		Comments
	Lateral	Third	
Figiel et al (1991)	++		
McDonald et al (1991)	0		Elderly sample
Woods et al (1995)	0		
Lewine et al (1995)	0		Radiologists reading only
Area/Linear assessments			
Pearlson & Veroff (1981)	++		a/w increased age
Nasrallah et al (1982,1984)	++		a/w fewer hospitalisation
Pearlson et al (1984, 1984b)	++		a/w unemployment
Schlegel & Kretzschmar (1987)	0	0	
Dewan et al (1988)	0	++	n/a EEG, cognitive testin
Iacono et al (1988)	0	0	First-episode patients
Johnstone et al (1989)	0		
Andreasen et al (1990)	++		Males only
Risch et al (1992)	0		
Kato et al (1994)	++		
Volumetric assessments			
Swayze et al (1990)	0		a/w hyperintensities
Strakowski et al (1993)	0	++	First- episode patients
Harvey et al (1994)	0		
Botteron et al (1995)	0	0	8-16 year old sample
Dupont et al (1987, 1995)	0		
Pearlson et al (1997)	++		
Zipursky et al (1997)	++		
Roy et al (1998)	0	0	
Strakowski et al (1999)	++	0	

a/w denotes associated with; n/a denotes not associated with
0 denotes no statistically significant difference between BP and healthy controls
++ denotes BP significantly greater than controls

Table 10. T_2 hyperintensities in individuals with bipolar disorder compared to control subjects without a history of psychiatric illness

Study	Presence of T_2 hyperintensities		RR (95%CI)	p-value	Common Location and number of subjects (if available)
	BP	Controls			
Dupont et al (1990) [a]	9 (47.4%)	0 (0%)	2.0 (1.3-3.1)	p=0.01	Frontal lobe (n=7); subcortical white mater regions (n=8); thalamus (n=1); corpus callosum (n=1)
Altshuler et al (1995)[b]	28 (50.9%)	6 (30%)	1.3 (1.0 –1.6)	p=0.17	
Aylward et al (1994)	11 (34.4%)	1 (3.2)	2.2 (1.5-3.2)	p=0.01	Frontal lobes; frontal/ parietal junction; occipital and temporal lobes (n=3)
Swayze et al (1990)	9 (19%)	2 (4.3%)	1.8 (1.2-2.5)	p=0.02	Lateral border of the ventricles
Brown et al (1992)[a]	1 (4.5%)	12 (7.8%)	0.6 (0.9-0.1)	p=0.02	

[a] white matter hyperintensities [b] periventricular white matter hyperintensities

Are the structural brain abnormalities involved in the development of bipolar disorder?

In order to determine whether these abnormalities are neurodevelopmental in origin, i.e. are the consequence of brain insult occurring while the brain is developing, or are a consequence of the disorder, it is useful to compare first episode BP patients and controls. The hypothesis being that if structural brain abnormalities precede BP and are neurodevelopmental in origin then they will be present at the onset of the disorder. The results of studies investigating this have been very inconsistent. For example, Botteron et al (1995) compared eight BP subjects (children and adolescent aged 8-16 years) and five similar aged non-psychiatric controls and found that 50% of the BP subjects had one or more MRI abnormalities in comparison to one of the controls. Strakowski et al (1993) found that individuals with first episode of mania demonstrated significantly larger third ventricles than non-psychiatric matched controls. However, in a later study, Strakowski et al (2002) reported that individuals with multiple episode BP[7] had significantly larger right and lateral ventricles than individuals with first episode BP[8] and healthy subjects with no personal or family history of psychiatric disorder. The controls and the first episode patients did not differ with regard to ventricle volume. Similarly, Iacono et al (1988) compared 18 individuals with first episode BP who were currently psychotic with 13 medical controls and 29 non-psychiatric controls and found that the three groups did not differ with respect to ventricle-brain ratio and third ventricle width.

There is limited research comparing the presence of T_2 hyperintensities in individuals with first episode BP compared to either non-psychiatric controls or individuals with multiple episode BP, however the research that does exists suggests that T_2 hyperintensities are present at the onset of the BP illness. For example, on comparison of first-episode BP patients and non-psychiatric controls, Strakowski et al (1993) found that 1.7 times as many individuals with BP exhibited subcortical hyperintensities, however this results failed to reach statistical significance possibly

[7] Individuals with multiple episodes BP had two or more prior manic episodes, one or more prior psychiatric hospitalisation and prior antipsychotic or mood–stabiliser medication.

[8] Individuals with first episode BP had no prior manic episode, no prior psychiatric hospitalisations and had had no treatment with mood stabilisers or antipsychotic medication.

due to the lack of statistical power.

It is also useful to investigate whether the brain abnormalities found in individuals with BP correlate with the clinical course of the disorder; if there is an association between brain abnormalities and clinical course then it may be argued that the brain abnormalities are associated with the disorder, worsening with each episode of illness. Earlier studies have consistently shown that lateral ventriculomegaly in BP is not associated with age of onset (Dewan et al, 1988), duration of illness (Dewan et al, 1988), duration since first hospitalisation or number of hospitalisations (Woods et al, 1995). However again these results have not always been replicated. For example Strakowski et al (2000) reported that the number of prior manic episodes was significantly associated with lateral ventricle volume ($p<0.02$). Pearlson et al (1982) reported that those with enlarged ventricles were at the more severe end of the spectrum with a past history of delusion and hallucinations and than those with dilated ventricles who in turn had more hospital admission than those with small ventricles. Several authors have reported no association between the presence of hyperintensities and the following clinical correlates: number of previous hospitalisation (Altshuler et al, 1995); history of psychosis (Altshuler et al, 1995; Dupont et al, 1987; Figiel et al, 1991); age of onset (Dupont et al, 1987; Figiel et al, 1991); duration of illness (Dupont et al, 1987) and prior treatment with medication (Dupont et al, 1987), in particular lithium (Figiel et al, 1991). However, again the results have been inconsistent. Dupont et al (1987 & 1990) reported that that those patients with hyperintensities had a trend towards an increased depression scores on the Hamilton Rating scale for depression. Altshuler et al, (1995) found that periventricular white matter hyperintensities were 1.6 times more common in individuals with BPI disorder in comparison to individuals with BPII disorder.

Are obstetric complications associated with the structural abnormalities found in individuals with bipolar disorder?

The suggestion that structural abnormalities may precede the onset of BP and the finding of studies suggesting that structural brain abnormalities are more commonly seen in individuals with no family history of mental illness (Dalen, 1965; Hays, 1976; Lewis et al, 1989; Perris, 1966) has lead several authors to suggest that at least in some individuals mental illness is associated with brain damage occurring in the prenatal period (between conception and birth).

Are OCs associated with brain damage in the prenatal period? In the preterm fetus hypoxia, the main denominator of many OCs, can lead through a series of events to haemorrhage in the lateral and third ventricles possibly resulting in enlargement of the ventricles. Hypoxia in the preterm fetus also leads to damage in the white matter. Drevets et al (1999) suggested that large T_2 signal hyperintensities may reflect white matter necrosis.

Several studies have shown an association between specific OCs and the structural brain abnormalities found in individuals with BP. The Copenhagen high-risk study found that enlarged ventricles were associated with low birth weight, and a difficult pregnancy and labour (Mednick et al, 1987). Koeningsberger & Kairam (2000) reported that 20% of newborns weighing less than 1,500 grams experience periventricular intraventricular haemorrhage. In more than 50% of cases, this bleeding ruptured into the lateral ventricle and resulted in progressive enlargement. Silvertone et al (1985) reported that ventricular enlargement was significantly negatively related to length ($p<0.05$) and weight ($p=0.001$) at birth. Premature birth drastically increases the risk of hypoxic episodes and of subependymal and intraventricular haemorrhage, which could result in necrosis and possibly in subsequent permanent enlargement of the ventricles (Lyon & Barr, 1991).

Animal studies have also provided evidence that OCs are associated with the

structural brain abnormalities found in individuals with BP. For example, by experimentally inducing intrauterine infection in 20-21 day gestation rabbits, Yoon (1997) found that intrauterine infection is associated with periventricular white matter lesion. These results can be considered to mimic that of the human fetus following infection as the pattern of cytokine response to intrauterine infection in this species is similar to that of humans (van Deventer et al, 1990). Post mortem of low birth weight animals has also shown that the incidence of antenatal white matter necrosis (related to T_2 hyperintensities) is inversely related to low birth weight and is more frequent in infants weighing less than 1000 grams (Bejar et al, 1988).

1.4.3 Biochemical hypotheses of Bipolar Disorder

The monoamine hypothesis of BP describes the relationship between excesses or deficiencies in monoamine neurotransmitter concentration in the central nervous system (CNS). The two main theories emerging from the monoamine hypothesis are the Catecholamine Hypothesis and the Permissive (Serotonin) Hypothesis.

Catecholamine Hypothesis

The Catecholamine Hypothesis proposes that depression is associated with a functional deficiency of catecholamines and mania an excess. Norepinephrine, epinephrine and dopamine are collectively known as catecholamines. In short norepinephrine (NE) is associated with ones sensitivity to a stimuli for example the release of NE increases the signal/noise ratio thus increasing sensitivity to stimuli, whilst Dopamine is linked to reinforcement, motivation and the psychomotor processes. It is believed that NE may be associated with the euphoric and grandiose characteristic of hypomania whilst dopamine abnormalities are primarily involved in the hyperactivity and psychosis associated with the more severe stages of mania (Goodwin & Sack, 1974).

There is extensive support for the Catecholamine Hypothesis of BP. Neuroleptics

that selectively block central dopamine are effective against severe mania. Amphetamines which promote dopamine release and prevent its reuptake can precipitate hypomania in BP patients and induce a hypomanic-like state in healthy individuals (Jacobs & Silverstone, 1986). Hypertensive patients treated with reserpine, which depletes catecholamine, develop major depression and drugs that increase catecholamine have antidepressant qualities (Potter et al, 1985). Significantly lower levels of MHPG (3-methoxy-4-hydroxyphenlglycol)[9], and HVA levels[10], have been found in the post mortem of individuals with depression compared to controls (Asberg et al, 1984; Ashcroft et al, 1976; Banki, 1977; Brodie et al, 1973; Koslow et al, 1983; Papeschi & McClure, 1971; Post et al, 1973; Subrahmanyam, 1975; Traskman et al, 1981). Furthermore, higher levels of MHPG and HVA have been found in individuals with mania compared to individuals with depression (Banki, 1977; Bowers & Heninger, 1977; Koslow et al, 1983; Vestergaard et al, 1978) and healthy controls (Ashcroft et al, 1976; Gerner et al, 1984; Koslow et al, 1983; Shopsin et al, 1974)

Permissive (Serotonin) hypothesis

Serotonin depletion is associated with activation or disinhibition of a whole range of behaviours. According to the permissive hypothesis both the manic and the depressive phases of BP are characterised by low central serotonin function. Extensive data from animal studies suggests that brain serotonin systems dampen or inhibit a variety of functions subserved by other neurotransmitters (Goodwin & Jamison, 1990). The permissive hypothesis proposes that defective dampening of these other neurotransmitters, such as NE or dopamine, permits the transfer between depression and mania.

Again, extensive evidence exists for the permissive hypothesis of BP. Lithium, which is used as mood stabiliser in BP, enhances or stabilises the serotonin systems

[9] which reflects the level of NE in the brain
[10] which reflects the level of dopamine

(Mandell & Knapp, 1979). Tricyclic antidepressants (TCA) inhibit the uptake of serotonin (Goodwin & Jamison, 1990).

Significantly lower levels of 5-HIAA, which reflects the levels of serotonin, have been found in the post mortem of individuals with depression compared with healthy controls (Asberg et al, 1984; Ashcroft et al, 1966; Ashcroft et al, 1976; Banki, 1977; Coppen et al, 1972; Takahashi et al, 1974; van Praag & Korf, 1971).

How do obstetric complications relate to the biochemistry models of BP?

The monoamine hypothesis of BP proposes that depression and mania are related to an excess or depletion of neurotransmitters, such as dopamine, serotonin and NE, in the CNS. McNeil (1988) documented unpublished evidence suggesting that at least in animals the functioning of the brain transmitter substances like dopamine, noradrenaline and serotonin become disturbed at low levels of hypoxia; both the synthesis and turn over of these neurotransmitters diminish dramatically under hypoxic conditions.

Furthermore, long lasting anoxia can result not just in temporary changes in the biochemistry of the brain but long- term biochemical damage (McNeil, 1988). El-Khodor & Boksa (2001) found that dopamine receptor binding was increased in the limbic areas of the brain in rats born by caesarean section compared with rats born vaginally. Rats born by caesarean section also displayed long term changes in the regulation of dopamine following stress compared to vaginally born rats.

1.5 CONCLUSION

Concordance rates for BP of less than 100% in identical twins suggests that environmental factors must contribute to the aetiology of BP. Schizophrenia and BP share many similarities with respect to diagnoses and premorbid abnormalities. Geddes et al (1999) reported that individuals exposed to obstetric complications are at increased risk of developing schizophrenia (OR 2.0). This has lead to the

suggestion that OCs may be one environmental risk factor for the development of BP.

OCs may increase the risk of BP in several ways. Firstly, OCs may alter the set-point of the HPA axis such that an individuals has an exaggerated and prolonged reaction to stress and therefore with respect to the stress- diathesis model of BP these individuals may require less psychological stress to precipitate an episode. Secondly, the neurodevelopmental hypothesis of BP suggests that early insult to the developing brain may result in structural changes that manifest as mental illness in adolescence or early adulthood. Research suggests that OCs may be one such brain insult that can cause structural brain abnormalities found in individuals with BP. For example, hypoxia the common denominator of OCs and in some cases a specific obstetric complication can lead to many of the structural brain abnormalities founding individuals with BP. Thirdly, the monoamine hypothesis of BP suggests that BP is associated with excesses and deficiencies of monoamine neurotransmitters concentration in the CNS. Several lines of evidence suggest that the functioning of substances such as dopamine, serotonin and NE can be disturbed by OCs.

1.6 STRUCTURE OF THE THESIS

This thesis aims to determine whether Ocs are more common in individuals with bipolar disorder in comparison to matched non-psychiatric controls. Before the hypotheses for this study were developed the author systematically reviewed studies reporting on the obstetric histories of individuals with bipolar disorder in comparison to non-psychiatric controls or individuals with another psychiatric diagnosis. This systematic review is presented in chapter 2. In order to shape the methodology of this study the author also carried out a methodological critique that .reviewed the methodological limitations of previous research in this area and also suggested ways in which this study could avoid these limitations. This is presented in chapter 3. Chapter 4 presents the results of the current study. Group analysis of the prevalence of pregnancy, labour and delivery and neonatal complications are

compared as are the number of complications experienced in each period. Odds ratios are calculated to investigate whether the experience of a pregnancy, labour and delivery or neonatal complications significantly increases the risk of bipolar disorder. In chapter 5 the results obtained are compared with those found by the studies reviewed in chapter 2 and possible explanations for the significant results are explored. Finally the methodological limitations of the present study are discussed at the end of chapter 5.

Chapter 2: SYSTEMATIC REVIEW OF STUDIES INVESTIGATING OBSTETRIC COMPLICATIONS AS A RISK FACTOR FOR BIPOLAR DISORDER

2.1 INTRODUCTION

As discussed in the previous chapter, extensive research (e.g. Nurnberger & Foroud, 2000) has shown genetic factors play a role in the development of BP. However, concordance rates of less than 100% in monozygotic twins (e.g. Bertelsen et al, 1977) imply that environmental factors may also be important in the aetiology of BP. The specific factors that may play a role are the subject of debate, but a number of researchers have highlighted possible parallels between causal models of BP and the neurodevelopmental hypothesis of schizophrenia. Magnetic resonance imaging (MRI) studies in BP subjects have demonstrated brain abnormalities that could support the notion that OCs had impaired early brain development and increased later vulnerability to BP (Dalen, 1965; Nasrallah, 1991; Pearlson et al, 1985). However, the quality of the empirical evidence for and against this has not been fully explored.

This chapter aims (1) to systematically review studies comparing the obstetric histories of BP patients and non-psychiatric control subjects and (2) to systematically review studies comparing the obstetric histories of BP patients and groups of patients with other psychiatric disorders.

2.2 METHOD

2.2.1 Definition of obstetric complications

Obstetric complications were defined according to McNeil (1987) as: 'the broad class of somatic deviations from an expected, normal course of events and offspring development during pregnancy, labour-delivery, and the early neonatal period'.

2.2.2 Inclusion criteria

All studies reporting the obstetric histories of patients with BP were eligible for inclusion in the review.

2.2.3 Exclusion criteria

The three exclusion criteria were:

1. Insufficient information to allow identification of a separate subgroup of BP subjects with OCs meeting defined criteria.
2. Failure to distinguish OCs from early developmental abnormalities.
3. Review papers with no new empirical datum included.

2.2.4 Search criteria

The computerised databases searched were: MEDLINE (1966- January 2005), PREMEDLINE (to January 2005), PSYCHINFO (1967- January 2005), COCHRANE LIBRARY (up to January 2005), BEST EVIDENCE (1991-January 2005), and EMBASE (1980-January 2005). The key words searched were [BIPOLAR AFFECTIVE DISORDER] or [MANIC-DEPRESSION] + [OBSTETRIC COMPLICATIONS]. The Thesaurus for Psychological Index Terms identified all terms mapping onto the key words. An additional search was carried out using each of these terms. Terms are listed in Appendix 2. All on-line abstracts were reviewed and relevant reports were obtained. Citations in relevant publications were also checked. Figure 2 illustrates the selection process for the review.

All authors of published datum were sent an email requesting unpublished data sets and enquiring whether they had knowledge of any other researchers with unpublished data sets. The authors of papers which compared control subjects with

individuals diagnosed with affective disorder were asked to identify, where possible, those with a diagnosis of BP and their matched controls.

2.2.5 Search Results

A total of 44 studies were obtained of which 41 were published papers and three were personal communications. Thirty-three were identified from electronic searches (Bain et al, 2000; Brown et al, 1995; Brown et al, 2000; Browne et al, 2000; Buka & Fan, 1999; Cannon et al, 1997; Cannon et al, 2002; Cornelius et al, 1994; Dalen, 1965; Done et al, 1991; Eaton et al, 2000; Gunduz et al, 1999; Gureje et al, 1994; Hultman et al, 1999; Kinney et al, 1993; Kinney et al, 1998; Machon et al, 1997; Marcelis et al, 1998; Morgan et al, 1997; Pearlson et al, 1985; Rifkin et al, 1994; Sacker et al, 1995; Stober et al, 1997; Takei et al, 1993; Torrey, 1999; Torrey et al, 2000; Verdoux & Bourgeois, 1993a; Verdoux & Bourgeois, 1993b; Vocisano et al, 1996; Waters et al, 1982; Waters et al, 1983; Watson et al, 1999; Wilcox, 1986). A further eight studies were identified following a manual search of reference lists (Byrne et al, 1996; Buka et al, 1993; Guth et al, 1993; Lewis & Murray, 1987; Schwarzkopf et al, 1989; Sigurdsson et al, 1999; Taylor & Abrams, 1981; Zornberg et al, 2000).

The unpublished data were received as a personal communication from Dr Gunduz (Hillside Hospital, New York). Dr Mortensen (Institute for Basic Psychiatric Research, Denmark) sent a draft copy of a paper being prepared for submission, and Dr Cannon (Institute of Psychiatry, London) provided an updated version of the SPSS database file from 'The Camberwell Collaborative Psychosis Study'. Three publications have reported earlier findings from that project (Cannon et al, 1997; Marcelis et al, 1998; Rifkin et al, 1994). These publications were included in the systematic review as the methodology had already been published and therefore peer reviewed. [1]

[1] Dr Gunduz research was published as Gunduz et al (1999). Dr Mortensen paper was published as Eaton et al (2000) and the Camberwell Collaborative Psychosis study had been reported by several authors as referenced above.

Twenty-four papers were excluded from the original forty-one published papers identified (Table 11). Eighteen papers were excluded because a subgroup of subjects specifically with BP and OCs could not be identified (in 12 papers BP subjects were included in a broad 'affective disorders' category). Three papers from 'The Camberwell Collaborative Psychosis Study' were excluded because the findings were superseded by new datum from the researchers (as noted above) (Cannon et al, 1997; Marcelis et al, 1998; Rifkin et al, 1994). Two papers were excluded because they were review articles (Buka & Fan, 1999; Torrey, 1999). One paper (Verdoux & Bourgeois 1993b) was excluded as it was written in French and the identical datum was available in an English Language journal (Verdoux & Bourgeois, 1993a)

The information in Gunduz et al (1999) was supplemented by the unpublished datum received and so these datum are referenced throughout the review as 'Gunduz et al (unpublished)'.

Figure 2: Flow chart of article selection process

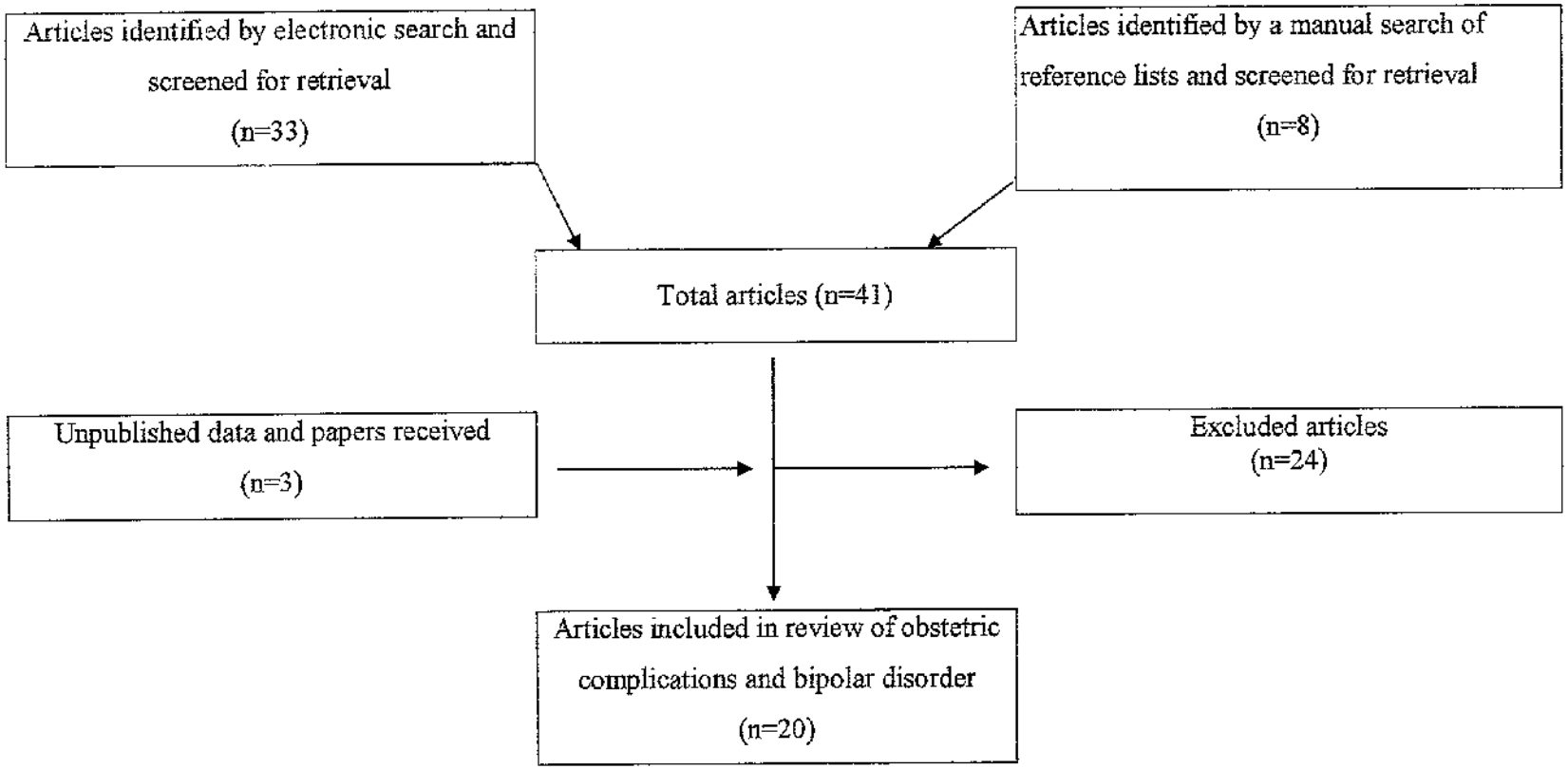


Table 11. Studies excluded from review and reason for exclusion

Article	Reason for exclusion
Gureje et al (1994) Pearlson et al (1985)	Combined history of OCs and early developmental abnormalities. Number of subjects with a history of OCs alone could not be obtained.
Cornelius et al (1994)	BP sample included secondary mania
Takei et al (1993)	Study of intra-uterine complications not OCs.
Bain et al (2000) [1] Brown et al (1995)[1] Buka et al (1993)[1] Done et al (1991)[2] Eaton et al (2000)[2] Guth et al (1993) [1] Hultman et al (1999)[2] Morgan et al (1997)[2] Sacker et al (1995)[2] Torrey et al (2000)[3] Waters et al (1983)[1] Watson et al (1999)[1]	BP sample included as part of major affective disorder[1], affective psychosis[2] or any psychosis[3] group. No separate datum for BP could be obtained.
Cannon et al (1997) Marcelis et al (1998) Rifkin et al (1994)	Results from Camberwell Collaborative Psychosis Study. Datum superseded by database received from Dr Cannon.
Verdoux & Bourgeois (1993b)	Paper published in French. English translation was available in another publication (Verdoux & Bourgeois 1993a).
Buka & Fan (1999) Torrey (1999)	Review papers with no new datum
Waters et al (1982)	Reported the obstetric histories of offspring of BP patients, 11 of who had a BP diagnosis. Unable to identify the BP offspring.
Wilcox (1986)	Reports RR of developing catatonia compared with mania following OCs. No separate datum concerning the frequency of OCs amongst manic group could be obtained.

2.2.6 Data Extraction

All reports were reviewed and the following methodological factors were recorded in a structured proforma: reported clinical diagnoses; method of assigning diagnoses (structured clinical questionnaire, interview with psychiatrist, information obtained from medical records); demography (age, gender, and ethnicity); family history of BP or other psychiatric disorders; source of data on obstetric history (maternal recall, birth records, birth registers); and assessment scale or tool used to identify and quantify OCs (no scale used; Lewis et al, 1989; McNeil-Sjostrom Scale, 1995; Parnas et al, 1982). The proforma also recorded whether healthy controls had been adequately screened to exclude individuals with a possible or definite DSM-IV diagnosis and whether cases and controls were significantly different with respect to gender, age and socio-economic status. Demographic data for cases and controls are shown in Table 12. Table 13 illustrates the method used to assign a diagnoses to the BP subjects and the comparison group. Table 14 illustrates the source of the obstetric data and the method used to quantify OCs.

For the purposes of the review, studies were grouped into four categories: those comparing the prevalence of OCs amongst (1) individuals with BP and non-psychiatric controls (2) individuals with BP and individuals with another psychiatric disorder (3) studies with no comparison group reporting the prevalence of OCs in early as compared with late onset BP or amongst BP subjects with and without a family history of BP (4) cohort studies reporting the RR of developing BP following possible intra-uterine exposure to a national epidemic. The papers identified in this category examined the RR of developing BP following assumed exposure to the Dutch Hunger Winter and the Greater Helsinki Influenza epidemic. Also included in this section was one prospective study examining the RR of developing BP following hypoxic-ischaemia-related fetal or neonatal complications. The term ischaemia refers to a lack of blood in an area of the body due to the mechanical obstruction or functional constriction of a blood vessel.

2.2.7 Statistical Analysis

Chi-squared comparisons of the frequency of OCs in the BP group compared to the comparison group were recorded or calculated if sufficient data were provided. For the 'Camberwell Collaborative Psychosis Study' and the Mortensen et al (unpublished) study, chi-squared analyses were performed separately for each specific obstetric complication recorded. Chi-squared analyses were interpreted in the following way; if the obtained p-value was less than 0.05 then the result was considered statistically significant.

Where possible, estimates of RR, OR and the 95% confidence intervals (95% CI) were recorded from each publication, or were calculated from the data available in the paper or provided by the author. The OR were interpreted in the following way; an OR of >1.0 suggested a positive association between OCs and BP whilst an OR of <1.0 a negative association. The 95% confidence intervals (95% CI) were interpreted in the same way. If the confidence interval included 1.0, the OR was assumed not to differ from chance whilst an interval not containing 1.0 suggested a statistically significant difference.

Statistically non-significant trends are presented and discussed in the following sections. The reason being that the current study will investigate several of the variables which failed to reach statistical significance and therefore help conclude whether these variables are risk factors for BP but failed previously to reach significance due to small sample size.

Table 12. Demographic information for studies included in systematic review

Study	Number of subjects		Age of Subjects in Years (Range/ Means & SD)	
	BP Group	Main Comparison Group(s)	BP Group	Main Comparison Group(s)
Schwarzkopf et al (1989)	10	ScZ= 15 ScA = 6	20-40	20-40
Lewis & Murray (1987)	110	ScZ =207 UP = 91 Other = 547	16-49	16-49
Sigurdsson et al (1999)	38	UP =41	NK	NK
Camberwell Collaborative Psychosis Study (unpublished)	49	ScZ = 100 UP = 18 C= 100	29.8 (8.1)	ScZ =26.7 (6.5) UP= 30.8 (8.4) C =27.5 (7.15)
Gunduz et al (unpublished)	13	ScZ = 61 ScA = 26 UP= 15 C= 21	NK	ScZ = 24.9 (6.7) ScA =26.1 (6.8) A= 29.1 (5.6) C= 28.4 (5.9)

Table 12 Continued. Demographic information for studies included in systematic review

Study	Number of subjects		Age of Subjects in Years (Range/ Means & SD)	
	BP Group	Main Comparison Group(s)	BP Group	Main Comparison Group(s)
Verdoux & Bourgeois (1993a)	23	ScZ = 23 C= 23	29.7 (8.0)	ScZ= 29.8 (7.1) C= 31.1 (7.3)
Stober et al (1997)	40	CP = 40 C= 40	31.9 (7.2)	CP= 31.1 (6.5) C= 34.0 (7.9)
Vocisano et al (1996)	23	UP = 29 ScZ = 29	NK	UP = NK ScZ = 48.1 (13.0)
Mortensen et al (unpublished)	40	ScZ= 132 C= 33,320	24-28	ScZ= 24-28 C= 24-28
Browne et al (2000)	76	C= 76	NK	C= NK
Kinney et al (1998)	24	C= 25	NK	C= 31.8 (6.4)
Kinney et al (1993)	16	C= 20	27.3 (7.5)	C= 27.6 (5.3)
Cannon et al (2002)	20	C=642	26	C=26

ScZ denotes schizophrenia; ScA denotes schizoaffective disorder; C denotes control subjects
CP denotes cycloid psychosis; A denotes affective disorder; UP denotes unipolar depression; NK denotes not known

Table 13. Method used to assign diagnoses to subjects.

Study	Methods of assigning diagnoses	
	Bipolar Disorder	**Comparison group(s)**
Schwarzkopf et al (1989)	SCID and medical records	SCID and medical records
Lewis & Murray (1987)	Discharge diagnoses	Discharge diagnoses
Sigurdsson et al (1999)	SCAN applied to casenotes	SCAN applied to casenotes
Camberwell Collaborative Psychosis Study (unpublished)	Interview with psychiatrist	Controls: none UP & Schizophrenia: interview with psychiatrist
Gunduz et al (unpublished)	SCID	SCID
Verdoux & Bourgeois (1993a)	NK	NK
Stober et al (1997)	Interview with psychiatrist	NK
Vocisano et al (1996)	SCID	SCID
Mortensen et al (unpublished)	Discharge diagnoses	Controls: None Schizophrenia: discharge diagnoses
Browne et al (2000)	Discharge diagnoses	None
Kinney et al (1998)	Chart review	SCID
Kinney et al (1993)	SCID & chart review	SCID and interview with reliable informants
Cannon et al (2002)	DIS	DIS

SCID denotes Structured Clinical Interview for DSM-IV Diagnosis; DIS denotes Diagnostic Interview Schedule
NK denotes not known

Table 14. Source of obstetric information and method used to summarise obstetric complications

Study	Source of obstetric information	Summary scale used
Schwarzkopf et al (1989)	Maternal recall	Parnas et al (1982) rating scale
Lewis & Murray (1987)	Psychiatric records	Lewis & Murray (1986) rating scale
Sigurdsson et al (1999)	Casenotes	Defined as absent, minimal or present
Camberwell Collaborative Psychosis Study (unpublished)	Maternal recall	Lewis et al (1989) rating scale
Gunduz et al (unpublished)	Maternal recall, birth records & birth certificates	McNeil-Sjostrom (1995) rating scale
Verdoux & Bourgeois (1993a)	Maternal recall	Parnas et al (1982) rating scale
Stober et al (1997)	Maternal recall	Lewis et al (1989) rating scale

Table 14 Continued. Source of obstetric information and method used to summarise obstetric complications

Study	Source of obstetric information	Summary scale used
Vocisano et al (1996)	Patient interview	Defined as absent or present
Mortensen et al (unpublished)	Danish medical birth register	None
Browne et al (2000)	Birth records	Parnas et al (1982) scale Lewis et al (1989) scale
Kinney et al (1998)	Maternal recall	Mirdal rating scale
Kinney et al (1993)	Birth records	Mirdal rating scale
Cannon et al (2002)	Birth records	None
Dalen (1965)	Birth records & maternal recall	None
Taylor & Abrams (1981)	Interview with patient & relatives Current medical records	Defined as absent or present

2.3 RESULTS

2.3.1 Studies comparing individuals with bipolar disorder with healthy controls

Nine studies compared the OCs experienced by individuals with BP and healthy controls (Browne et al, 2000; Cannon et al, 2002; Camberwell Collaborative Psychosis Study, unpublished; Gunduz et al, unpublished; Kinney et al, 1993; Kinney et al, 1998; Mortensen et al, unpublished; Stober et al, 1997; Verdoux & Bourgeois, 1993a). All except the results of Cannon et al (2002), Mortensen et al (unpublished) and Gunduz et al (unpublished) are presented in Table 15[1]. As can be seen, the sample sizes of the published studies are small and the findings are inconsistent. Only Kinney et al (1993; 1998) reported a statistically significant difference between BP probands and healthy controls. Kinney et al (1993) found that compared with their healthy siblings, BP probands were significantly more likely to experience a wide range of non-specific OCs (such as maternal anaemia, rubella, bleeding/spotting during pregnancy, prematurity or low birth weight, prolonged duration of labour, use of drugs during labour, breech delivery, emergency caesarean section and neonatal respiratory problems) (mean obstetric complication score: BP vs. siblings= 3.56 sd 2.19 vs. 1.95 sd 2.26, p=0.01) and the OCs experienced were significantly more severe (mean severity score: BP vs. siblings= 1.75 sd 0.58 vs. 1.2 sd 0.83, p=0.034). Similar results were obtained by Kinney et al (1998); compared to their healthy siblings, BP probands scored significantly higher (p=0.002) on overall obstetric complication score resulting from a wide range of OCs. Browne et al (2000) found a non-significant trend for male BP subjects to have experienced more frequent OCs (mean frequency score: BP vs. controls = 0.1, sd 0.3 vs. 0.01, sd 0.2) and more severe OCs (mean severity score: BP vs. controls = 0.2, sd 0.6 vs. 0.04, sd 0.2) compared with male controls.

[1] These authors reported on the prevalence of specific OC. The results of Mortensen et al (unpublished) are presented in Table 16, Cannon et al (2002) in table 17 and Gunduz et al (unpublished) in table 18.

The above results have not been replicated. Gunduz et al (unpublished) summarised the obstetric history of 34 subjects (13 BP probands and 21 non-psychiatric controls) using the McNeill- Sjostrom (1994) scale which categorises OCs into levels depending on their presumed potential for damage (particularly to the central nervous system). Gunduz et al (unpublished) found that individuals with BP were not more likely to have a history of level four ("clearly potentially harmful or relevant") or level five ("clearly potentially greatly harmful or relevant") pregnancy, labour or delivery complications compared with healthy controls (table 18). By comparison the mean number of complications experienced by healthy control subjects which were categorised as either level four, five & six[2] complications was nearly double that experienced by the subjects who developed BP (mean frequency score: BP vs. controls = 1.0, sd 1.0 vs. 1.8, sd 1.78; table 18). However, this result failed to reach statistical significance. Cannon et al (2002) compared the obstetric history of 20 individuals enrolled in the Dunedin Multidisciplinary Health and Development Study at birth who were subsequently diagnosed with mania at age 26 years using the DIS with 642 individuals enrolled in the same study who were not subsequently diagnosed with either mania, schizophreniform disorder, depression or anxiety. The authors found that obstetric history was not significantly associated with a later diagnosis of mania (β=0.03; 95% CI –0.15- 0.21). By comparison, Verdoux & Bourgeois (1993a) found that an equal number of BP subjects and healthy control subjects experienced pregnancy complications (17.4%). Furthermore, the average number of perinatal complications experienced (mean frequency score: BP vs. controls = 0.48, sd 0.7 vs. 0.52, sd 0.85) and the severity of the perinatal complications experienced (mean severity score: BP vs. controls = 0.8, sd 1.3 vs. 0.9, sd 1.5) was similar for both groups.

Data on the frequency of specific OCs were available from two unpublished studies (The Camberwell Collaborative Psychosis Study; Mortensen et al). Data on the specific complications measured by Cannon et al (2002) was also received from the author. Data for the unpublished studies are presented in Table 16. The additional data for

[2] Level 6 complications are defined as complications that can cause "great harm to, or deviation in, the offspring"

Cannon et al (2002) is presented in Table 17. The Camberwell Collaborative Psychosis Study (unpublished) and Mortensen et al (unpublished) compared BP subjects and healthy control subjects and found that there was a marginally increased risk of BP given a birth weight of 4000 grams or more. Mortensen et al (unpublished) found that the RR of developing BP given a birth weight of 4000 grams or more was 1.2 (95% CI 0.5 - 3.1) compared with healthy controls. However, individuals with a birth weight of 2500-3000 grams were equally likely to be BP subjects or healthy control subjects (RR 1.1, 95% CI 0.5 - 2.4). In comparison, The Camberwell Collaborative Psychosis Study found that the RR of developing BP given a birth weight of 4000 grams or more was 1.4 (95% CI 0.7- 2.9) when compared with healthy controls, whilst individuals with a birth weight of 2500-3000 grams had nearly a two-fold increased risk of developing BP (RR 1.7, 95% CI 0.9 - 3.4) as compared with controls.

Mortensen et al (unpublished) also reported that the RR of developing BP was more than double if the mother was 34 years or older at the time of delivery (RR 2.2, 95% CI 0.8-6.1; table 16). By comparison, The Camberwell Collaborative Psychosis Study (unpublished) found that the RR of BP was less if the mother was 34 years or older (RR 0.5, 95% CI 0.1-1.9; table 16).

Unlike Mortensen et al (unpublished) and the Camberwell Collaborative study (unpublished), Cannon et al (2002) compared the incidence of antepartum haemorrhage and rhesus antibodies. Cannon et al (2002) found that these variables resulted in a non-significant increased risk of mania when compared with healthy non-psychiatric controls (antepartum haemorrhage: OR 3.6, 95% CI 0.4-29.5; rhesus: OR 3.7 95% CI 0.4-31.7; Table 17)

Three studies examined whether BP is associated with OCs occurring during a specific period of reproduction (Gunduz et al, unpublished; Kinney et al, 1993; Kinney et al, 1998). Kinney et al (1993) found that BP was associated with significantly more frequent and more severe perinatal [3]complications (mean frequency score: BP vs.

[3] peri-natal complications are from the 28 weeks gestation through to the first 7 days after delivery.

siblings = 1.75 sd 1.0 vs. 0.80 sd 0.77, p=0.006; mean severity score: BP vs. siblings– 1.56 sd 0.73 vs. 0.90 sd 0.85, p=0.027). However BP probands did not differ from their healthy siblings with respect to prenatal[4] complications (mean frequency score: 0.69, sd 0.87 vs. 0.50, sd 0.83, p=0.40; mean severity score: 0.88, sd 0.96 vs. 0.60, sd 0.94, p=0.36). By comparison, Kinney et al (1998) found that BP probands in comparison to their healthy siblings experienced significantly more prenatal complications (p=0.02) and perinatal complications (p=0.04). Gunduz et al (unpublished) found a non-significant trend for individuals with BP to experience a greater mean number of pregnancy complications which were categorised as either level five or level six complications compared to non-psychiatric controls (mean number of level 5 or 6 pregnancy complications: BP vs. controls = 0.15, sd 0.37 vs. 0.05, sd 0.22; table 18). However, both groups experienced a similar mean number of labour/delivery and neonatal complications that were categorised as either level five or level six complications (labour/ delivery complications: BP vs. controls = 0 vs. 0.1, sd 0.44; neonatal complications: BP vs. controls= 0.08, sd 0.28 vs. 0.1, sd 0.3) (Table 18).

[4] pre-natal complications are from conception to birth

Table 15. Studies comparing obstetric complications in bipolar patients and healthy controls

Author	Prenatal or Perinatal complications		Estimated OR (95% CI)
	BP	Controls	
Kinney et al (1998)	severe OCs =10 (33%)	severe OCs=1 (4%)	12.0 (1.4 –101.9)
Kinney et al (1993)	Perinatal OCs= 15 (94%)	Perinatal OCs= 12 (60%)	10.0 (1.1- 91.5)
Camberwell Collaborative Psychosis Study (unpublished)	definite OCs= 9 (24%)	definite OCs=28 (28%)	0.8 (0.3- 2.0)
Verdoux & Bourgeois (1993a)	P= 4 (17.4%)	P= 4 (17.4%)	1.0 (0.2- 4.6)
Stober et al (1997)	gestational infection = 8 (20%) definite or equivocal OCs= 18 (45%)	gestational infection = 7 (17.5%) definite or equivocal OCs= 20 (50%)	1.2 (0.4 -3.6) 0.8 (0.3- 2.0)
Browne et al (2000)	definite OCs= 9 (11.8%) any OCs= 17 (22.4%)	definite OCs=11(14.5%) any OCs=14(18.4%)	0.8 (0.3-2.3) 1.3 (0.5-3.1)

P denotes complications during pregnancy

Table 16. Specific obstetric complications experienced by individuals with bipolar disorder compared to healthy controls.

OCs	Mortensen et al (unpublished)			Camberwell Collaborative Psychosis Study (unpublished)		
	BP	Controls	RR (95%CI)	BP	Controls	RR (95%CI)
Birth weight (grams)						
<2500	0	1680 (5%)	-	2 (5.5%)	8 (8%)	0.74 (0.2-2.7)
2500-3000	7 (17.5%)	5558 (16.7%)	1.1 (0.5-2.4)	6 (16.7%)	8 (8%)	1.7 (0.9-3.4)
3000-4000	28 (70%)	22559 (67.7%)	1.1 (0.7-2.2)	22 (61.1%)	73 (73%)	0.7 (0.4-1.2)
>4000	5 (12.5%)	3523 (10.6%)	1.2 (0.5-3.1)	6 (16.7%)	11 (11%)	1.4 (0.7-2.9)
Gestation age						
>40 weeks	-	-	-	8 (22.2%)	24 (24%)	0.9 (0.5-1.8)
40 weeks	39 (97.5%)	30312 (91%)	3.9 (0.5-28.2)	24 (66.7%)	55 (55%)	1.4 (0.8-2.6)
37-39 weeks	1 (2.5%)	1966 (5.9%)	0.4 (0.1-2.98)	3 (8.3%)	18 (18%)	0.5 (0.2-1.5)
Mothers age (years)						
<20	3 (7.5%)	2129 (6.4%)	1.2 (0.4-3.9)	5 (13.5%)	10 (10%)	1.3 (0.6-2.8)
20-34	33 (82.5%)	29568 (88.7%)	0.6 (0.3-1.4)	30 (81.1%)	79 (79%)	1.1 (0.5-2.2)
>34	4 (10%)	1623 (4.9%)	2.2 (0.8-6.1)	2 (5.4%)	12 (12%)	0.5 (0.1-1.9)
Caesarean	1 (2.5%)	2033 (6.1%)	0.4 (0.65-2.9)	0	10 (10%)	-
Breech	1 (2.5%)	1441 (4.3%)	0.6 (0.1-4.1)	0	5 (5%)	-

Table 17. Obstetric complications experienced by individuals with bipolar disorder and healthy controls. Unpublished data from Cannon et al (2002)

Obstetric complication	Mania (n=20)	Controls (n=642)	OR (95% CI)
Parity of 1	8 (40%)	192 (29.9%)	1.6 (0.6-3.8)
Parity of 4 or greater	5 (25%)	131 (20.4%)	1.3 (0.5-3.7)
Maternal diabetes	0	7 (1.1%)	-
Maternal hypertension	0	55 (8.6%)	-
Antepartum haemorrhage	1 (5%)	10 (1.6%)	3.6 (0.4-29.5)
Forceps delivery	6 (30%)	133 (20.7%)	1.6 (0.6-4.2)
Caesarean section	0	29 (4.5%)	-
Apgar <10	0	6 (0.9%)	-
Hypoxia	0	16 (2.5%)	-
Small for gestation age	2 (10%)	48 (7.5%)	1.4 (0.3-6.2)
Gestation age <37 weeks	0	27 (4.2%)	-
Rhesus/ ABO/ jaundice	1 (5%)	9 (1.4%)	3.7 (0.4-31.7)
Neurological signs at birth	1 (5%)	15 (2.3%)	2.2 (0.3-18.2)
Birth weight <2500g	1 (5%)	32 (5.0%)	1.0 (0.1-7.7)
Length< 48 cm	0	26 (4.0%)	-
Head circumference < 31 cm	0	4 (0.6%)	-

Table 18. Comparison of individuals with bipolar disorder and healthy controls. Data from Gunduz et al (unpublished)

	BP (n=13)	Controls (n=21)	OR (95% CI)
Number (%) of subjects with level 4 complications			
Pregnancy	3 (23%)	7 (33%)	0.6 (0.1-2.9)
Labour & Delivery	6 (46%)	13 (62%)	0.5 (0.1-2.1)
Neonatal	1 (8%)	5 (24%)	0.3 (0.03-2.6)
Any OCs [1]	8 (62%)	15 (71%)	0.6 (0.1-2.8)
Number (%) of subjects with level 5 complications			
Pregnancy	2 (15%)	1 (5%)	3.6 (0.29-44.8)
Labour & Delivery	0	1 (5%)	-
Neonatal	1 (8%)	2 (10%)	0.8 (0.06-9.7)
Any OCs [1]	3 (23%)	3 (14%)	1.8 (0.3-10.6)
Mean (sd) number of level 4, 5 & 6 complications per subject			
Pregnancy	0.31 (0.63)	0.43 (0.68)	-
Labour & delivery	0.62 (0.77)	1.05 (1.07)	-
Neonatal	0.08 (0.28)	0.33 (0.66)	-
Any OCs [1]	1.0 (1.0)	1.81 (1.78)	-
Mean number (sd) of level 5 & 6 complications per subject			
Pregnancy	0.15 (0.37)	0.05 (0.22)	-
Labour & Delivery	0	0.1 (0.44)	-
Neonatal	0.08 (0.28)	0.1 (0.3)	-
Any OCs [1]	0.23 (0.44)	0.24 (0.7)	-

[1] All OCs denotes complications occurring during pregnancy, labour, delivery or the neonatal period

2.3.2 Studies with a psychiatric comparison group

Studies comparing bipolar disorder and schizophrenia

As noted by Geddes et al (1999) complications of labour and pregnancy are among the most extensively studied putative risk factor for schizophrenia. Eight studies compared the number of individuals with schizophrenia and the number of individuals with BP who experienced OCs (Byrne et al, 1996; Camberwell Collaborative Psychosis Study, unpublished; Gunduz et al, unpublished; Lewis & Murray, 1987; Mortensen et al, unpublished; Schwarzkopf et al, 1989; Verdoux & Bourgeois, 1993a; Vocisano et al, 1996). Five of these studies are summarised in Table 19. The results of Mortensen et al (unpublished)[5], Gunduz et al (unpublished)[5] and Byrne et al (1996) were excluded from Table 19. (The latter because no appropriate numerical data were available).

All, but one, of the studies in Table 19 suggest that more individuals with schizophrenia experienced OCs compared to individuals with BP. However, this trend reached statistical significance in only one study. Verdoux and Bourgeois (1993a) reported that 47% (n=11) of mother of individuals with schizophrenia experienced OCs during pregnancy compared with 17% (n=4) of mothers of individuals with BP (Fischer's exact test $p = 0.03$). This was largely due to the difference between mothers of females, as analysis by gender indicated that only mothers of females with schizophrenia experienced significantly more pregnancy complications than mothers of females with BP (Fischer's exact test, $p< 0.005$), whereas mothers of males with BP and the mothers of males with schizophrenia did not differ. Vocisano et al (1996) found that individuals with BP did not experience significantly more OCs than individuals with schizophrenia (Table 19), however experiencing OCs increased the risk of

[5] The result of Mortensen et al (unpublished) are presented in Table 21. The results of Gunduz et al (unpublished) are presented in Table 20

developing functionally deteriorated BP[6] compared with schizophrenia (RR 2.0, 95% CI 0.7-5.3).

[6] Functionally deteriorated BP was defined as those patients who were continually hospitalised or were outpatients dependent on others for necessities such as food or clothing, who had no useful work or employment and who did not have full symptom remission over the previous five years.

Table 19. Studies comparing obstetric complications in individuals with bipolar disorder and schizophrenia

Author	Prenatal or Perinatal complications		Estimated OR (95% CI)
	BP	Schizophrenia	
Vocisano et al (1996)	6 (24%)	ScZ = 7 (24%)	1.0 (0.3-3.5)
Lewis & Murray (1987)	12 (11%)	ScZ=35 (17%)	0.6 (0.3- 1.2)
Camberwell Collaborative Psychosis Study (unpublished)	9 (24%)	ScZ=30 (35%)	0.6 (0.2-1.4)
Schwarzkopf et al (1989)	mean number of OCs per person 0.8 (s.d 0.42)	mean number of OCs per person ScZ = 2.2 (s.d 1.6)	
Verdoux & Bourgeois (1993a)	4 (17.4%)	ScZ = 11 (47.4%)	0.2 (0.1- 0.9)

ScZ denotes schizophrenia

Four studies compared the mean number of OCs experienced by individuals with schizophrenia and individuals with BP (Byrne et al, 1996; Gunduz et al, unpublished; Schwarzkopf et al, 1989; Verdoux & Bourgeois, 1993a). Verdoux and Bourgeois (1993a) found that mothers of individuals with schizophrenia had experienced significantly more perinatal complications compared to mothers of individuals with BP (mean frequency score: BP vs. schizophrenia = 0.5, sd 0.7 vs. 1.2, sd 0.1; Mann-Whitney U-test, $p< 0.01$). Byrne et al (1996) found only a significant difference between mothers of males with schizophrenia as compared with mothers of males with mania (using Lewis et al, 1989 scale, $p=0.007$; using Parnas et al 1982, scale $p< 0.001$). Similar results were reported by Schwarzkopf et al (1989), however this result failed to reach significance (mean frequency score for peri- natal complications: BP vs. schizophrenia = 0.8, sd 0.42 vs. 2.2, sd 1.6).

Two studies compared the severity of the OCs experienced by mothers of individuals with schizophrenia and mothers of individuals with BP (Byrne et al, 1996; Verdoux & Bourgeois, 1993a). In a comparison of 23 BP probands and 23 schizophrenic probands, Verdoux & Bourgeois (1993a) found that the perinatal complications experienced by the mothers of individuals with schizophrenia were significantly more severe than those experienced by the mothers of individuals with BP (mean severity score BP vs. schizophrenia = 0.8, sd 1.3 vs. 1.9, sd 1.7; Mann-Whitney U-test, $p<0.02$). Again Byrne et al (1996) confirmed this finding in male populations ($p=0.02$).

Data on the frequency of specific OCs were available from three studies (The Camberwell Collaborative Psychosis Study, unpublished; Mortensen et al, unpublished; Schwarzkopf et al, 1989). In the Camberwell Collaborative Psychosis Study (unpublished), significantly more mothers of individuals with schizophrenia (n=9, 11%) reported infections, such as rubella, during pregnancy compared with mothers of individuals with BP disorders (0%) (Fisher's exact test $p=0.03$). Schwarzkopf et al (1989) found that the mothers of individuals who developed schizophrenia were

significantly more likely to have had a prolonged labour compared to mothers of BP subjects (Fisher's exact test p=0.02).

The Camberwell Collaborative Psychosis Study database also reported that the risk of developing BP was double the risk of developing schizophrenia if an individual had a birth weight of 4000 grams or more (RR 2.1, 95% CI 1.2 – 3.8; Table 21). Mortensen et al (unpublished) agreed that the RR of BP in comparison to schizophrenia, is increased given a birth weight of 4000 grams or more, with a RR of 1.6 (95% CI 0.5- 4.8; Table 21).

Unlike Mortensen et al (unpublished), the Camberwell Collaborative Psychosis Study database compared the number individuals with BP and schizophrenia who were born post term (after 40 weeks of gestation). The Camberwell Collaborative Psychosis Study found that babies who remained in gestation beyond 40 weeks were significantly more at risk of BP than schizophrenia (RR 1.9, 95% CI 1.1-3.4).

Table 20. Comparison of the obstetric complications experienced by individuals with bipolar disorder and schizophrenia. Data from Gunduz et al (unpublished)

	BP (n= 13)	Schizophrenia (n=61)	OR (95% CI)
Number (%) of subjects with level 4 complications			
Pregnancy	3 (23%)	21 (34%)	0.6 (0.1 –2.3)
Labour & Delivery	6 (46%)	29 (48%)	1.0 (0.3 –3.1)
Neonatal	1 (8%)	9 (15%)	0.5 (0.1 –4.2)
Any OCs [1]	8 (62%)	42 (69%)	0.7 (0.2-2.5)
Number (%) of subjects with level 5 complications			
Pregnancy	2 (15%)	13 (21.3%)	0.2 (0.04-1.1)
Labour & Delivery	0	5 (8%)	-
Neonatal	1 (8%)	2 (3%)	2.5 (0.2 –29.3)
Any OCs [1]	3 (23%)	14 (23%)	1.0 (0.2-4.2)
Mean (sd) number of level 4, 5 & 6 complications per subject			
Pregnancy	0.31 (0.63)	0.49 (0.83)	-
Labour & delivery	0.62 (0.77)	0.64 (0.84)	-
Neonatal	0.08 (0.28)	0.18 (0.47)	-
Any OCs [1]	1.0 (1.0)	1.31(1.32)	-
Mean (sd) number of level 5 & 6 complications per subject			
Pregnancy	0.15 (0.37)	0.13 (0.34)	-
Labour & Delivery	0	0.11 (0.41)	-
Neonatal	0.08 (0.28)	0.03 (0.18)	-
Any OCs [1]	0.23 (0.44)	0.28 (0.55)	-

[1] All OCs denotes complications occurring during pregnancy, delivery, labour and the neonatal period.

Table 21. Comparison of the specific obstetric complications experienced by individuals with bipolar disorder and schizophrenia.

OCs	Mortensen et al (unpublished)			Camberwell Collaborative Psychosis Study (unpublished)		
	BP	ScZ	RR (95% CI)	BP	ScZ	RR (95%CI)
Birth weight (grams)						
<2500	0	8 (6%)	-	2 (5.5%)	13 (16.5%)	0.4 (0.1-1.5)
2500-3000	7 (17.5%)	25 (19%)	0.9 (0.4-2.3)	6 (16.7%)	18 (22.8%)	0.8 (0.4-1.6)
3001-4000	28 (70%)	88 (66.7%)	1.2 (0.5-2.5)	22 (61.1%)	44 (55.7%)	1.2 (0.7-2.0)
>4000	5 (12.5%)	11 (8.3%)	1.6 (0.5-4.8)	6 (16.7%)	4 (5%)	**2.1 (1.2- 3.8)**
Mothers age (years)						
<20	3 (7.5%)	13 (9.8%)	0.7 (0.4-3.9)	5 (13.5%)	7 (8.4%)	1.4 (0.7-2.9)
21-34	33 (82.5%)	110 (83.3%)	0.9 (0.4-2.4)	30 (81.1%)	64 (77.1%)	1.2 (0.6-2.4)
>34	4 (10%)	9 (6.8%)	1.5 (0.4-5.2)	2 (5.4%)	12 (14.4%)	0.4 (0.1-1.6)
Gestation age						
>40 weeks	-	-		8 (36%)	7 (8.9%)	**1.9 (1.1-3.4)**
40 weeks	39 (97.5%)	118 (89.4%)	4.6 (0.6-36.3)	24 (66.7%)	55 (70%)	0.9 (0.5-1.6)
37-39 weeks	1 (2.5%)	9 (6.8%)	0.3 (0.04-2.8)	3 (8.3%)	12 (15.2%)	0.6 (0.2-1.7)
< 36 weeks	0	5 (3.8%)	-	1 (2.8%)	5 (6.3%)	0.5 (0.1-3.2)
Caesarean	1 (2.5%)	9 (6.8%)	0.3 (0.1-2.9)	0	3 (5.5%)	-
Breech	1 (2.5%)	7 (5.3%)	0.5 (0.05-3.8)	0	6 (7.6%)	-

ScZ denotes schizophrenia

Studies comparing bipolar disorder and unipolar depression

Five studies have compared OCs in BP and UP (Camberwell Collaborative Psychosis Study, unpublished; Gunduz et al, unpublished; Lewis & Murray, 1987; Sigurdsson et al, 1999; Vocisano et al, 1996). As shown in Table 22, the results are inconsistent and there were no reported statistically significant differences.

Only one study compared the mean number of OCs experienced by individuals with BP and individuals with UP. Gunduz et al (unpublished) found that the mean number of level four, five or six OCs experienced by individuals with UP with psychotic symptoms (2.2, sd 1.3) and individuals with UP with no psychotic symptoms (1.3, sd 1.3) was greater than that experienced by those with BP (1.0, sd 1.0). This result did not reach statistical significance. Although Vocisano et al (1996) did not find a difference between all individuals with BP and individuals with UP, the authors found a non-significant difference between individuals with functionally deteriorated BP and individuals with UP; individuals who experienced OCs had an increased risk of developing functionally deteriorated BP (RR 1.9, 95% CI 0.7-5.5) but not non-functionally deteriorated BP (RR 0.8, 95% CI 0.4-1.7) compared with UP.

Table 22. Studies comparing obstetric complications in individuals with bipolar disorder and individuals with unipolar depression

Author	Prenatal or Perinatal complications		Estimated OR
	BP	UP	(95% CI)
Vocisano et al (1996)	6 (24%)	UP = 6 (21%)	1.2 (0.3- 4.4)
Lewis & Murray (1987)	12 (11%)	UP = 9 (10%)	1.1 (0.5 - 2.8)
Camberwell Collaborative Psychosis Study (unpublished)	9 (24%)	UP = 2 (17%)	1.6 (0.3- 8.7)
Gunduz et al (unpublished)	Potentially harmful OCs P= 3 (23%) L&D= 6 (46%) N= 1(8%) Potentially greatly harmful OCs P= 2 (15%) L&D = 0 N= 1 (8%)	Potentially harmful OCs P=4 (26.4%) L&D= 9 (60%) N= 5 (33.3%) Potentially greatly harmful OCs P=1 (6.7%) L&D= 2 (13%) N= 1 (6.7%)	Potentially harmful OCs P= 0.8 (0.2 -4.6) L & D=0.6 (0.2- 2.6) N= 0.2 (0.1-1.7) Potentially greatly harmful OCs P= 2.5 (0.2-31.9) N= 1.2 (0.07-20.7)
Sigurdsson et al (1999)	5 (14%)	UP = 6 (15%)	0.9 (0.3 – 3.2)

UP denotes unipolar depression;

L&D denotes complications occurring during labour and delivery;

P denotes complications occurring during pregnancy;

N denotes complications occurring during the neonatal period

Studies comparing individuals with bipolar disorder and individuals with schizoaffective disorder

Two studies compared OCs in individuals with BP and individuals with schizoaffective disorder (Gunduz et al, unpublished; Schwarzkopf et al, 1989). As shown in Table 12 the sample sizes in both studies were small; six schizoaffective and ten BP subjects in Schwarzkopf et al (1989) and 26 schizoaffective and 13 BP subjects in Gunduz et al (unpublished). The number of individuals with schizoaffective disorder and BP who had a history of OCs did not differ significantly in either study (Table 23). Schwarzkopf et al (1989) found that the mean number of perinatal complications experienced by individuals with schizoaffective disorder was three times that experienced by those with BP (mean frequency score: BP vs. schizoaffective disorder = 0.8, sd 0.4 vs. 2.5, sd 3.1; table 23). However, this result failed to reach statistical significance. In addition, Schwarzkopf et al (1989) reported a non-significant trend for individuals with schizoaffective disorder to experience more severe perinatal complications compared to individuals with BP (mean severity score: BP vs. schizoaffective disorder = 1.0, sd 0.8 vs. 4.2, sd 6.2). However, Gunduz et al (unpublished) found that individuals with schizoaffective disorder and BP had experienced a similar number of OCs; (mean number of OCs categorised as level four, five or six complications: BP vs. schizoaffective disorder = 1.0, sd 1.0 vs. 1.08, sd 1.3). Few inferences can be drawn from the findings of these studies because of small sample size (Table 12) and inadequate statistical power.

Table 23. Studies comparing obstetric complications in individuals with bipolar and schizoaffective disorder

Author	Prenatal or Perinatal complications		Estimated OR (95% CI)
	BP	Schizoaffective	
Schwarzkopf et al (1989)	mean number of OCs per person (s.d) 0.8 (0.4)	mean number of OCs per person (s.d) 2.5 (3.1)	
Gunduz et al (unpublished)	Potentially harmful OCs P= 3 (23%) L&D= 6 (46%) N= 1 (8%) Potentially greatly harmful OCs P = 2 (15%) L & D= 0 N= 1 (8%)	Potentially harmful OCs P = 6 (23%) L & D= 13 (50%) N= 4 (15%) Potentially greatly harmful OCs P = 0 L & D= 5 (15%) N= 1 (4%)	Potentially harmful OCs P= 1.0 (0.2- 4.9) L & D= 0.7 (0.2 –2.6) N= 0.5 (0.05-4.6) Potentially greatly harmful OCs N= 2.1 (0.1-36.2)

P denotes complications occurring during pregnancy;
L&D denotes complications occurring during labour and delivery; N denotes complications occurring during the neonatal period

Studies comparing subjects with bipolar disorder and subjects with other DSM-IV diagnosis

There is limited research comparing the frequency of OCs in probands with BP compared and probands with other psychiatric disorders (Table 24). Lewis and Murray (1987) reported a non-significant trend for more individuals with BP (11%) to have experienced definite OCs compared to individuals diagnosed as having neurosis (5%), personality disorder (6%) and drug or alcohol dependence (3%). In contrast, the same study noted a non-significant trend for more individuals with anorexia nervosa (16%) to have experienced OCs compared to individuals with BP (11%; table 24)

Stober et al (1997) found that a greater, but non-significant, number of mothers of individuals with cycloid psychosis experienced gestational infections (23%) and in particular first trimester respiratory infections (10%) compared to mothers of individuals with BP (20% & 0% respectively; table 24)

2.3.3 Studies with no comparison group

Studies of the prevalence of OCs amongst individuals with BP that have no comparison group can be useful when the BP subjects are categorised into distinct subgroups such as early or late onset and familial or non-familial BP. Such studies have shown that OCs are more common in individuals with early onset compared to late onset BP (Taylor & Abrams, 1981). For example, Taylor & Abrams (1981) found that 10 out of 80 (12.5%) probands with an early onset BP (an episode before the age of 29 years) had experienced gestational or neonatal OCs compared with only two out of 54 (3.7%) probands with late onset BP. However, a history of OCs was not significantly associated with age at first presentation to psychiatric services (Browne et al, 2000; Camberwell Collaborative Psychosis Study, unpublished) or age at first psychiatric admission (Camberwell Collaborative Psychosis Study, unpublished; Stober et al, 1997) (Table 25).

Only two studies have compared the number of OCs experienced by BP subjects with a family history of BP and BP subjects without such a history (Browne et al, 2000; Dalen, 1965). In a study of 35 subjects, Dalen (1965) found that BP subjects with a family history of BP were as likely to experience perinatal complications as BP subjects without a family history of BP (16.7% vs. 17%). Similarly, Browne et al (2000) found that BP subjects with a family history of psychiatric disorder did not experience significantly more labour or delivery complications than the BP subjects without a family history of psychiatric disorder.

The relationship between OCs and the clinical course of BP is unclear. The Camberwell Collaborative Psychosis Study (unpublished) found a non-significant trend for fewer psychiatric admissions amongst patients with a history of definite OCs (mean 2.33, SD = 1.32) compared to those who had no or equivocal OCs (mean 4.46, SD =3.08). Unfortunately, length of stay was not recorded; so it was not possible to look at mean total number of occupied bed days per group (so we cannot exclude the possibility that individuals experiencing OCs may have had fewer but longer admissions). In a study of 25 BP patients (14 with functionally deteriorated BP and 11 with non-functionally deteriorated BP), Vocisano et al (1996) reported that there was a non- significant increase in individuals with functionally deteriorated BP (40%) who had experienced OCs compared to individuals with non-functionally deteriorated BP (18%).

Table 24. Studies comparing obstetric complications in bipolar patients and other psychiatric patients

Author	Prenatal or Perinatal Complications		OR
	BP	Comparison group(s)	(95%CI)
Lewis & Murray (1987)	12 (11%)	anorexia nervosa n=12 (16%)	0.7 (0.3-1.5)
		other psychosis n=6 (7%)	1.6 (0.6-4.5)
		personality disorder n=7 (6%)	1.9 (0.7-5.0)
		neurosis n=11 (5%)	2.13 (0.9-5.0)
		alcohol/drug dependence n=2 (3%)	4.0 (0.9-18.4)
Stober et al (1997)		cycloid psychosis	
	gestational infection: 8 (20%)	gestational infection: 9 (22.5%)	0.9 (0.3-2.5)
	definite or equivocal OCs: 18 (45%)	definite or equivocal OCs: 24 (60%)	0.5 (0.2-1.3)

Table 25. Mean age of onset for bipolar subjects with and without a history of definite obstetric complications

	History of Definite OCs	No history of Definite OCs
Age at first presentation at psychiatric services		
Browne et al (2000)	33.7 (10.0)	38.0 (15.0)
Camberwell Collaborative Psychosis Study (unpublished)	22.6 (6.6)	22.1 (4.9)
Age at first psychiatric admission		
Stober et al (1997)	26.6 (6.1)	26.9 (7.4)
Camberwell Collaborative Psychosis Study (unpublished)	23.6 (5.1)	22.8 (5.1)

2.3.4 Studies investigating whether the incidence of bipolar disorder is increased as a result of obstetric complications

Three cohort studies investigated whether individuals who experienced hypoxic-ischaemia-related fetal or neonatal complications or possible intrauterine exposure to a national epidemic were more likely to develop BP (Brown et al, 2000; Machon et al, 1997; Zornberg et al, 2000). Machon et al (1997) found a non-significant increase in the prevalence of BP amongst the offspring of women who were pregnant during the 1957 Greater Helsinki influenza epidemic. Five percent (3/56) of probands with mothers who were in their second trimester during the Greater Helsinki influenza epidemic were admitted to a psychiatric hospital before the age of 30 years with an ICD-8 diagnosis of BP in comparison to 1.6 % (7/442) of those born in the same county before the outbreak. Thus the RR of BP following possible intrauterine exposure to the Greater Helsinki influenza epidemic during the second trimester was 3.38 (95% CI 0.9-12.7). Maternal influenza is considered an obstetric complication as it is commonly associated with fetal mortality and can leave the fetus oxygen deprived as the mother's oxygen requirements are increased (with a fever of 104°c the fetal oxygen supply can be reduced by 50%) (Towbin, 1998). Similarly, Brown et al (2000) reported a non-significant increase in the cumulative incidence of BP amongst the offspring of mothers who were in their second trimester (2.2 per 1000 persons) and third trimester (2.1 per 1000 persons) during the Dutch Hunger Winter compared to individuals born in the same region before the outbreak (1.6 per 1000 persons). Brown et al (2000) presumed that the former individuals were exposed to prenatal under-nourishment and thus concluded that the RR of developing BP following exposure to prenatal under-nourishment in the second trimester was 1.4 (95% CI 0.9 -2.1) and the third trimester was 1.3 (95% CI 0.9 -1.9). Zornberg et al (2000) found that those who had experienced hypoxic-ischaemia-related fetal or neonatal complications had a two-fold increased risk of developing BP compared to those who had not (RR 2.0, 95% CI 0.4 - 8.6). Of 174 individuals from the 1959-1966 birth cohort exposed to hypoxic-ischaemia-related complications, 2.3% were diagnosed as having BP using the DIS during a prospective study. By comparison, only 1.2% of the 519

individuals who were not exposed to hypoxic-ischaemia-related complications had a BP diagnosis. This result failed to reach significance.

2.4 SUMMARY OF RESULTS

There are few statistically significant findings from this systematic review.

With respect to studies comparing individuals with BP and non-psychiatric controls, the statistically significant results are as follows. Kinney et al (1993; 1998) found that compared with their healthy siblings, BP probands were more likely to experience a wide range of non-specific OCs and the OCs experienced were more severe. Kinney et al (1993) concluded that this was due to OCs occurring exclusively during the perinatal period. Kinney et al (1998) found that BP probands in comparison to their healthy siblings experienced more prenatal complications and perinatal complications.

With respect to studies comparing individuals with BP and individuals with another psychiatric disorder, the statistically significant results are as follows. Verdoux & Bourgeois (1993a) found that more mothers of females with schizophrenia experienced perinatal complications compared to mother of females with BP. Furthermore, individuals with schizophrenia experienced a greater number of perinatal complications and the OCs experienced were significantly more severe (Byrne et al, 1996[7]; Verdoux & Bourgeois, 1993a). The specific obstetric complication found to be significantly more prevalent in individuals with schizophrenia were infection during pregnancy (Camberwell Collaborative Psychosis Study, unpublished) and prolonged labour (Schwarzkopf et al, 1989). The specific obstetric complication found to be significantly more prevalence in individuals with BP were birth weight greater than 4000grams and gestation age more than 40weeks (Camberwell Collaborative Psychosis Study, unpublished)

[7] Byrne et al (1996) only found a significant difference between males with schizophrenia and males with mania.

2.5 CONCLUSIONS

This systematic review clearly shows that there are insufficient data to establish the role of OCs in vulnerability to BP. The methodological inadequacies (particularly sample sizes) of the studies reported are compounded by a lack of a detailed hypotheses about the mechanism(s) by which OCs affect the fetus in such a way as to increase future risk of BP. For example, in studies with a statistically significant difference between BP cases and comparison groups no specific obstetric complication is consistently found to be associted with BP.

2.6 LIMITATIONS

This review would have been strengthened by a meta-analysis or logistic regression analysis which would have compensated for the lack of power in many studies due to small sample size. The results of logistic regression are not presented in this thesis as only work solely attributable to the author is included. Scott et al (2006) adapted the results of this systematic review to include logistic regression. A copy of this is enclosed at the end of the thesis.

The results of the logistic regression support the conclusions of the systematic review that there is no robust evidence that exposure to obstetric complications increases the risk of bipolar disorder.

2.7 IMPLICATIONS FOR FUTURE RESEARCH

The principal research implication of this review is the need for more rigorous systematic studies with adequate sample sizes and carefully defined subject groups.

The results of The Camberwell Collaborative Psychosis study (unpublished) and Mortensen et al (unpublished) suggested that high birth weight is a risk factor for BP. In order to verify this and investigate whether any other individual obstetric complication is a significant risk factor for BP, future studies should report on

the frequency of specific OCs in addition to reporting the number of subjects in each group who experienced any definite OCs.

CHAPTER 3. METHODOLOGY

The present study aims to explore the relationship between OCs and the subsequent development of BP. In order to develop the methodology for this study, the author began by reviewing the methodology of the papers included in the systematic review. Several methodological limitations were identified. The methodological critique below details some of these limitations. In each section the methodology adopted in the present study is discussed with the aim of describing how some of the limitations of previous research have been overcome.

3.1 METHODOLOGICAL CRITIQUE

3.1.1 Sample size

A type II error occurs when the null hypothesis is retained when it should be have been rejected. There are several ways to reduce the likelihood of making a type II error. One of these is to increase the power of the study. Power is the probability of correctly rejecting the null and can be increased by increasing the sample size of the study. The larger the sample size, the greater the power to detect a meaningful difference, and consequently the greater the probability that a correct decision will be made about rejecting or retaining the null hypothesis.

Using large samples in case control studies is also advisable as large samples increase the probability of obtaining a statistically significant result that is also clinically meaningful. Obtaining a significant difference with a small sample size requires that the experimental effect or difference between the groups is greater than that required by a study with a large sample size. For example, demonstrating treatment efficacy with a sample of 10 per group might require that the treatment effect accounts for 30% or more of the variance in the outcome. Obtaining the same significance level with a large sample size (say 300 per group) might only require one or two percent of the variance to be accounted for (Kaplan & Grant, 2000).

The largest published case-control study of OCs and BP contains just 76 BP and 76 control subjects (Browne et al, 2000). Thus small sample size may limit the power of previous studies investigating OCs as a risk factor for BP and may explain some of the inconsistent results as insignificant results may be due to type II error.

Future studies therefore need to have a large sample so that very little variance is needed between the groups in order to obtain a significant result.

Analysis in the present study is based on 313 BP probands and 313 control subjects and therefore has adequate power to detect a meaningful difference, and consequently the greater the probability that a correct decision will be made about rejecting or retaining the null hypothesis. Having a large sample will also assist in the interpretation of the variables which are reported as resulting in non-significant trends in chapter two. If these variables still do not reach statistical significance with a larger sample it could be assumed that they are not risk factors which failed to reach statistical significance due to lack of power.

3.1.2 Controlling confounding factors

Confounding is defined as an exposure-outcome association brought about by another factor that is associated with the outcome and exposure. One method of avoiding confounding in a case-control study is to choose control subjects that are deliberately matched to the exposed or case subjects on all known confounding factors.

Several studies investigating OCs as a risk factor for BP (Camberwell Collaborative Psychosis Study; Gunduz et al, unpublished; Verdoux & Bourgeois, 1993a) have failed to match cases and controls and thus have introduced confounding factors because of differences in such things as socio-economic status and access to prenatal care. The results of these studies are therefore difficult to interpret; although it is possible that OCs are a risk factor for BP it is equally possible that poor prenatal care or low socio-economic class increases the risk of OCs and later development of BP.

Case-control matching is not without its disadvantages. For example the matched variables can no longer be investigated in the analysis. Secondly, there can be instances where overmatching occurs. Matching on a variable that is associated only with the exposure (OCs) and not the disease (BP) reduces the statistical efficiency: the investigator has to stratify on the matching variable, while in an unmatched design adjustment for the variable would have been unnecessary.

Despite these limitations the present study is of a matched case-control design.

3.1.3 Gathering obstetric information retrospectively from maternal recall

The majority of studies investigating OCs as a risk factor for BP have gathered obstetric data retrospectively from mothers (Camberwell Collaborative Psychosis study, unpublished; Gunduz et al, unpublished; Kinney et al, 1998; Schwarzkopf et al, 1989; Stober et al, 1997; Verdoux & Bourgeois, 1993a; Vocisano et al, 1996). Comparison of retrospective reports of obstetric events gathered from mothers and prospective reports such as medical records suggest that reliance on maternal recall may introduce methodological limitations.

Firstly, mothers may not accurately recall events occurring during the prenatal period many years after the birth of their offspring. Whilst several authors have found that mothers have accurate long-term recall of their offsprings' birth weight (Tomeo et al, 1999) and gestation age (Hakim et al, 1992) and their own reproductive history (Drews et al, 1993; Martin, 1987; Olson et al, 1997). Maternal reports of labour associated problems and illness during pregnancy are reported to be unreliable. For example, Cantor-Graae et al (1998) interviewed 79 mothers comparing their recall of labour and delivery events with information recorded in hospital records. Sixty-two mothers had experienced OCs but in only four cases were the complications reported during the interview identical to that documented in medical records. Furthermore, when Casey et al (1992) interviewed 10 mothers, who had had medical problems such as diabetes, hepatitis, adult respiratory distress syndrome, abdominal trauma, and placenta

praevia during their pregnancy, none of the mothers reported any illness during pregnancy.

Secondly, gathering obstetric complication data retrospectively from mothers may increase the probability of a type I or a type II error. In case control studies this can happen in two ways, firstly as a result of reporting bias and secondly as a result of recall bias. Reporting bias is where mothers inaccurately recall events that did not occur. This is more commonly observed in cases as the mothers recall is often unconsciously altered by their need to explain their child's current medical status. Reporting bias results in an exaggeration of the difference between groups and thus increases the probability of a type I error. Recall bias by comparison is not an altered memory of events but a lack of memory for or underreporting of events. Loss of memory by both groups will not result in recall bias but will lead to a loss of statistical power,biasing results towards the null hypothesis and increasing the probability of a type II error. However, if the cases have more memory loss than controls or vice versa the difference between groups is inflated, increasing the probability of a type I error. On comparing maternal recall of obstetric events with information recorded in hospital records for 45 mothers of schizophrenics and 34 mothers with psychiatrically normal offspring Cantor-Graae (1998) demonstrated reporting and recall bias in a case-control study investigating OCs as a risk factor for mental illness. Although the results failed to reach significance, mothers of non-psychiatric probands reported their child's birth weight more accurately in comparison to the mothers of schizophrenics. The mothers of the schizophrenics also reported significantly more OCs than were reported in their medical records whereas mothers of the control group reported significantly fewer labour and delivery complications than were reported in their medical records, thus demonstrating reporting bias.

The present study is prospective in design and obstetric information is obtained from computerised medical records.

3.1.4 Use of obstetric complication summary scales

Seven of the studies reviewed in chapter 2 summarised the subjects obstetric

history using scales specifically designed for this purpose. Schwarzkopf et al (1989) and Verdoux & Bourgeois (1993a) used the Parnas et al (1982) scale, which consists of 25 OCs each weighted on a severity scale from 1-4 points. Three different summary scores can be calculated from this scale, the number of OCs experienced, severity rating for the most severe single obstetric complication and the total severity score (which is the sum of the severity weights for the specific OCs that occurred for the individual). The Lewis et al (1989) scale and the Lewis & Murray (1986) scale used by Browne et al (2000), the Camberwell Collaborative Psychosis study (unpublished), Lewis & Murray (1987) and Stober et al (1997) consists of 17 OCs constituting either definite or equivocal OCs. The McNeil-Sjostrom (1995) scale used by Gunduz et al (unpublished) consists of seven hundred OCs, each weighted on a seven-point severity scale. Use of these scales help replication of methodology, comparison and pooling of results. However, the scales themselves have several limitations and choice of scale can influence the sensitivity of the results.

Firstly the scores obtained from obstetric complication summary scales often do not reflect an individual's obstetric history. With the Lewis et al (1989) scale, patients with any one of the "definite complications" listed will obtain the highest possible score for total reproduction regardless of the varying amount of obstetric complications. For example a birth characterised by perinatal bleeding through placenta praevia, an emergency caesarean section at less than 37 weeks gestation, a birth weight of less than 2000 grams, requiring incubation and remaining in hospital for four weeks due to poor condition will result in a final score of two which is the same score assigned to a labour lasting less than 3 hours (McNeil et al, 1994). Furthermore with the Parnas et al (1982) scale the weightings assigned to some of the complications seem irregular e.g. complications occurring when the infant is no longer physically dependant on the mother such as "mother bleeding after delivery" are assigned the same severity weight as labour lasting 24 hours or more. Secondly, obstetric complication summary scales often lack adequate definitions. For example, in the Parnas et al (1982) scale no temporal boundaries are set for "contraction of the pelvis during listed labour" and no distinction is drawn between the terminology "mother's illness during pregnancy" and "mother's serious illness during pregnancy".

McNeil et al (1994) demonstrated how the scale chosen can influence the sensitivity of the results by using different scales to compare the obstetric histories of 70 schizophrenic patients and 70 non-psychiatric controls. When the data was analysed using the McNeil & Sjostrom (1994) scale and Lewis et al (1989) scale individuals with schizophrenia were found to have significantly more OCs. However, analysing the data using the Parnas et al (1982) scale resulted in a non-significant difference. Furthermore when the authors compared the obstetric histories of concordant twins for schizophrenia, discordant twins for schizophrenia and control twins, the scale chosen again largely affected the results. Analysing the data using the McNeil & Sjostrom (1995) scale and the Parnas et al (1982) scale produced similar results showing the highest rates in discordant twins and the lowest in the control twins. However analysing the data using the Lewis et al (1989) scale failed to show any significant difference amongst the groups and tended to reverse the rank of the groups. Similarly, McNeil (1997) found that the relationship observed between OCs, family history of psychosis and season of birth were influenced by the scale used to score and weight identical obstetric information for 70 schizophrenic patients and 70 matched controls. The results obtained from the McNeil & Sjostrom (1995) scale suggested that OCs amongst schizophrenics was related only to birth in January to April and to a negative family history of psychosis. In contrast the results obtained from the Lewis et al (1989) scale suggested that OCs amongst schizophrenics was related to birth in May to December but not related a family history of psychosis. By comparison use of the Parnas et al (1982) scale suggested that OCs was unrelated to both season of birth and family history of psychosis.

Finally, each obstetric complication has a different impact on the fetus and therefore combining several events in one subcategory does not make clinical or biological sense and will not aid the understanding of the origins and development of BP.

Therefore, future studies investigating OCs as a risk factor for BP should avoid use of these summary scales or should follow the methodology adopted by

Brown et al (2000) and analyse and report the results using more than one scale.

The present study has not used obstetric complication summary scales.

3.1.5 Multiple comparisons

Studies investigating whether specific OCs are a risk factor for BP involve large numbers of significance tests (Cannon et al, 2002; Camberwell Collaborative Psychosis Study, unpublished; Mortensen et al, unpublished). Significant results in these studies are often difficult to interpret. Although it is possible that a significant difference exists between the groups, it is equally possible that significance is the result of multiple comparisons. To explain, if we test a null hypothesis which is true using a significance level of p=0.05, we have a probability of 0.95 of coming to a correct conclusion. However if we test two independent true null hypotheses the probability that neither test will be significant is 0.90 (0.95 X 0.95). If we test 20 such hypotheses the probability of a correct conclusion is 0.36 (0.95^{20}). Thus the probability of getting at least one significant result when 20 comparisons are carried out is 0.64 (1.0 minus 0.36), which is greater than the probability of getting a non-significant result.

There are several ways to avoid incorrectly rejecting the null hypothesis due to multiple testing. Firstly, you can apply the Bonferroni correction, which adjusts the statistical significance for the number of tests that have been preformed on the study data. Applying the Bonferroni correction involves dividing the obtained p-value by the number of comparisons made and only if the obtained p-value is still less than this figure is the difference between the two groups considered statistically significant. A second method is to perform a logistic regression analysis which aims to find a subset of all the explanatory variables (obstetric complications) that can be combined to predict the value of the outcome variable (absence or presence of BP). The outcome of logistic regression is an equation where the outcome variable on the left hand side and a combination of the explanatory variables in on the right. For any future patient, the values of their explanatory variables can be fed into the equation to predict the value of their outcome variable.

The above methods can only be applied to datum in which there is only two study groups e.g. individuals with BP and healthy controls. Several studies investigating OCs as a risk factor for BP have compared individuals with BP to both healthy controls and groups of individuals with some other DSM-IV diagnoses such as schizophrenia or major depression. Comparing the individuals with BP and the controls and then the individuals with BP and the other psychiatric group could introduce the problems of multiple comparisons. Applying the multiple analysis of variance (MANOVA) where all three groups are compared at one time could reduce the number of comparisons. Using this method only if a statistical result is found should the two groups be compared independently.

In conclusion it is suggested that studies investigating the relationship between specific OCs and BP are aware of the consequences of multiple comparisons and take steps to reduce the probability of making a type I error.
The present study will apply the Bonferroni correction were appropriate.

3.2 METHODS

3.2.1. Introduction

This case-control study aims to explore the relationship between OCs and the development of BP in individuals born in Scotland between the 1st January 1969 and the 31st December 1974. The frequency of pregnancy, labour and delivery and neonatal complications in individuals with BP will be compared with a matched sample of non-psychiatric controls.

A recent meta-analysis reported that schizophrenia was associated not only with obstetric complications as a whole but also more specifically with distinct complications linked with hypoxia (Geddes et al, 1999). To date the specific complications associated with BP have not been identified. Thus the present study will investigate specific OCs and maternal reproductive variables recorded at the Information Statistics Division (ISD) of the National Health Service in

Scotland and explore the association between these and the development of BP.

The present study will involve a large sample and will use obstetric information recorded at the time of birth. This study will therefore avoid many of the limitations of previous research such as bias from maternal recall and insufficient power to detect statistically significant differences.

3.2.2 Research aims

The study aims are as follows:

1. To test the hypothesis that OCs are more common in individuals diagnosed as having BP than in a matched sample of non-psychiatric controls.
2. To compare the prevalence of individual OCs in BP probands and a matched sample of non-psychiatric controls.

3.2.3 Hypotheses

1. More individuals with BP will have experienced OCs compared to matched controls.
2. Individuals with BP will have experienced a greater number of OCs compared to matched controls.

3.2.4 Description of the Scottish morbidity records used

Scottish Morbidity Record 4

The Mental Health and Day Case Register was computerised in 1958 and became Scottish Morbidity Record 4 (SMR4). The SMR4 contains information on all psychiatric admissions and day hospital treatments in Scotland. Information in the SMR4 file includes the diagnoses leading to admission or treatment diagnoses. Before March 1996 this information was coded using the 9th edition of the International Classification of Diseases (ICD-9) and thereafter using the 10th edition (ICD-10).

Scottish Morbidity Record 2

The maternity inpatient and day case register was computerised in January 1969 and is now known as Scottish Morbidity Record 2 (SMR2). SMR2 includes information on approximately 64% of Scottish births in 1969, 79% between 1971 and 1973 and 83% in 1974. A SMR2 form is completed for all patients receiving care in the obstetrics specialities/ health professions in Scotland. The form contains five sections covering personal and demographic information, previous pregnancies, past obstetric history, current pregnancy and records of labour. In addition, information on prenatal and puerperium complications are held in ICD-8 codes.

3.2.5 Sample

Method used to select the bipolar disorder group

Information recorded in SMR4 was used to identify all individuals born in Scotland between 1st January 1969 and 31st December 1974 with a current diagnosis of BP (ICD10: F30.0 –F30.9 and F31.0 – F31.8). To obtain the most current diagnosis, previous and subsequent SMR4 episodes were examined.

The computerised psychiatric records (SMR4) for each BP proband and the computerised maternity records (SMR2) for the proband were then linked together. In order to ensure that the SMR4 and SMR2 entries referred to the same individual, this link was constructed by comparing surname/maiden name; postcode/parish; code/common unit; gender and date of birth. The decision of whether the psychiatric and maternity records belonged together was made from the results of a probability matching algorithm. This system of linking computerised medical records is well established at ISD and is currently being used to link together all computerised hospital records belonging to the same patient (Kendrick & Clarke, 1993). Clerical checking of records linked using this method have shown that the rate of false positive (the proportion of linked records which in fact do not refer to the same individual) and the rate of false negative (the proportion of truly matched pairs which the system fails to link) is

around 1%.

A reliable link could be made for 335 (40.5%) of the 828 individuals with a current diagnosis of BP and born in 1969-1974 and originally identified from the SMR4 (psychiatric) file. The main reasons for failure to identify an individuals SMR2 (obstetric) file were change of surname following adoption, coding error, failure of the psychiatric unit to record the original maiden name of the married women and, as previously mentioned, the fact that around a quarter of births were not recorded on SMR2 due to home delivery or birth outside Scotland.

Five of the BP subjects were twins. As the SMR4 (psychiatric) file contains date of birth but not order of birth for twins it was not possible to differentiate which information on the SMR2 (obstetric) file belonged to the BP proband and which belonged to their twin. Therefore twins were excluded from the final analysis.

Method used to select the control group

Each BP case was matched to a live birth recorded on SMR2 between 1st January 1969 and 31st December 1974 and not subsequently admitted to a psychiatric hospital in Scotland, i.e. an individual who was not registered on SMR4. The control sample was matched to the BP case on the following variables: obstetric unit of birth, gender, calendar year of birth, mother's age group, maternal parity (first baby vs. second or subsequent baby), father's occupation (manual vs. non-manual). Twins and singletons were matched separately.

In the present study all potential controls were extracted from the SMR2 database and randomly sorted within the matching variables. The control subjects were then sorted on a generated random number prior to matching. This ensured that the controls were not selected in the SMR2 file sequential order and hence the present study is not subject to the methodological limitation of Kendell et al (1996) paper (see appendix 3).

The SMR2 database contained a matched control for 313 (94.8%) of 330 BP probands. Thus the BP-healthy controls comparisons were based on obstetric histories of 313 BP probands and 313 healthy controls.

3.2.6 Data

All information was obtained from the Information Statistics Division (ISD) of the National Health Service of Scotland. The data was received in SPSS format with the SMR4 (psychiatric) and SMR2 (obstetric) data stored adjacently and marked with unique patient identifiers[1]. The format of the SMR2 SPSS file is shown in appendix 4. Information obtained from the psychiatric probands SMR4 file included age, gender, ICD (version 9 or 10) diagnoses at first psychiatric admission and age at first admission, current ICD (version 9 or 10) diagnoses and age at first admission for current diagnoses.

Any SMR2 variable considered an obstetric complication in a study included in the systematic review was considered an obstetric complication in the present study. The SMR2 variables considered OCs are presented in table 26. As shown in table 26, the variables were categorised as follows; variables concerning the mothers reproductive history, complications of pregnancy [2], complications of labour[3] and complications of delivery [4] and complications of the neonatal period[5]. The references for the publications which considered each SMR2 variable an obstetric complication are presented in appendix 6. The definition of each obstetric complication and the associated risks to the fetus are presented in appendix 6.

For several probands it was not possible to calculate the number of complications experienced due to missing datum. However for some of these individuals it was

[1] Patient identifiers were provided only to allow the author to obtain further information on the same individuals at a later date; it was not possible to identify any of the subjects from the information received.
[2] Complications occurring between conception and the onset of labour.
[3] Complications occurring whilst the fetus, placenta and membranes are being expelled through the birth canal.
[4] Complications occurring during the removal of the fetus from the uterus.
[5] Complications occurring in the first 4 weeks after birth

possible to confirm the history of OCs in any period. For example if the SMR2 record of an individual did not contain information on the duration of labour it was not possible to calculate the number of labour and delivery complications that the individual had experienced because they may or may not have had a labour less than three or more than 24 hours (which is considered a labour and delivery complication). However, if this individual had experienced a breech delivery it was possible to conclude that they had a history of labour and delivery complications (because breech delivery is considered a labour and delivery). Likewise, it was possible to confirm that an individual had a history of obstetric complications if the author could determine that the individual had a history of complications in one period but could not confirm a history of complications in any of the other periods. For example, if the author was unable to determine whether an individual had experienced a complication of pregnancy or of labour and delivery due to missing datum but was able to determine that the individual had experienced a complication of the neonatal period then it was possible to confirm that the individual had a history of OCs. The number of probands excluded from each stage of the analysis due to missing datum is presented in the appropriate results section.

To investigate whether the effects of OCs were confined to a subgroup of individuals with BP, separate analysis was carried out for gender. These results are only reported if the results are statistically significant or show strong non-significant trends. Non-significant trends are presented in the results chapter as discussed previously to allow comparison with the results presented in chapter 2.

3.2.7 Statistical analysis

Dichotomous variables

Estimated odd ratios (OR) were calculated for dichotomous variables. In this study the BP probands were the case group. The OR were interpreted in the following way; an OR of >1.0 suggested a positive association between OCs and BP whilst an OR of <1.0 a negative association. The 95% confidence intervals (95% CI) were interpreted in the same way. If the confidence interval included

1.0, the OR was assumed not to differ from chance whilst an interval not containing 1.0 suggested a statistically significant difference. The OR for specific OCs are only presented if they are statistically significant or have strong non-significant trends.

Continuous variables

The mean and standard deviation were calculated for all continuous variables. Case-control comparisons were carried out using a two-tailed independent t-test. To be considered a statistically significant result, the obtained p-value must be less than p=0.05. Where a large number of comparisons were carried out the Bonferroni correction was applied to all significance levels.

3.2.8 Ethics approval

Ethics approval was obtained from the ISD, National Health Service in Scotland and the Greater Glasgow Primary Care NHS trust (reference 00AM12). The ISD database was paid for by the Research and Development section of the Greater Glasgow Primary Care NHS trust

Table 26. SMR2 variables considered OCs.

Mothers reproductive history	**Pregnancy Complications**	**Labour and delivery Complications**	**Neonatal Complications**
Parity ≥ 4	Rhesus antibodies	Induced labour	Birth weight < 2500 grams
Previous spontaneous abortion	**ICD-8 codes**	Brow, shoulder, breech and face presentation	Birth weight ≥4000 grams
Previous stillbirth	Diabetes	Labour > 24 hours	Gestation age > 42 weeks
	Glycosuria	Labour < 3 hours	Gestation age ≤ 36 weeks
	Maternal anaemia	Assisted delivery	
	Threatened spontaneous abortion	**ICD-8 codes**	**ICD-8 codes**
	Antepartum haemorrhage	Delivery complicated by: placenta praevia or antepartum haemorrhage; fetopelvic disproportion; a prolonged labour	Haemolytic disease in the newborn with rhesus incompatibility
	Placenta abnormalities NOS		
	Pre-eclampsia		
	Eclampsia		
	Malpresentation of the fetus in the uterus		
	Hydraminios	Cord prolapse	
	Syphilis	Hypoxia and anoxia	
	Rubella		

CHAPTER 4: RESULTS

A non-psychiatric control could be matched to 91.5% (n=160) of the BP females and 97.4% (n=153) of the BP males. The demographic and clinical characteristics of the 1969-1974 BP birth cohort and their matched non-psychiatric controls are shown in table 27. At the time the SRM2 data was extracted (August 2002) the age of the 313 BP probands and 313 non-psychiatric controls ranged from 28-33 years with a mean of 31 (sd 1.64) years.

Table 27. Demographic and clinical characteristics of the 1969-1974 birth cohort with a diagnosis of bipolar disorder and their matched non-psychiatric controls. Data extracted August 2002.

	BP (n=313)	Controls (n=313)
Male	160	160
Female	153	153
Mean age (sd) at first psychiatric admission with any diagnosis (sd)	22.0 (3.5) Range: 14-31	N/A
Mean age (sd) at first psychiatric admission with diagnosis of BP (sd)	23.0 (3.6) Range: 15-32	N/A

4.1 OBSTETRIC COMPLICATIONS IN ANY PERIOD

A history of OCs could be confirmed for 262 individuals with BP and 268 non-psychiatric controls. As shown in table 28, individuals with a history of OCs were not at significantly increased risk of BP in comparison to matched non-psychiatric controls.

Due to missing datum, the total number of OCs experienced could only be calculated for 256 individuals with BP and 267 non-psychiatric controls. The mean number of OCs experienced did not differ between the groups (mean number of OCs: BP vs. controls= 0.2, sd 0.4 vs. 0.2, sd 0.5). The author investigated whether there was a trend for an increased risk of BP with an

increasing number of obstetric complications experienced. However, no trend was found.

Analysis by gender for all the above variables also failed to show significant results or strong non-significant trends. The mean number of OCs experienced by the BP males and BP females were 0.2 (sd 0.44) and 0.2 (sd 0.4) and by the male and female controls were 0.2 (sd 0.5) and 0.2 (0.5) respectively.

Table 28 Estimated risk of bipolar disorder in individuals with a history of obstetric complications: Comparison with matched non-psychiatric controls

Obstetric complication		Subject Group		OR (95% CI)
		BP (n=262)	Controls (n=268)	
Males	Yes	99 (79%)	95 (73%)	1.4 (0.8-2.5)
	No	26 (21%)	35 (27%)	
	Total	125	130	
Females	Yes	103 (75%)	104 (75%)	1.0 (0.6-1.7)
	No	34 (25%)	34 (25%)	
	Total	137	138	
All subjects	Yes	202 (77%)	199 (74%)	1.2(0.8-1.7)
	No	60 (23%)	69 (26%)	
	Total	262	268	

4.2 MOTHERS REPRODUCTIVE HISTORY

At the time of the probands delivery the mothers ranged in age from 16-45 years. The cases and controls were matched on maternal age and therefore as expected the mother age did not differ significantly (mother's age: BP vs. controls 26.19 sd 5.9 vs. 26.18, sd 5.8).

The offspring of mothers who had experienced a previous stillbirth, previous spontaneous abortion or who had a parity of four or greater were not at significantly increased risk of BP (table 29). However, analysis by gender indicated that the female offspring had a 60% greater risk of developing BP. This result reached statistical significance (table 29). On application of the Bonferroni

correction this result did not remain statistically significant as the p-value obtained (p=0.03) was not less than p=0.016.

Table 29. Estimated risk of bipolar disorder in the offspring of mothers with a history of reproductive complications or a parity of four or greater.

Maternal history of reproductive complications or parity ≥ 4		Subject Group		OR (95% CI)
		BP (n=313)	Controls (n=313)	
Males	Yes	37 (24%)	36 (24%)	1.0 (0.6-1.8)
	No	115 (76%)	116 (76%)	
	Total	152	152	
Females	Yes	45 (28%)	31 (19%)	**1.6 (1.1-2.7)**
	No	116 (72%)	130 (81%)	**p=0.03**
	Total	161	161	
All subjects	Yes	82 (26%)	67 (21%)	1.3 (0.9-1.9)
	No	231 (74%)	246 (79%)	
	Total	313	313	

Individual BP-control comparisons of all SMR2 variables concerning the mothers reproductive history individually indicated that the average number of previous spontaneous abortions and stillbirths experienced by the mothers of the BP probands and the mothers of the non-psychiatric controls subjects were similar (previous spontaneous abortions: BP vs. Controls = 0.2, sd 0.6 vs. 0.2, sd 0.5 ; previous stillbirths: BP vs. controls= 0.02, sd 0.1 vs. 0.01, sd 0.1). By comparison, the mothers of individuals with BP had significantly more previous pregnancies (table 30) and thus a significantly higher parity than the mothers of the non-psychiatric control subjects (table 31). Analysis by gender indicated that significance was limited to female subjects (tables 30 and 31). Further analysis of the variable "parity" indicated that the female offspring of mothers with a parity of three or greater were at significantly increased risk of BP (table 32).

It is important to note however that when the Bonferroni correction is applied, the p-value obtained must be less than 0.016[1] to be considered statistically significant. Therefore the only statistically significant result that remains after

[1] Three comparisons were carried out for each of the analysis presented in tables 30, 31 and 32 thus for the Bonferroni correction the level of significance should be 0.05 divided by three which equals 0.016.

correction for multiple comparisons is that the female offspring of mothers with a parity of three of more were at significantly increased risk of BP; the obtained p-value was p=0.005.

Table 30. Mean number of previous pregnancies: Comparison of the mothers of bipolar probands and the mothers of non-psychiatric controls.

	BP (n=313)	Controls (n=313)	Significance
Males (n=153)	1.5 (1.7	1.4 (1.6)	NS
Females (n=160)	1.8 (2.0)	1.4 (1.5)	**p=0.02**
Total sample	1.7 (1.9)	1.4 (1.9)	**p=0.04**

Table 31. Mean parity: Comparison of the mothers of bipolar probands and the mothers of non-psychiatric controls

	BP (n=313)	Controls (n=313)	Significance
Females (n=160)	1.6 (1.9)	1.2 (1.4)	**p=0.03**
Males (n=153)	1.2 (1.4)	1.1 (1.4)	NS
Total sample	1.4 (1.7)	1.2 (1.4)	**p=0.045**

Table 32. Estimated risk of bipolar disorder in the offspring of mothers with a parity of three or more.

Parity ≥ 3		Diagnostic Group		OR (95% CI)
		BP (n=313)	Controls (n=313)	
Males	Yes	20 (13.%)	22 (15%)	0.9 (0.5-1.7)
	No	132 (87%)	130 (86%)	
	Total	152	152	
Females	Yes	42 (26%)	22 (14%)	**2.2 (1.3-3.9) p=0.005**
	No	119 (74%)	139 (86%)	
	Total	161	161	
All Subjects	Yes	62 (20%)	44 (14%)	1.5 (1.0-2.3)
	No	251 (80%)	269 (86%)	
	Total	313	313	

4.3 COMPLICATIONS OF PREGNANCY

4.3.1 Analysis of the SMR2 variables considered pregnancy complications.

The SMR2 record for 20 BP probands and 16 non-psychiatric controls had missing datum regarding rhesus antibodies. Therefore, the total number of pregnancy complications experienced was calculated for 293 mothers of BP and 297 mothers of non-psychiatric controls. The SMR2 record of 2 of the BP probands with no rhesus information contained ICD-8 codes considered pregnancy complications. Therefore, it was possible to compare 295 mothers of BP probands and 297 mothers of non-psychiatric controls for the occurrence of pregnancy complications.

A similar number of mothers of cases and controls had experienced complications during pregnancy (table 33) and the mean number of pregnancy complications experienced were similar (mean number of pregnancy complications experienced by mother: BP vs. controls = 0.2, sd 0.4 vs. 0.2, sd 0.4). Furthermore, the risk of BP did not increase in proportion to the number of pregnancy complications experienced by the mother.

Table 33. Estimated risk of bipolar disorder in the offspring of mothers who experienced pregnancy complications

Pregnancy complications		Subject Group		OR (95% CI)
		BP (n=295)	Controls (n=297)	
Males	Yes	29 (20%)	28 (19%)	1.1 (0.6-1.9)
	No	114 (80%)	116 (81%)	
	Total	143	144	
Females	Yes	23 (15%)	27 (18%)	0.8 (0.5-1.5)
	No	129 (85%)	126 (82%)	
	Total	152	153	
All subjects	Yes	52 (18%)	55 (18%)	0.9 (0.6-1.4)
	No	243 (82%)	242 (82%)	
	Total	295	297	

4.3.2 Prevalence of individual pregnancy events recorded in SMR2

On analysis of each individual pregnancy event recorded on SMR2, the number of mothers of BP probands and mothers of non-psychiatric controls who experienced each specific pregnancy event, with the exception of the variable "more than one x-ray during pregnancy", did not differ.

With respect to maternal x-ray, four times as many mothers of BP probands (4%, n=12) had had "more than one x-ray" during their pregnancy compared to the mothers of their matched controls (1.0%, n=3). The occurrence of a single x-ray (OR 1.0, 95% CI 0.7-1.5) or the location of the x-ray (abdomen, pelvis or chest) did not significantly increase the risk of BP. However, the occurrence of more than one x-ray significantly increased the risk of BP four-fold (OR 4.2, 95% CI 1.2-14.7). This result did not remain statistically significant on application of the Bonferroni correction as the p-value obtained (p=0.019) was compared to greater than p=0.012.[2]

Why would a pregnant women have more than 1 x-ray? Today this would only be carried out if the pregnant women had an accident. However, it is important to note that this study analyses the obstetric history of individuals born from 1969 to 1974. Ultrasound scans were unavailable for pregnant women during this period and thus an x-ray was often used to assess the pelvic proportions and shape (Llewellyn-Jones, 1982) in the case of suspected fetal pelvic disproportion (Beischer et al, 1997). Although no data is available concerning the mother's pelvic proportion, mothers with dystocia are more likely to delivery by caesarean section and are more likely to have a small stature. Mothers who had more than one x-ray (OR 9.0, 95% CI 2.9-28.0) or had a pelvic x-ray (OR 5.3, 95% CI 1.4-20.2) were significantly more likely to deliver by caesarean section. Furthermore, significantly more mothers below the median height for the sample (suggesting small stature) had a pelvic x-ray (OR 6.4, 95% CI 1.4-28.8).

BP-control comparisons for each pregnancy event were also carried out for females and males separately. Analysis by gender indicated that the risk of BP in the offspring of a mother who had more than one x-ray whilst pregnant was increased six-fold if the offspring was male (OR 6.2, 95% CI 0.7-52.2) but only three-fold if the offspring was female (OR 3.1, 95% CI 0.6-15.5). By comparison the estimated risk of BP in the female offspring of mothers who had a blood transfusion during pregnancy increased six-fold (OR 6.2, 95% CI 0.7-52.0), but

[2] Four comparisons were carried out for x-ray (single x-ray, abdomen, pelvis or chest x-ray and multiple x-rays) therefore the p-value 0.05 was divided by 4.

did not increase in males (OR 1.0, 95% CI 0.3-3.5). Analysis by gender for each of these variables did not reach statistical significance.

When the ICD-8 diagnostic codes held on the SMR2 database were decoded, the BP probands were found to have a marginally higher prevalence of all the pregnancy diagnoses recorded with the exception of maternal anaemia. None of the ICD-8 diagnoses significantly increased or decreased the risk of BP but a pregnancy complicated by pre-eclampsia or eclampsia increased the risk of BP in the offspring by 40% (OR 1.4, 95% CI 0.9-2.2). Although this result failed to reach statistical significance, the lower 95% confidence interval was close to statistical significance.

4.4 COMPLICATIONS OF LABOUR AND DELIVERY

4.4.1 Analysis of the SMR2 variables considered labour and delivery complications

The total number of labour and delivery complications experienced could only be calculated for 295 mothers of individuals with BP and 302 mothers of non-psychiatric controls due to missing datum regarding the duration of labour. The SMR2 records of eighteen of the BP probands and 10 of the non-psychiatric controls with missing data indicated that the mother had experienced at least one of the SMR2 variables considered a labour and delivery complication. Thus the author was able to compare the SMR2 records of 313 BP probands and 312 non-psychiatric controls for a history of labour and delivery complications.

As shown in table 34 the offspring of mothers who experienced labour and delivery complications were not at increased risk of BP. Furthermore, the mean number of complications did not differ significantly by diagnostic group (mean number of labour and delivery complications experienced by the mother: BP vs. controls= 0.6, sd 0.8 vs. 0.6, sd 0.7). Furthermore, the risk of BP in the offspring did not increase in proportion to the number of complications the mother experienced.

Table 34. Estimated risk of bipolar disorder in the offspring of mothers who experienced labour and delivery complications

Labour and delivery complication		Subject Group		OR (95% CI)
		BP	Controls	
Males	Yes	75 (49%)	65 (43%)	1.3 (0.8-2.0)
	No	77 (51%)	86 (57%)	
	Total	152	151	
Females	Yes	70 (44%)	79 (49%)	0.8 (0.5-1.2)
	No	91 (57%)	82 (51%)	
	Total	161	161	
All subjects	Yes	145 (46%)	144 (46%)	1.0 (0.7-1.4)
	No	168 (54%)	168 (54%)	
	Total	313	312	

4.4.2 Analysis of individual labour events recorded in SMR2

Nearly three times as many mothers of BP probands had a long labour (more than 24 hours). As a result the OR suggested that a labour of more than 24 hours increased the risk of BP in comparison to matched non-psychiatric controls three-fold (OR 2.9, 95% CI 0.9-9.2). However this result failed to reach statistical significance. When all other labour information recorded on SMR2 was analysed no individual labour event significantly increased the risk of BP in comparison to matched non-psychiatric controls.

BP –control comparisons were carried out for females and males separately. Again no individual labour event significantly increased or decreased the risk of BP and males and females showed similar non-significant trends.

4.4.3 Analysis of individual delivery events recorded on SMR2

When a diagnostic comparison of the individual delivery events recorded on SMR2 was carried out no delivery event significantly increased the risk of BP in the offspring. However, there was a non-significant trend for face presentation at delivery and delivery complicated by placenta praevia, antepartum haemorrhage,

retained placenta, or malpresentation of the fetus to increase the risk of BP more than two-fold.

Analysis by gender showed that breech presentation at delivery increased the risk of BP by 70% in males (OR 1.7, 95% CI 0.4-7.2) but reduced the risk of BP in females by 70% (OR 0.3, 95% CI 0.03-3.2). This result failed to reach statistical significance.

4.5 COMPLICATIONS OF THE NEONATAL PERIOD

4.5.1 Analysis of SMR2 variables considered neonatal complications

The SMR2 records of 23 individuals with BP and 21 non-psychiatric controls had missing datum concerning their estimated gestation age. For one of the individuals with BP and three of the non-psychiatric controls, the birth weight information that was available indicated that the individual had a birth weight less than 2500 grams or 4000 grams or more. Thus it was possible to compare the SMR2 records of 291 individuals with BP and 295 non-psychiatric controls for the presence of neonatal complications.

A similar number of BP probands and non-psychiatric controls had experienced neonatal complications (table 35) and the mean number of complications experienced was similar (mean number of neonatal complications: BP vs. controls= 0.2, sd 0.4 vs. 0.2, sd 0.4). The risk of BP also failed to increase in proportion to the number of neonatal complication experienced.

Table 35. Estimated risk of bipolar disorder in individuals who experienced neonatal complications: Comparison of individuals with bipolar disorder and non-psychiatric controls.

Neonatal complications		Subject Group		OR (95% CI)
		BP (n=291)	Controls (n=295)	
Males	Yes	27 (19%)	29 (21%)	0.9 (0.5-1.6)
	No	116 (81%)	112 (79%)	
	Total	143	141	
Females	Yes	27 (18%)	29 (19%)	1.0 (0.5-1.7)
	No	121 (82%)	125 (81%)	
	Total	148	154	
All subjects	Yes	54 (19%)	58 (20%)	0.9 (0.6-1.4)
	No	237 (81%)	237 (80%)	
	Total	291	295	

4.5.2 Analysis of neonatal information recorded in SMR2

As shown in table 36, BP males weighed significantly less at birth than their matched controls. However, on application of the Bonferroni correction the obtained p-value was compared to a significance level of p=0.016 and therefore the result was no longer considered statistically significant.

When birth weight was categorised and treated as a dichotomous variable, low birth weight (<2500grams) and high birth weight (≥4000grams) did not significantly increase the risk of BP in comparison to non-psychiatric controls (tables 37 and 38).

With respect to gestation age, individuals with BP and their matched non-psychiatric controls did not differ significantly (table 39). Furthermore when gestation age was treated as a dichotomous variable, premature birth, whether defined as gestation age less than 36 weeks or less than 33 weeks, did not significantly increase the risk of BP (tables 40 and 41).

Table 36. Mean birthweight in grams: Comparison of bipolar probands and matched non-psychiatric controls

	BP	Controls	Significance
Males	3282.54 (474.28)	3398.41 (469.54)	**p=0.03**
Females	3300.03 (523.48)	3292.03 (489.50)	NS
All subjects	3291.54 (499.47)	3343.69 (482.09)	NS

Table 37. Estimated risk of bipolar disorder in individuals with a birthweight less than 2500 grams: Comparison of bipolar probands and matched non-psychiatric controls

BW < 2500 grams		Subject Group		OR
		BP	Controls	(95% CI)
Males	Yes	7 (5%)	5 (3%)	1.4 (0.4-4.6)
	No	145 (95%)	147 (97%)	
	Total	152	152	
Females	Yes	10 (6%)	6 (4%)	1.7(0.6-4.8)
	No	151 (94%)	155 (96%)	
	Total	161	161	
All subjects	Yes	17 (5%)	11(4%)	1.6 (0.7-3.4)
	No	296 (95%)	302 (96%)	
	Total	313	313	

BW denotes birth weight

Table 38. Estimated risk of bipolar disorder in individuals with a birthweight more than or equal to 4000 grams: Comparison of bipolar probands and matched non-psychiatric controls

BW ≥ 4000 grams		Subject Group		OR
		BP	Controls	(95% CI)
Males	Yes	8 (5%)	13 (9%)	0.6 (0.2-1.5)
	No	144 (95%)	139 (91%)	
	Total	152	152	
Females	Yes	13 (8%)	14 (9%)	0.9 (0.4-2.0)
	No	148 (92%)	147 (91%)	
	Total	161	161	
All subjects	Yes	21(7%)	27 (9%)	0.8 (0.4-1.4)
	No	292 (93%)	286(91%)	
	Total	313	313	

Table 39. Mean Gestation age in weeks: Comparison of bipolar probands and matched non-psychiatric controls

	BP (n=290)	Controls (n=292)	Significance
Males	39.5 (1.8)	39.5 (2.0)	NS
Females	39.8 (1.9)	40.0 (1.9)	NS
All subjects	39.6 (1.89)	39.8 (1.95)	NS

Table 40. Estimated risk of bipolar disorder in individuals with a gestation age less than or equal to 36 weeks: Comparison of bipolar probands and matched non-psychiatric controls

GA ≤ 36 weeks		Subject Group		OR (95% CI)
		BP (n=290)	Controls (n=292)	
Males	Yes	11(8%)	9 (6%)	1.2 (0.5-3.0)
	No	131(92%)	131 (94%)	
	Total	142	140	
Females	Yes	6 (4%)	4 (3%)	1.6 (0.4-5.7)
	No	142 (96%)	148 (97%)	
	Total	148	152	
All subjects	Yes	17 (6%)	13(5%)	1.3 (0.6-2.8)
	No	273 (94%)	279 (95%)	
	Total	290	292	

GA denotes gestation age

Table 41. Estimated risk of bipolar disorder in individuals with a gestation age less than 33 weeks: Comparison of bipolar probands and matched non-psychiatric controls

GA <33 weeks		Subject Group		OR (95% CI)
		BP (n=290)	Controls (n=292)	
Males	Yes	0	2 (1%)	-
	No	142 (100%)	138 (%)	
	Total	142	140	
Females	Yes	2 (1%)	0	-
	No	146 (99%)	152 (100%)	
	Total	148	152	
All subjects	Yes	2 (1%)	2 (1%)	1.0 (0.1-7.2)
	No	288 (99%)	290 (99%)	
	Total	290	292	

Only 290 BP and 292 non-psychiatric controls had both birth weight and gestation age recorded on the SMR2 database. For these individuals the variables birth weight and gestation age were combined to investigate whether individuals born prematurely with a low birth weight would be at increased risk of BP (table 42). The results showed a marginal non-significant increased risk of BP in comparison to non-psychiatric controls. By comparison, individuals with a large birth weight (>4000 grams) born post term (gestation age > 42 weeks) had a non-significant decreased risk of BP in comparison to non-psychiatric controls (OR 0.7, 95% CI 0.4-1.2). Analysis by gender showed similar non-significant trends.

Table 42. Estimated risk of bipolar disorder in individuals born preterm with a low birth weight. Comparison of bipolar probands and non-psychiatric controls.

BW < 2500 grams & GA < 33 weeks		Subject Group		OR (95% CI)
		BP (n=290)	Controls (n=292)	
Males	Yes	6 (4%)	5 (4%)	1.2 (0.3-4.0)
	No	136 (96%)	135 (96%)	
	Total	142	140	
Females	Yes	11 (7%)	6 (4%)	2.0 (0.7-5.4)
	No	137 (93%)	146 (96%)	
	Total	148	152	
All subjects	Yes	17 (6%)	11 (4%)	1.6 (0.7-3.5)
	No	273 (94%)	281 (96%)	
	Total	290	292	

4.6 SUMMARY OF THE RESULTS

The results of this large prospective study indicate that OCs are not a risk factor for the subsequent development of BP as a similar number of individuals with BP and non-psychiatric controls experienced OCs. Furthermore when obstetric information was categorised into specific periods of reproduction the results indicated that complication of pregnancy, labour and delivery or the neonatal period did not increase the risk of BP; An equal number of individuals in each diagnostic group had experienced pregnancy complications (BP vs. controls:

18% vs. 18%) and labour and delivery complications (BP vs. controls: 46% vs. 46%) and neonatal complications (BP vs. controls: 18.6% vs. 19.7%).

The present study also compared the mean number of complications experienced by individuals with BP and matched non-psychiatric controls. However, the mean number of pregnancy, labour and delivery, neonatal complications experienced did not differ significantly by diagnostic group.

Case-control comparison were carried out for each SMR2 variable. This led to the only statistically significant results. The mothers of females with BP had significantly more previous pregnancies (1.8, sd 2.0 vs. 1.4, sd 1.5) and therefore a significantly higher parity (1.6, sd 1.9 vs. 1.2, sd 1.4) than mothers of controls. Further analysis of this variable indicated that the female offspring of mothers with a parity of three or more were at significantly increased risk of BP (OR 2.2, 95% CI 1.3-3.9). Furthermore the offspring of mothers who had had more than one x-ray during their pregnancy were at increased risk of BP (OR 4.2, 95% CI 1.2-14.7). Comparison of the mean birthweight of each diagnostic group indicated that the male probands were significantly smaller at birth (3282 grams vs. 3398 grams) however low birth weight (<2500 grams) did not significantly increase the risk of BP (OR 1.6, 95% CI 0.7-3.4). However the bonferroni correction was applied to each of these results only parity of three or more remained statistically significant risk factor for BP.

The estimated odds ratios obtained for several OCs resulted in a non-significant increased risk of BP in comparison to matched non-psychiatric controls. Labour lasting more than 24 hours increased the risk of BP nearly three-fold (OR 2.9, 95% CI 0.9-9.2) in comparison to matched non-psychiatric controls. A small number of other OCs resulted in a non-significant increased risk of BP in comparison to matched non-psychiatric controls however for these variables the 95% confidence intervals were wide and were not close to statistical significance. These included previous stillbirth (OR 2.0, 95 % CI 0.5-8.1); face presentation at delivery (OR 2.5, 95% CI 0.5-13.1); delivery complicated by placenta praevia or antepartum haemorrhage (OR 2.4, 95% CI 0.6-9.2) or by

retained placenta (OR 2.5, 95% CI 0.5-3.1) and maternal blood transfusion (females OR 6.2, 95% CI 0.7-52.0).

CHAPTER 5. DISCUSSION

5.1 HOW DO THE RESULTS FIT WITH THE HYPOTHESES

Based on the findings from previous research the current study hypothesised that more individuals with BP would have a history of OCs in comparison to matched non-psychiatric controls. Furthermore the mean number of complications experienced by the individuals with BP would be significantly greater than the mean number of OCs experienced by the non-psychiatric controls. The results of this study have failed to support these hypotheses. An equal number of BP probands and controls had experienced pregnancy, labour and delivery and neonatal complications. Therefore, a similar number of individuals with BP and controls had a history of OCs. The mean number of complications experienced in each specific period of reproduction was also similar.

The author investigated whether an individual with BP had a significantly higher prevalence of any individual obstetric event. The results indicated that significantly more mothers of BP had had more than one x-ray during their pregnancy and that the male BP probands weighed significantly less at birth. Analysis of the mother's reproductive history indicated that the mothers of BP probands had more previous pregnancies and that a parity of three or more was associated with a significantly increased the risk of BP in the female offspring. However once the Bonferroni correction was applied to these results, only the later (parity≥3) remained statistically significant.

5.2 HOW DO THE RESULTS COMPARE WITH THE RESULTS OF OTHERS

The systematic review presented in chapter 2 concluded that there are insufficient data to establish the role of OCs in vulnerability to BP. The present study supports this conclusion as the results obtained have failed to support the hypothesis that more individuals with BP experience OCs in comparison to matched non-psychiatric controls.

Only three studies (Cannon et al, 2002; Camberwell Collaborative Psychosis study, unpublished and Mortensen et al, unpublished) have reported on the frequency of specific OCs in individuals with BP in comparison to healthy controls. The number of specific OCs reported is limited however it is possible to compare some of the results from the present study with previous findings.

With respect top the rpesent study , the only specific OCs found to significantly increase the risk of BP was parity of three or more; female offspring of mothers with parity of three or more had a significantly increased risk of BP in comparison to matched non-psychiatric controls (OR 2.2, 95% CI 1.3-3.9). To the authors knowledge only one other study has reported on parity as an independent factor. Cannon et al (2002) reported that the offspring of mothers with a parity of four or more had a nonsignificant increased risk of BP in comparison to healthy controls (OR 1.3, 95% CI 0.5-3.7). Kinney et al (1993 & 1998) included maternal parity as component of OCs; the author reported that parity contributed to individuals with BP having significantly more OCs in general in comparison to their healthy siblings. The author did not report separate data for maternal parity but stated that increased parity alone did not increase the risk of BP.

Several non-significant trends reported in the current study can be compared with non-significant trends obtained by studies reviewed in chapter 2. The current study found that individuals with a birth weight less 2500 grams had a 60% increased risk of BP (OR 1.6, 95% CI 0.7-3.4) whilst individuals with a birth weight of more than or equal to 4000 grams had a 20% decreased risk of BP (OR 0.8, 95% CI 0.4-1.4). This is in direct comparison to the results obtain in the Camberwell Collaborative Psychosis study (unpublished) which found that the risk of BP in comparison to non-psychiatric controls decreased by 26% in individuals with a birth weight less than 2500 grams (RR 0.74, 95% CI 0.2-2.7) and increased by 40% in individuals with a birth weight more than 4000 grams (RR 1.4, 95% CI 0.7-2.9). Mortensen et al (unpublished) reported similar results to the Camberwell study in that individuals with a birth weight more than 4000 grams had a 20% increased risk (RR 1.2, 95% CI 0.5-3.1) of BP in comparison to

non-psychiatric controls. Cannon et al (2002) found that a birth weight of more than 4000 grams neither increased nor decreased the risk of BP (OR 1.0, 95% CI 0.1-7.7). With respect to gestation age whilst the present study found that individuals born prematurely (gestation age $\leq$ 36 weeks) were at marginally increased risk of BP (OR 1.3, 95% CI 0.6-2.8) the Camberwell Collaborative Psychosis Study (unpublished) found that prematurity decreased the risk of BP by 20% (RR 0.8, 95% CI 0.1-4.5). Although the Camberwell Collaborative Psychosis Study (unpublished) was unable to calculate the estimated risk of BP for individuals born post term (gestation age > 42 weeks) the study did report that 2% (n=2) of the control subjects in comparison to none of the BP subjects were born post term. This trend is similar to that obtained in the present study where more controls than cases were born post term (cases vs. controls = 2%, n=6 vs. 4%, n=11). In the present study delivery complicated by placenta praevia or antepartum haemorrhage was a non-significant risk factor for the later development of BP (OR 2.4, 95% CI 0.6-9.2). This is similar to the result reported by Cannon et al (2002); antepartum haemorrhage increased the risk of BP more than three fold in comparison to controls (OR 3.6, 95% CI 0.4-29.5). In the present study method of delivery had an impact on the risk of developing BP; the risk of developing BP following delivery by caesarean section was increased by 30% (OR 1.3, 95% C I 0.7-2.6) whilst the risk of developing BP following a forceps delivery was reduced by 30% (OR 0.7, 95 % CI 0.4-1.2). This is in direct comparison to the finding of Mortsensen et al (unpublished) who reported that the risk of BP in comparison to healthy controls decreased following delivery by caesarean section (RR 0.4, 95% C I 0.65-2.9) and Cannon et al (2002) who reported that the risk of BP following forceps delivery increased by 60% (OR 1.6, 95% CI 0.6-4.2).

It is important to note that the results discussed above are not statistically significant but rather are non-significant trends. The comparison is only presented to show a how the results of the current study compare with those obtained by studies reviewed in chapter 2. As this study contains a large sample it could be argued that in previous studies these specific OCs did not fail to reach statistical significance due to lack of statistical power.

5.3 DISCUSSION OF SIGNIFICANT RESULTS

5.3.1 Parity

To the authors knowledge with the exceptional of Cannon et al (2002) no other author has reported separate datum for maternal parity in individuals with BP. However, several authors have reported an association between maternal parity and risk of schizophrenia. Hultman et al (1999) found that schizophrenia was significantly (OR 2.0) associated with multiparity and that boys who were number four or more in the birth order were 3.6 times more at risk of schizophrenia compared with controls. Furthermore Sham et al (1993) found an increased risk of schizophrenia amongst individuals who had two or more siblings of a young age while in utero. Similarly in a population based cohort study of the association between risk of schizophrenia, birth order, sibship size and interval to sibling, Westergaard et al (1999) found an increased risk of schizophrenia associated with having many siblings regardless of birth order or interval between siblings.

There are several possible explanations why increased maternal parity is associated with an increased risk of BP in comparison to matched non-psychiatric controls and each of these will be considered here. It is important to note that each of these explanations have been developed by the author from literature reviews in relevant areas and thus are preliminary and require further hypothesis testing.

Does increased parity reflect advanced maternal age?

It is possible to argue that parity is not a risk factor for BP but actually reflects advanced maternal age as increasing parity is bound to go with increasing maternal age. Mortensen et al (unpublished) reported that advanced maternal (more than 34 years) was a risk factor for BP in comparison to controls. Obstetricians are well aware that older women are at increased risk of OCs such as hypertensive, proteinuric disorder, antepartum haemorrhage and abnormalities

of the placenta (Chamberlain & Bowen- Simpkins, 2000). In the current study the cases and controls were matched on maternal age and therefore it is not possible to investigated whether maternal age itself was a significant risk factor for BP.

Is increased parity associated with increased intrauterine exposure to viral infections?

Respiratory viral infections are frequently introduced into the family by young infants who are making increased contact with people outside the family unit whilst still lacking in immunity (Sham et al, 1993). Thus a pregnant mother who has three or more children whilst pregnant may be at increased risk of viral infections and the associated adverse effects on the fetus. There is limited research investigating intrauterine exposure to infectious disease as a risk factor for BP, indeed only Machon et al (1997) has investigated this risk factor. Machon et al (1997) found that there was an increased risk of early onset BP following possible intrauterine exposure to the Greater Helsinki Influenza epidemic in the second trimester[2] (2.8, 95% CI 1.0-7.4). However studies reporting that individuals with BP are more likely to be born during the winter and spring months may be explained by viral infection (Kelly & Murray, 2000; Tex et al, 2001).

Of course children are unlikely to bring home influenza epidemics as studed by Machon et al (1997), however can viral infection increase the risk of BP? It is possible that some viral infections may adversely affect the development of the brain, which in accordance with the neurodevelopmental hypothesis of BP could result in brain changes that are fixed, non-progressive and lie dormant until they manifest as mental illness in adolescence or early adulthood. Secondly as discussed in chapter 2 respiratory viral infections may increase the mothers oxygen demand or result in the mother experiencing a fever both of which increase the risk of hypoxia in the fetus.

[2] 15th to the 28th week of gestation

Do women with increased parity have increased prenatal stress?

It is plausible that pregnant women with three or more children to care for are more likely to be under stress during their pregnancy. Stress has frequently been found to have an adverse effect on the fetus. Firstly, stress during pregnancy increases the risk of many OCs such as prematurity and low birth weight for gestation age (Cooper et al, 1996; Hedegaard et al, 1993; Pagel et al 1990), lower Apgar scores at one and five minutes (Pagel et al, 1990) and reduction of blood flow to the baby via the uterine artery which may lead to fetal distress (Teixeira et al, 1999). For example in a prospective study of 90 pregnant women, Wadhwa et al (1993) found that independent of obstetric risk, each unit increase in prenatal life event stress was significantly associated with a 55 gram decrease in infant birth weight and with a 32% increase in the RR of low birth weight (< 2500 grams). Moreover, each unit increase in prenatal pregnancy-specific anxiety[3] was significantly associated with a 3-day decrease in gestation. Secondly, evidence exists for a link between maternal anxiety[3] and fetal brain development. Lou et al (1994) followed 3021 women through their pregnancy recording levels of anxiety[3] by questionnaire. On comparing the 70 most anxious with 50 controls from the same sample, they found that antenatal anxiety[3] had a similar magnitude of effect as smoking and that the offspring of the most anxious mothers had a significantly smaller head circumference when corrected for birth weight, in fact maternal anxiety[3] corresponded approximately to one weeks intrauterine growth. Prenatal anxiety[3] also significantly worsened neonatal neurological examinations.

Animal studies have also provided evidence of the effects of prenatal stress on fetal development. Stressing mothers of monkeys by exposure to an unpredicted noise during mid- to late gestation resulted in the offspring having raised basal cortisol levels and a raised adrenocorticotrophin[4] response during stress (Clarke et al, 1994). Similar finding were obtained in studies of rodents. Henry et al

[3] In this context, the term "anxiety" does not refer to a diagnosis of anxiety but rather psychological stress. The term stress is not used to avoid confusion with the previous use of the term "stress" to refer to anything that disrupts physiological balance

[4] adrenocorticotrophin modulates the release of cortisol from the adrenalins, a key hormone involved in the stress-response.

(1994) reported that prenatal stress in the mother resulted in an elevated response to stress in rats. As discussed in a previous section, prenatal stress may alter the HPA axis such that in accordance with the Stress Vulnerability model of BP the individual requires a less severe life stressor to precipitate an episode of BP.

Although limited, there is research suggesting an association between stress during pregnancy and later psychiatric illness in the offspring. Huttunen & Niskanen, (1978) reported that maternal psychological stress during pregnancy increased the risk of schizophrenia. O'Connor et al (2002) found that levels of anxiety[3] in late pregnancy were significantly associated with hyperactivity/ inattention in boys at age four and total behavioural problems in both boys and girls at age four when multiple reports of postnatal anxiety were controlled for in a multivariate analysis. Similarly, Wadhwa et al (1998) reported that higher levels of prenatal stress and stress hormone were significantly associated with infants temperamental difficulties at ages 6 weeks, 4 months, and 3 years.

5.4 LIMITATIONS OF THE PRESENT STUDY

This population based case control study fulfils many of the methodological criteria proposed in chapter three for the study of the association between OCs and BP. The obstetric information was obtained from a comprehensive data file recorded in a set numerical format within a few days of delivery. Thus the obstetric information was not influenced by subsequent events and diagnoses and therefore not at risk of recall or reporting bias. Furthermore, this study contained larger numbers of BP-non-psychiatric control pairs than any other study and the BP-control pairs were matched on several confounding variables. However, the limitations of this study should be acknowledged.

5.4.1 Selection of the non-psychiatric comparison group.

Several authors have noted that there are potentially serious limitations of adopting a methodology that compares patients with controls subjects or other

psychiatric patients as it is not possible to match the subjects on all relevant factors such as mother's predisposition to OCs (Eagles et al 1990). Studies using unaffected siblings as a comparison group however will control for many relevant confounding variables such as intrauterine environment, mothers predisposition to particular perinatal complications and genetic factors (Eagles et al, 1990). However, unaffected sibling controls will not address whether OCs increase the risk of BP independently, in interaction with genetic vulnerability, or whether OCs are themselves the result of a genetic predisposition. Examining whether OCs are more common in unaffected siblings compared to the general population would go someway to understanding the mechanism by which OCs possibly increase the risk of BP. Thus, future studies investigating the role of OCs in the aetiology of BP would benefit from having three subject groups, individuals with BP, their unaffected siblings, and matched unrelated healthy control subjects drawn from the general population.

5.4.2 Classification of the case group

The BP subjects in the present study were selected from the psychiatric inpatient register (SMR4) and thus were likely to be individuals with BPI i.e. individuals that have been admitted to hospital for mania. Several of the studies presented in chapter two have also restricted the case group to severe cases of BP by including only inpatients or those who have BPI (Kinney et al, 1993; Kinney et al, 1998; Lewis & Murray, 1987; Sigurdsson et al, 1999). To fully understand the relationship between OCs and BP, researchers must investigate the association between OCs and BPI and also OCs and BPII. Studies where two case groups, BPI and BPII, are compared with unaffected siblings and matched controls will help understand whether OCs are a risk factor for BP in general or more specifically mania.

5.4.3 Misclassification of cases and controls

The controls in the present study were individuals from the same birth cohort as the cases who were not recorded on the psychiatric inpatient register (SMR4) i.e. individuals who have never been admitted to a psychiatric unit in Scotland. Thus

it is possible that the control group included individuals who have a psychiatric diagnosis that that has not lead to psychiatric admission and more specifically individuals with BPII. Misclassification, which is including in the control group individuals who are possibly cases, will have a dilution effect and bias the results towards the null value. With events that are relatively rare, which is the case with some specific OCs, this dilution effect can be considerable. Although it is unlikely with such a large control sample that this dilution effect may have been responsible for the nonsignificant results in the present study, this is an area of the study that could have been improved upon.

5.4.4 Missing information

The obstetric events investigated in the present study were limited to those recorded on the maternity inpatient and day case register. Previous studies have suggested that prenatal exposure to infection (Machon et al, 1997) and malnutrition (Brown et al, 2000) may be a risk factor for BP. Given the large sample size the present study missed an opportunity to investigate all prenatal events that may be involved in the aetiology of BP. Furthermore many of the OCs not investigated have an influence on brain development therefore investigating whether these OCs are a risk factor for BP in comparison to controls will help answer the question "is BP a neurodevelopment disorder?"

5.4.5 Clinical significance of results

Approximately 1% of the population develop BP. That is, for every one hundred babies born one will develop BP. The results of this study suggest that the female offspring of mothers with a parity of three or more are twice as likely to develop BP. Therefore in a sample of one hundred babies of mothers with a parity of three or more, two babies will develop BP. When viewed in this context although the current study identified a statistically significant risk factor for BP it failed to identify a clinically significant risk factor. To explain, the additional number of individuals developing BP due to maternal parity of three or more is only one in every hundred therefore it would not be worthwhile for the health service to develop interventions to reduce the likelihood of that individual developing BP.

5.5 CONCLUSION

This large prospective study suggests that OCs are not a risk factor for BP. The principal research implication of this study is the need for more systematic studies reporting on the frequency of specific OCs in addition to reporting the number of subjects in each group who experienced any definite OCs. Future studies should have carefully defined subject groups including individuals with BP (with defined BPI and BPII subgroups), their unaffected siblings, and matched unrelated healthy control subjects drawn from the general population which are large enough to ensure the statistical power to detect differences in rates of OCs.

Future studies should also examine the clinical correlates of individuals with a history of OCs. For example, compare the obstetric history of individuals with early onset BP and individuals with late onset BP whilst controlling for family history of psychiatric illness.

REFERENCE LIST

Akiskal, H., Downs, J., Jordan, P., *et al* (1985) Affective disorders in referred children and younger siblings of manic-depressives: Mode of onset and prospective course. Archives of General Psychiatry, **42**, 996-1003.

Allen, M. G., Cohen, S., Pollin, W., *et al* (1974) Affective illness in veteran twins: a diagnostic review. American Journal of Psychiatry, **131**, 1234-1239.

Altshuler, L. L., Curran, J., Hauser, P., *et al* (1995) T_2 hyperintensities in bipolar disorder: Magnetic resonance imaging comparison and literature meta-analysis. American Journal of Psychiatry, **152**, 1139-1144.

Ambelas, A. (1987) Life events and mania. British Journal of Psychiatry, **150**, 235-240.

Andreasen, N. C., Swayze, V., Flaum, M., *et al* (1990) Ventricular abnormalities in affective disorder: clinical and demographic correlates. American Journal of Psychiatry, **147**, 893-900.

Angst, J., Scharfetter, C. (1985) Familial aspects of bipolar schizoaffective disorder. In Affective Disorders. World Psychiatric Association. Cambridge University Press.

Angst, J. (1986) Zurich genetic findings. Presented at the NIMH affective disorders workshop. Goodwin, F. K. and Jamison, K. R.

Angst, J. (1998) The emerging epidemiology of hypomania and bipolar II disorder. Journal of Affective Disorders, **50**, 143-151.

Asberg, M., Bertilsson, L., Martensson, B., *et al* (1984) CSF monoamine metabolites in melancholia. Acta Psychiatrica Scandinavica, **69**, 201-219.

Ashcroft, G. W., Crawford, T. B. B., Eccleston, D., *et al* (1966) 5-hydroxyindole compounds in cerebrospinal fluid of patients with psychiatric or neurological diseases. Lancet, **2**, 1049-1052.

Ashcroft, G. W., Dow, R., Yates, C. M. (1976) Significance of lumbar CSF metabolite measurements in affective illness. In CNS and Behavioral Pharmacology. (eds J. Tuomisto & M. Paasonen), pp. 277-284. Helsinki.

Atkinson, M., Zibin, S., and Henry, C. (1997) Characterizing quality of life among patients with chronic mental illness: A critical examination of the self-report methodology. American Journal of Psychiatry, **154**, 99-105.

Atre-Vaidya, N., Taylor, M., Seidenberg, M., *et al* (1998) Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. Neuropsychiatry, Neuropsychology, and Behavioural Neurology, **11**, 120-126.

Aylward, E. H., Roberts-Twillie, J. V., Barta, P. E., *et al* (1994) Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. American Journal of Psychiatry, **151**, 687-693.

Bain, M., Juszczak, E., McInneny, K., *et al* (2000) Obstetric complications and affective psychoses: Two case-control studies based on structural obstetric records. The British Journal of Psychiatry, **176**, 523-526.

Ballenger, J. C., Reus, V. I., and Post, R. M. (1982) The "atypical" picture of adolescent mania. American Journal of Psychiatry, **139**, 602-206.

Banki, C. M. (1977) Correlation between cerebrospinal fluid amine metabolites, tryptophane and clinical parameters in depression. Journal of Neurochemistry, **28**, 255-257.

Barbato, N. and Hafner, J. (1998) Comorbidity of bipolar and personality disorder. Australian and New Zealand Journal of Psychiatry, **32**, 276-280.

Barker, D. J. P. (1998) Programming the baby. In Mothers, Babies and Health in Later Life (ed D. J. P. Barker), pp. 13-41. Edinburgh.

Baron, M., Gruen, L., and Kane, J. (1982) Schizoaffective illness, schizophrenia and affective disorders: morbidity risk and genetic transmission. Acta Psychiatrica Scandinavica, **65**, 253-262.

Beischer, N. A., MacKay, E. V,. and Colditz, P. B. (1997) Obstetrics and the Newborn. London: Sanders.

Bejar, R., Wozniak, P., Allard, M. B., ***et al*** **(1988)** Antenatal origin of neurological damage in newborn infants. I. Preterm infants. American Journal of Obstetrics and Gynecology, **159**, 357-363.

Benazzi, F. (1999) A comparison of the age of onset of BP I and BPII. Journal of Affective Disorders, **54**, 249-253.

Bertelsen, A., Harvald, B., and Hauge, M. (1977) A Danish twin study of manic depressive illness. British Journal of Psychiatry, **130**, 330-351.

Black, D. and Nasrallah, H. A. (1989) Delusions and hallucinations in 1715 patients with unipolar and bipolar affective disorders. Psychopathology, **22**, 28-34.

Bland, R. C., Winokur, G., Hulbert, J., ***et al*** **(1988)** Epidemiology of psychiatric disorders in Edmonton. Acta Psychiatrica Scandinavica, 77, supplement 338.

Botteron, K. N., Vannier, M. W., Geller, B., ***et al*** **(1995)** Preliminary study of magnetic resonance imaging characteristics in 8- to 16-years-olds with mania. Journal of the American Academy of Child and Adolescent Psychiatry., **6**, 742-749.

Bowers, M. B. and Heninger, G. R. (1977) Lithium: Clinical effects on cerebrospinal fluid acid monoamine metabolites. Communications in Psychopharmacology., **1**, 135-145.

Boyd, J. H., Weissman, M. M. (1982) Epidemiology. In Handbook of Affective Disorders (ed E. S. Paykel), pp. 109-125. Edinburgh.

Boyd, J. H., Burke, J. D., and Gruenberg, E. (1984) Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. Archives of General Psychiatry, **41**, 983-989.

Brodie, H., Sach, R., Siever, L. (1973) Clinical studies of L-5-hydroytryptophan. In Serotonin and Behavior. (eds J. Barchas & E. Usdin), pp. 549-559. New York.

Brown, A. S., Susser, E. S., Lin, S. P., *et al* (1995) Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944- 1945. British Journal of Psychiatry, **166**, 601-606.

Brown, A. S., Van Os, J., Driessens, C., *et al* (2000) Further evidence of the relation between prenatal famine and major affective disorder. American Journal of Psychiatry, **157**, 190-195.

Brown, F., Lewine, R. J., Hudgins, P., *et al* (1992) White matter hyperintensity signals in psychiatric and nonpsychiatric subjects. American Journal of Psychiatry, **149**, 620-625.

Browne, R., Byrne, M., Mulryan, N., *et al* (2000) Labour and delivery complications at birth and later mania : An Irish case register study. British Journal of Psychiatry, **176**, 369-372.

Buka, S. L., Tsuang, M. T., and Lipsitt, L. P. (1993) Pregnancy/ delivery complications and psychiatric diagnosis. A prospective study. Archives of General Psychiatry, **50**, 151-156.

Buka, S. L. and Fan, A. P. (1999) Association of prenatal and perinatal complications with subsequent bipolar disorder and schizophrenia. Schizophrenia Research, **39**, 113-119.

Byrne, M., Morris, M, Browne, R., *et al* (1996) Obstetric complications in schizophrenia and mania: A comparative study. Schizophrenia Research, **18**, 97-98.

Byrne, M., Browne, R., Mulryan, N., *et al* (2000) Labour and delivery complications and schizophrenia:case-control study using contemporaneous labour ward records. British Journal of Psychiatry, **176**, 531-536.

Canino, G. J., Bird, H. R., Shrout, P. E., *et al* (1987) The prevalence of specific psychiatric disorder in Puerto Rico. Archives of General Psychiatry, **44**, 727-735.

Cannon, M., Jones, P., Gilvarry, C., *et al* (1997) Premorbid social functioning in schizophrenia and bipolar disorder : Similarities and differences. American Journal of Psychiatry, **154**, 1544-1550.

Camberwell Collaborative Psychosis Study (unpublished). Institute of Psychiatry, London. head of research group: Mary Cannon. Personal communication

Cannon, M., Caspi, A., Moffit, T. E., *et al* (2002) Evidence of early-childhood, Pan developmental impairment specific to schizophreniform disorder. Results from a longitudinal birth cohort. Archives of General Psychiatry, **59**, 449-456.

Cantor-Graae, E., Cardenal, S., Ismail, B., *et al* (1998) Recall of obstetric events by mothers of schizophrenic patientts. Psychological Medicine, **28**, 1239-1243.

Cardno, A. G., Marshall, E. J., and Coid, B. (1999) Heritability estimates for psychotic disorders. Archives of General Psychiatry, **56**, 162-168.

Casey, R., Rieckhoff, M., Beebe, S. A., *et al* (1992) Obstetric and Perinatal Events: The accuracy of maternal report. Clinical Pediatrics, **31**, 200-204.

Cassidy, F., Ritchie, J., and Carroll, B. (1998) Plasma dexamethasone concentration and cortisol response during manic episodes. Biological Psychiatry, **43**, 747-754.

Chamberlain, G., Dewhurst, J., Harvey, D. (1991) Illustrated Textbook of Obstetrics. Gower Medical Publications.

Chamberlain, G., Pearce, J. M. (1992) Lecture notes on obstetrics. Oxford: Blackwell Scientific.

Chamberlain, G., Bowen-Simpkins, P. (2000) A practice of obstetrics and gynaecology: A textbook for general practice and the DRCOG. Edinburgh: Churchill Livingstone.

Chen, Y-W. and Dilsaver, S. C (1996) Lifetime rates of suicide attempts among subjects with bipolar disorder and unipolar disorders relative to subjects with other axis I disorders. Biological Psychiatry, **39**, 896-899.

Clarke, A. S., Wittwer, D. J., Abbott, D. H., *et al* (1994) Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys. Developmental Psychobiology, **27**, 257-269.

Clarke, P., Hindmarsh, P., Shiell, A., *et al* (1996) Size at birth and adrenocortical function in children. Clinical Endocrinology, **45**, 721-726.

Coppen, A., Prange, A. J. Jnr., Whybrow, P. C., *et al* (1972) Abnormalities of indoleamines in affective disorders. Archives of General Psychiatry, **26**, 474-478.

Cornelius, J. R., Fabrega, H., Mezzich, J., *et al* (1994) Characterizing organic mood syndrome, manic type. Comprehensive Psychiatry, **35**, 354-360.

Coryell, W., Endicott, J., Reich, T., *et al* (1984) A family study of bipolar II disorder. British Journal of Psychiatry, **145**, 49-54.

Coryell, W., Andreasen, N., Endicott, J., *et al* (1987) The significance of past mania or hypomania in the course and outcome of major depression. American Journal of Psychiatry, **144**, 309-315.

Cotter, D., MacKay, D., Landau, S., *et al* (2001) Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Archives of General Psychiatry, **58**, 545-53.

Craddock, N. and Jones, I. (1999) Genetics of bipolar disorder. Journal of Medical Genetics, **36**, 585-594.

Dalen, P. (1965) Family history, the electroencephalogram and perinatal factors in manic conditions. Acta Psychiatrica Scandinavica, **41**, 527-563.

Dalman, C., Allebeck, P., Cullberg, J., *et al* (1999) Obstetric complications and the risk of schizophrenia: longitudinal study of a national birth cohort. Archives of General Psychiatry, **56**, 234-240.

Daly, I., Webb, M., and Kaliszer, M. (1995) First admission incidence study of mania, 1975-1981. British Journal of Psychiatry, **167**, 463-468.

Daniels, B., Kirkby, K., Hay, D., *et al* (1998) Predictability of rehospitlisation over 5 years for schizophrenia, bipolar disorder and depression. Australian and New Zealand Journal of Psychiatry, **32** , 281-286.

Der, G. and Bebbington, P. E. (1987) Depression in inner London; a register study. Social Psychiatry, **22**, 73-84.

Dewan, M. J., Maldipur, C. V., Lane, E. E., *et al* (1988) Bipolar affective disorder: I. Comprehensive quantitative computed tomography. Acta Psychiatrica Scandinavica, 77, 670-676.

Done, J., Johnstone, E. C., Firth, C. D., *et al* (1991) Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample. British Medical Journal, **302**, 1576-1580.

Drevets, W. C., Gadde, K. M., Krishnan, K. R. R. (1999) Neuroimaging studies of mood disorders. In Neurobiology of Mental Illness (eds D. Charney, E. Nestler, & B. Bunney), pp. 394-418. Oxford.

Drews, C. D., Greenland, S., and Flanders, W D. (1993) The use of restricted controls to prevent recall bias in case-control studies of reproductive outcome. Annals of Epidemiology, **3**, 86-92.

Dugan, M., Choy, D., Ngai, A., *et al* (1993) Multicenter phase II trial of mitoxantrone in patients with advanced nasopharyngeal carcinoma in Southeast Asia: an Asian-Oceanian Clinical Oncology Association Group study. Journal of Clinical Oncology, **11**, 70-76.

Dupont, R. M., Jernigan, T. L., Gillin, J. C., *et al* (1987) Subcortical signal hyperintensities in bipolar patients detected by MRI. Psychiatry Research, **21**, 357-358.

Dupont, R. M., Jernigan, T. L., Butters, N., *et al* (1990) Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging: clinical and neuropsychological difference. Archives of General Psychiatry, **1**, 55-59.

Dupont, R. M., Jernigan, T. L., Heindel, W., *et al* (1995) Magnetic resonance imaging and mood disorders: localization of white matter and subcortical abnormalities. Archives of General Psychiatry, **52**, 747-755.

Eagles, J., Gibson, I., Bremner, M. H., *et al* (1990) Obstetric complications and DSM-III schizophrenia and their siblings. Lancet, **335**, 1139-1141.

Eastwood, S. L. and Harrison, P. J. (2001) Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a western blot study of synaptophysin, GAP-43 and the complexins. Brain Research Bulletin, **55**, 569-578.

Eaton, W., Mortensen, P., and Frydenberg, M. (2000) Obstetric factors, urbanization, and psychosis. Schizophrenia Research, **43**, 117-123.

Egeland, J. A., Blumenthal, R. L., Nee, J., *et al* (1987) Reliability and relationship of various ages of onset criteria for major affective disorder. Journal of Affective Disorders., **12**, 159-165.

El-Khodor, B. and Boksa, P. (1997) Long term reciprocal changes in dopamine levels in prefrontal cortex versus nucleus accumbens in rats born by Caesarean section compared to vaginal birth. Experimental Neurology, **145**, 118-129.

El-Khodor, B. and Boksa, P. (2001) Caesarean section birth produces long term changes in dopamine D1 receptors and in stress induces regulation of D3 and D4 receptors in the rat brain. Neuropsychopharmacology, **25**, 423-439.

Elman, I., Adler, C., Malhotra, A., *et al* (1998) Effects of acute metabolic stress on pituitary-adrenal axis activation on patients with schizophrenia. American Journal of Psychiatry, **155**, 979-981.

Evans, D. L. and Nemeroff, C B. (1983) The dexamethasone suppression test in mixed bipolar disorder. American Journal of Psychiatry, **140**, 615-617.

Ferrier, I. N., Stanton, B. R., Kelly, T. P., *et al* (1999) Neuropychological function in euthymic bipolar patients. British Journal of Psychiatry, **175**, 246-251.

Fieve, R. R., Go, R., Dunner, D. L., *et al* (1984) Search for biological/ genetic markers in a long-term epidemiological and morbid risk study of affective disorders. Journal of Psychiatric Research, **18**, 425-445.

Figiel, G. S., Krishnan, K. R. R., Rao, V. P., *et al* (1991) Subcortical hyperintensities on brain magnetic resonance imaging: a comparison of normal and bipolar subjects. Neuropsychiatry and Clinical Neuroscience, **318- 322**.

Fride, E., Dan, Y., Feldon, J., *et al* (1986) Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. Physiology and Behaviour, **37**, 681-687.

Gale, C. (2004) Birth weight and later risk of depression in a national birth cohort. British Journal of Psychiatry, **184**, 28-33.

Geddes, J. R., Verdoux, H., Takei, N., *et al* (1999) Schizophrenia and complications of pregnancy and labor: A individual patient data meta-analysis. Schizophrenia Bulletin, **25**, 413-423.

Gerner, R. H., Fairbanks, L., Anderson, G. M., *et al* (1984) CSF neurochemistry in depressed, manic, and schizophrenic patients compared with that of normal controls. American Journal of Psychiatry, **141**, 1533-1540.

Gershon, E. S., Hamovit, J., Guroff, J. J., *et al* (1982) A family study of schizoaffective, bipolar I, bipolar II, unipolar and normal control probands. Archives of General Psychiatry, **39**, 1157-1167.

Goodwin, F. K., Sack, R. L. (1973) Affective disorders: The catecholamine hypotheses revisited. In Frontiers in Catecholamine Research. (eds E. Usdin & S. Snyder), pp. 1157-1164. New York.

Goodwin, F. K., Jamison, K. R. (1990) Manic-Depressive Illness. New York; Oxford: Oxford University Press.

Gould, J. B. and LeRoy, S. (1988) Socioeconomic status and low birth weight: a racial comparison. Pediatrics, **82**, 896-904.

Gunduz, H., Woerner, M. G., Alvir, J. M., *et al* (1999) Obstetric complications in schizophrenia, schizoaffecive disorder and normal comparison subjects. Schizophrenia Research, **40**, 237-243.

Gunduz, H. (unpublished) The obstetric histories for the 13 BP subjects includedin Gunduz et al (1999). Hillside Hospital, New York. Personal Communication.

Gureje, O., Bamidele, R., and Raji, O. (1994) Early brain trauma and schizophrenia. American Journal of Psychiatry, **151**, 368-371.

Guth, C., Jones, P., and Murray, R. (1993) Familial psychiatric illness and obstetric complications in early-onset affective disorder. A case-control study. British Journal of Psychiatry, **163**, 498.

Hakim, R. B., Tielsch, J. M., and See, L. C. (1992) Agreement between maternal interview and medical records-based gestational age. American Journal of Epidemiology, **136**, 566-573.

Harvey, I., Persaud, R., Ron, M. A., *et al* (1994) Volumetric MRI measurements in bipolars compared with schizophrenics and healthy controls. Psychological Medicine, **24**, 689-699.

Hays, J., Krishnan, K., George, L., *et al* (1998) Age of first onset of bipolar disorder: demographic, family history and psychosocial correlates. Depression and Anxiety, 7, 76-82.

Hays, P. (1976) Etiological factors in manic-depressive psychoses. Archives of General Psychiatry, **33**, 1187-1188.

Hedegaard, M., Henriksen, T. B, Sabroe, S., *et al* (1993) Psychological distress in pregnancy and preterm delivery. British Medical Journal, **240**, 234-239.

Hemminki, E. and Gissler, M. (1993) Quantity and targetting of antenatal care in Finland. Acta Obstetricia et Gynecologica Scandinavica, **72**, 24-30.

Henry, C., Kabbaj, M., Simon, H., *et al* (1994) Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. Journal of Neuroendocrinology, **6**, 341-345.

Hirschfeld, R., Klerman, G. L., Keller, M. B., *et al* (1986) Personality of recovered patients with bipolar disorder. Journal of Affective Disorders, **11**, 81-89.

Holsboer, F. (1995) Neuroendocrinology of mood disorders. In Psychopharmacology: The fourth generation of progress. (eds F. E. Bloom & D. J. Kupfer), pp. 957-969. New York.

Hultman, C. M., Sparen, P., Takei, N., *et al* (1999) Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. British Medical Journal, **318**, 421-426.

Hunt, G. E., Johnson, G. F. S., and Caterson, I. D. (1989) The effects of age on cortisol and plasma dexamethasone concentrations in depressed patients and controls. Journal of Affective Disorder, **15**, 21-32.

Huttunen, M. O. and Niskanen, P. (1978) Prenatal loss of fathers and psychiatric disorders. Archives of General Psychiatry, **35**, 429-431.

Hwu, H. G., Yeh, E-K., and Chang, L-Y. (1989) Prevalence of psychiatric disorders in Tiawan defined by the Chinese Diagnostic Interview Schedule. Acta Psychiatrica Scandinavica, **79**, 736-147.

Hwu, H. G. and Lin, H. N. (1990) Serial dexamethasone concentrations in depressed patients and controls. Biological Psychiatry, **27**, 609-616.

Iacono, W. G., Smith, G. N., Moreau, M., *et al* (1988) Ventricular and sulcal size at the onset of psychosis. American Journal of Psychiatry, **145**, 820-824.

Isometsa, E., Heikkinen, M., and Henriksson, M (1995) Recent life events and completed suicide in bipolar affective disorder. Journal of Affective Disorders, **33**, 99-106.

Jacobs, D. and Silverstone, T. (1986) Detroamphetamine-induced arousal in human subjects as a model for mania. Psychological Medicine, **16**, 323-329.

Johnstone, E. C., Owens, D. G. C., Crow, T. J., *et al* (1989) Temporal lobe structure as determined by nuclear magnetic resonance in schizophrenia and bipolar affective disorder. Journal of Neurology and Neurosurgical Psychiatry, **52**, 736-741.

Jones, P. B., Bebbington, P., Foerster, A., *et al* (1993) Premorbid social underachievement in schizophrenia. Results from the Camberwell Collaborative Psychosis Study. British Journal of Psychiatry, **162**, 65-71.

Jones, P. B., Rantkallio, P., Hartikainen, A-L., *et al* (1998) Schizophrenia as a longterm outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 North Finland general population birth cohort. American Journal of Psychiatry, **155**, 355-364.

Kanitz, E., Otten, W., Tuschscherer, M., Mantcuffel, G. (2003) Effects of prenatal stress on corticosteroid receptors and monoamine concentrations in limbic areas of suckling piglets (Sus scrofa) at different ages. Journal of Veterinary Medicine - Series A, **50**, 132-139.

Kato, T., Shioiri, T., Murashita, J., *et al* (1994) Phosphorus-31 magnetic resonance spectroscopy and ventricular enlargement in bipolar disorder. Psychiatry Research, **55**, 41-50.

Katz, R. (1982) Animal models of depression:pharmacological sensitivity of the hedonic deficit. Pharmacology, Biochemistry and Behavior, **16**, 965-968.

Kelly, J. and Murray, R. M. (2000) What risk factors tell us about the causes of schizophrenia and related psychoses. [Review]. Current Psychiatry Reports, **2**, 378-385.

Kendell, R. E., Juszczak, E., and Cole, S. K. (1996) Obstetric complications and schizophrenia: A case control study based on standardised obstetric records. The British Journal of Psychiatry, **168**, 556-561.

Kendell, R. E., McInneny, K., Juszaczak, E., *et al* (2000) Obstetric complications and schizophrenia. British Journal of Psychiatry, **176**, 516-522.

Kendler, K. S., Gruenberg, A. M., and Tsuang, M. T. (1985) Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients: a family study using DSM-III criteria. Archives of General Psychiatry, **42**, 770-779.

Kendler, K. S., Pedersen, N., Johndon, L., *et al* (1993) A pilot Swedish twin study of affective illness, including hospital- and population- ascertained subsamples. Archives of General Psychiatry, **50**, 699-706.

Kendrick, S. and Clarke, J. (1993) The Scottish Record Linkage system. Health Bulletin, **51**, 72-79.

Kennedy, S., Thompson, R., Stancer, H., *et al* (1983) Life events precipitating mania. British Journal of Psychiatry, **142**, 403.

Keshet, G. I. and Weinstock, M. (1995) Maternal naltrexone prevents morphological and and behavioral alternations induced in rats by prenatal stress. Pharmacology, Biochemistry and Behavior, **50**, 413-419.

Kessler, R. C., Rubinow, D. R., Holmes, C., *et al* (1997) The Epidemiology of DSM-III bipolar disorder in the general population. Psychological Medicine, **27**, 1079-1089.

Kinney, D. K., Yurgelun-Todd, D. A., Levy, D. L., *et al* (1993) Obstetric complications in patients with bipolar disorder and their siblings. Psychiatry Research, **48**, 47-56.

Kinney, D. K., Yurgelun-Todd, D. A., Maurcio, T., *et al* (1998) Pre- and Perinatal complications and risk of bipolar disorder: A retrospective study. Journal of Affective Disorders, **50**, 117-124.

Kiriike, N., Izumiya, Y., Nishiwaki, S., *et al* (1988) TRH test and DST in schizoaffective mania , mania and schizophrenia. Biological Psychiatry, **24**, 415-422.

Klemcke, H., Lunstra, D., Brown-Borg, H., *et al* (1993) Association between low birth weight and increased adrenocortical function in neonatal pigs. Journal of Animal Science, 71, 1010-1018

Koeningsberger, R., and Kairam, R. (2000) Birth injuries and developmental abnormalities. In Neonatal Neurology (eds R. Koenigsberger & R. Kairam),

Koslow, S. H., Maas, J. W., Bowden, C. L., *et al* (1983) CSF and urinary biogenic amines and metabolites in depression and mania: A controlled, univariate analysis. Archives of General Psychiatry, **40**, 999-1010.

Kringlen, E. (1967) Heredity and environment in the functional psychoses. London: Heinemann.

Krishnan, K. R. R., Maltbie, A. A., and Davidson, R. T. (1983) Abnormal cortisol suppression in bipolar patients with simultaneous manic and depressive symptoms. American Journal of Psychiatry, **140**, 203-205.

Lee, C. K., Kwat, Y. S., Yamamoto, J., *et al* (1990) Psychiatric epidemiology in Korea. Part 1. Gender and age differences in Seoul. Journal of Nervous and Mental Disorders, **178**, 242-246.

Leff, J. P., Fischer, M., and Bertelsen, A. (1976) A cross national epidemiological study of mania. British Journal of Psychiatry, **129**, 428-442.

Leibenluft, E. (1996) Women with bipolar illness : Clinical and research issues. American Journal of Psychiatry, **153**, 163-173.

Leveno, K. J., Cunningham, F. G., Roark, M. L., *et al* (1985) Prenatal care and the low birth weight infant. Obstetrics & Gynecology, **66**, 599-605.

Levitt, N. S., Lindsay, R. S., Holmes, M. C., *et al* (1996) Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring of rats. Neuroendocrinology, **64**, 412-418.

Lewine, R. R. J., Hudgins, P., Brown, F., *et al* (1995) Differences in qualitative brain morphology findings in schizophrenia, major depression, bipolar disorder and normal volunteers. Schizophrenia Research, **15**, 253-259.

Lewis, S. and Murray, R (1986). Obstetric complications and risk of schizophrenia. Paper presented at the International Conference on Schizophrenia.

Lewis, S. and Murray, R (1987) Obstetric complications, neurodevelopmental deviance and risk of schizophrenia. Journal of Psychiatric Research, **21**, 413-421.

Lewis, S., Owen, M. J., Murray, R. (1989) Obstetric complications and schizophrenia: methodology and mechanisms. In Schizophrenia: scientific progress (eds S. C. Schulz & C. A. Tamminga), pp. 56-68. New York.

Llewellyn-Jones, D. (1982) Fundamentals of obstetrics and gynaecology. London: Faber.

Loranger, A. W. and Levine, P. M. (1978) Age at onset of bipolar affective disorder. Archives of General Psychiatry, **35**, 1345-1348.

Lou, H. C., Hansen, D., Nordentoft, M., *et al* (1994) Prenatal stressors of human life affect fetal brain development. Developmental Medicine and Child Neurology, **36**, 826-832.

Lyon, M., Barr, C. G. (1991) Obstetrical events and fetal brain development. In Fetal Neural Development and Adult Schizophrenia (eds S. Mednick, T. Cannon, C. Barr, & M. Lyon), pp. 134-149.

Machon, R., Mednick, S., and Huttunen, M. (1997) Adult major affective disorder after prenatal exposure to an influenza epidemic. Archives of General Psychiatry, **54**, 322-328.

Mandell, A. J. and Knapp, S. (1979) Asymmetry and mood emergent properties of serotonin regulation. Archives of General Psychiatry, **36**, 909-916.

Marcelis, M., Van Os, J., Sham, P., *et al* (1998) Obstetric complications and familial morbid risk of psychiatric disorders. American Journal of Medical Genetics, **81**, 29-36.

Marneros, A., Deister, A., and Rohde, A. (1990) Psychopathological and social status of patients with affective, schizophrenic and schizoaffecive disorders after long-term course. Acta Psychiatrica Scandinavica, **82**, 352-358.

Martin, C. J. (1987) Monitoring maternity services by questionnaire: Congruity between mothers' reports and their obstetric records. Statistical Medicine, **6**, 613-627.

McCarley, R. W., Wible, C. G., Frumin, M., *et al* (1999) MRI anatomy of schizophrenia. Biological Psychiatry, **45**, 1099-1119.

McCormick, C. M., Smythe, J. W., Sharma, S., *et al* (1995) Sex-specific effects of prenatal stress on hypothalamic-pituitary-adrenal responses to stress and brain glucocorticoid receptor density in adult rats. Developmental Brain Research, **84**, 55-61.

McDonald, W. M., Krishnan, K. R. R., Doraiswamy, M., *et al* (1991) Occurrence of subcortical hyperintensities in elderly subjects with mania. Psychiatry Research: Neuroimaging, **40**, 211-220.

McElroy, S., Keck, P. E., Pope, H., *et al* (1992) Clinician and research implications of the diagnosis of dysphoric or mixed mania or hypomania. American Journal of Psychiatry, **149**, 1633-1644.

McNeil, T. (1987) Perinatal influences in the development of schizophrenia. In Biological Perspectives of Schizophrenia. (eds H. Helmchen & F. A. Henn), pp. 125-138. New York.

McNeil, T., Cantor-Graae, E., and Sjostrom, K. (1994) Obstetric complications as antecedents of schizophrenia: empirical effects of using different obstetric complication scales. Journal of Psychiatric Research, **28**, 519-530.

McNeil, T. F. (1988) Obstetric complications and perinatal injuries. In Handbook of Schizophrenia, Vol. 3: Nosology, Epidemiology and Genetics

McNeil, T. F. and Sjostrom, K. (1995) The McNeil-Sjostrom OC scale: a comprehensive scale for measuring obstetric complications. Personal Communication.

Mednick, S., Parnas, J., and Schulsinger, F. (1987) The Copenhagen high risk project, 1962 - 1987. Schizophrenia Bulletin, **13**, 485-495.

Miller, A., Callander, R. (1989) Obstetrics Illustrated. Edinburgh: Churchill Livingstone.

Moreau, J. L., Jenck, F., Martine, J. R., *et al* (1994) Curative effects of the atypical antidepressant mianserin in the chronic mild stress anhedonia model of depression. Journal of Psychiatry and Neuroscience, **19**, 51-56.

Morgan, V., Castle, D., Page, A., *et al* (1997) Influenza epidemics and incidence of schizophrenia, affective disorders and mental retardation in Western Australia: no evidence of a major effect. Schizophrenia Research, **26**, 25-39.

Mortensen, P., Eaton, W., Thomsen, P., and Frydenberg, M. (unpublished) Perinatal risk factors for hospitalized mental disorders in young adults in Denmark. Institute for Basic Psychiatric Research, Denmark. 2000. Personal communication.

Multale, T., Creed, F., Maresh, M., *et al* (1991) Life events and low birth weight- analysis by infant preterm and small for gestation age. British Journal of Obstetrics and Gynaecology, **98**, 166-172.

Nasrallah, H. A., McCalley-Whitters, M., and Jacoby, C. G. (1982) Cortical atrophy in schizophrenia and mania: A comparative CT study. Journal of Clinical Psychiatry, **43**, 439-441.

Nasrallah, H. A., McCalley-Whitters, M., and Pfohl, B. (1984) Clinical significance of large cerebral ventricles in manic males. Psychiatry Research, **13**, 151-156.

Nasrallah, H. A. (1991) Neurodevelopmental aspects of bipolar affective disorder. Biological Psychiatry, **29**, 1-2.

Nurnberger, J. I. and Foroud, T. (2000) Genetics of bipolar affective disorder. Current Psychiatry Reports, **2**, 147-157.

O'Connor, T. G., Heron, J., Golding, J., *et al* (2002) Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. British Journal of Psychiatry, **180**, 502-508.

Olson, J. E., Shu, X. O., Ross, J. A., *et al* (1997) Medical record validation of maternally reported birth characteristics and pregnancy related events: a report from the childrens cancer group. American Journal of Epidemiology, **145**, 58-67.

Orn, H., Newman, S. C., and Bland, R. C. (1988) Design and field methods of the Edmonton survey of psychiatric disorders. Acta Psychiatrica Scandinavica, 77, 17-23.

Pagel, M. D., Smilkstein, G., Regen, H., *et al* (1990) Psychosocial influences on new born outcomes: a controlled prospective study. Social Science and Medicine, **30**, 597-604.

Papeschi, R. and McClure, D. J. (1971) Homovanillic and 5-hydroxyindoleacetic acid in the cerebrospinal fluid of depressed patients. Archives of General Psychiatry, **25**, 354-358.

Parikh, S. V., Wasylenki, D., Goering, P., *et al* (1996) Mood disorder: rural/ urban differences in prevalence, health care utilisation, and disability in Ontario. Journal of Affective Disorders, **38**, 57-65.

Parnas, J., Schulsinger, F., Teasdale, T. W., *et al* (1982) Perinatal complications and clinical outcome within the schizophrenia spectrum. British Journal of Psychiatry, **140**, 420.

Pearlson, G. D and Veroff, A. E. (1981) Computerised tomographic scan changes in manic-depressive illness. The Lancet, **71**, 470.

Pearlson, G. D, Veroff, A. E., and Wise, T. N. (1982) Use of CT scanning in psychiatry. Psychosomatics, **23**, 993-1004.

Pearlson, G. D, Garbacz, M. A., Tompkins, R. H., *et al* (1984) Clinical correlates of lateral ventricle enlargement in bipolar affective disorder. American Journal of Psychiatry, **141**, 253-256.

Pearlson, G. D, Garbacz, M. A., Breakey, W. R., *et al* (1984) Lateral ventricle enlargement associated with persistent unemployment and negative symptoms in both schizophrenia and bipolar disorder. Psychiatry Research, **12**, 1-9.

Pearlson, G. D, Barta, P. E., Powers, R. E., *et al* (1997) Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biological Psychiatry, **41**, 1-4.

Pearlson, G. D., Garbacz, D. J., Moberg, P. J., *et al* (1985) Symptomatic, familial, perinatal and social correlates of computerized axial tomography (CAT) changes in schizophrenia and bipolars. Journal of Nervous and Mental Disease, **173**, 42-50.

Perris, C. (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. Acta Psychiatrica Scandinavica, **42**, 118-152.

Phillips, D. I. W., Walker, B. R., Reynolds, R. M., *et al* (2000) Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. Hypertension, **35**, 1301.

Plotsky, P. M., Owens, M. J., Nemeroff, C. B. (1995) Neuropeptide alternations in affective disorders. In Psychopharmacology: The fourth generation of progress (eds F. E. Bloom & D. J. Kupfer), pp. 971-981. New York.

Post, R. M., Gordon, E. K., Goodwin, F. K., *et al* (1973) Central norepinephrine metabolism in affective illness: MHPG in the cerebrospinal fluid. Science, **179**, 1002-1003.

Potter, W. Z., Scheinin, M., and Golden, R. (1985) Selective antidepressants and cerebrospinal fluid. Lack of specificity on norepinephrine and serotonin metabolites. Archives of General Psychiatry, **42**, 1171-1177.

Rajokowska, G., Wei, J. J., Miguel-Hidalgo, J. J., *et al* (1999) Glial and neuronal pathology in rostral orbitofrontal cortex in schizophrenic postmortem brain. Schizophrenia Research, **36**, 84.

Rasanen, P., Tihonen, J., and Hakko, H. (1998) The incidence and age of onset of hospitalised bipolar affective disorder in Finland. Journal of Affective Disorders, **48**, 63-68.

Regier, D. A., Kaelber, C. T. (1995) The Epidemiological Catchment Area (ECA) program: study in the prevalence and incidence of psychopathology. In Textbook of Psychiatric Epidemiology. (eds M. T. Tsuang, M. Tohen, & G. E. P. Zahner), pp. 133-157. New York.

Rice, J., Reich, T., Andreasen, N. C., *et al* (1987) The familial transmission of bipolar illness. Archives of General Psychiatry, **44**, 441-447.

Rifkin, L., Lewis, S., Jones, P., *et al* (1994) Low birth weight and schizophrenia. British Journal of Psychiatry, **165**, 357-362.

Risch, S. C., Lewine, R. J., Kalin, N. H., *et al* (1992) Limbic-hypothalamic-pituitary adrenal axis activity and ventricular- to- brain ratio studies in affective illness and schizophrenia. Neuropsychopharmacology, **6**, 95-100.

Robins, L. N., Regier, D. (1991) Psychiatric disorders in America. The Epidemiological Catchment Area Study. New York: The Free Press.

Rosen, L., Rosenthal, N., van Dusen, P., *et al* (1983) Age of onset and number of psychotic symptoms in bipolar 1 and schizoaffective disorder. American Journal of Psychiatry, **140**, 1523-1524.

Rosoklija, G., Toomayan, G., Ellis, S. P., *et al* (2000) Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders. preliminary findings. Archives of General Psychiatry, **57**, 349-356.

Roy-Byrne, P., Post, R. M., Uhde, T. W., *et al* (1985) The longitudinal course of recurrent affective illness: Life chart data from research patients at the NIMH. Acta Psychiatrica Scandinavica, **317**, 1-34.

Roy, P. D., Zipursky, R. B., Saint-Cyr, J. A., *et al* (1998) Temporal horn enlargement is present in schizophrenia and bipolar disorder. Biological Psychiatry, **44**, 418-422.

Ryan, G. M., Jr., Sweeney, P. J., and Solola, A. S. (1980) Prenatal care and pregnancy outcome. American Journal of Obstetrics & Gynecology, **137**, 876-881.

Rybakowski, J. and Twardowska, K. (1999) The dexamethasone/ corticotropin- releasing hormone test in depression in bipolar and unipolar affective illness. Journal of Psychiatric Research, **33**, 36-370.

Sacker, A., Done, J., Crow, T. J., *et al* (1995) Antecedents of schizophrenia and affective illness: Obstetric complications. British Journal of Psychiatry, **166**, 734-741.

Schlegel, S. and Kretzschmar, K. (1987) Computed tomography in affective disorders: Part I. Ventricular and sulcal measurements. Biological Psychiatry, **22,** 4-14.

Schmider, J., Lammers, C. H., Gotthardt, U., *et al* (1995) Combines dexamethasone/corticotropin-releasing hormone test in acute and remitted manic patients, in acute depression and in normal controls. Biological Psychiatry, **38,** 802.

Schwarzkopf, S. B., Nasrallah, H. A., Olson, S. C., *et al* (1989) Perinatal complications and genetic loading in schizophrenia: Preliminary findings. Psychiatry Research, **27**, 233-239.

Scott, J., *et al* (2006) Exposure to obstetric complications and subsequent development of bipolar disorder: systematic review. British Journal of Psychiatry, **189 (1)**. 3-11

Sham, P. C., Maclean, C., Kendler, K.S. (1993) Risk of schizophrenia and age difference with older siblings. Evidence for maternal viral infection hypotheses? British Journal of Psychiatry, **163**, 627-633.

Shopsin, B., Wilk, S., Sathananthan, G., *et al* (1974) Catecholamines and affective disorders revisited: A clinical assessment. Journal of Nervous and Mental Disorders., **158**, 369-383.

Shulman, K. and Post, F. (1980) Bipolar affective disorder in old age. British Journal of Psychiatry, **136**, 6-32.

Sigurdsson, E., Fombonne, E., Sayal, K., *et al* (1999) Neurodevelopmental antecedents of early onset bipolar affective disorder. British Journal of Psychiatry, **174**, 121-127.

Silvertone, l., Finello, K., Schulsinger, F., *et al* (1985) Low birth weight and ventricular enlargement in a high risk sample. Journal of Abnormal Psychology, **94**, 405-409.

Steer, R. A., Scholl, T. O., and Hediger, M. L. (1992) Self-reported depression and negative pregnancy outcomes. Journal of Clinical Epidemiology, **10**, 1093-1099.

Stenninger, E., Flink, R., and Eriksson, B. (1998) Long term neurological dysfunction and neonatal hypoglycaemia after diabetic pregnancy. Archives of Disease in Childhood: Fetal and neonatal edition, **79**, F174-F179.

Stober, G., Kocher, I., Franzek, E., *et al* (1997) First trimester maternal gestational infection and cycloid psychosis. Acta Psychiatrica Scandinavica, **96**, 314-319.

Stokes, P. E., Stott, D. H., Koslow, S. H., *et al* (1984) Pretreatment DST and hypothalamic-pituitary- adrenal function in depressed patients and comparison groups. Archives of General Psychiatry, **41**, 257-267.

Strakowski, S., Delbello, M., Adler, C., *et al* (2000) Neuroimaging in bipolar disorder. Bipolar Disorders, **2**, 148-164.

Strakowski, S., Delbello, M., Zimmerman, M. E., *et al* (2002) Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. American Journal of Psychiatry, **159**, 1841-1847.

Strakowski, S. M., Wilson, D. R., Tohen, M., *et al* (1993) Structural brain abnormalities in first-episode mania. Biological Psychiatry, **33**, 602-609.

Strakowski, S. M., DelBello, M. P., Sax, K. W., *et al* (1999) Brain magnetic imaging of structural abnormalities in bipolar disorder. Archives of General Psychiatry, **56**, 254-260.

Subrahmanyam, S. (1975) Role of biogenic amines in certain pathological conditions. Brain Research, **87**, 355-362.

Swayze, V., Andreasen, N. C., Allinger, R., *et al* (1990) Structural brain abnormalities in bipolar affective disorder: ventricular enlargement and focal signal hyperintensities. Archives of General Psychiatry, **47**, 1054-1059.

Szadoczky, E., Papp, Z., Vitrai, J., *et al* (1998) The prevalence of major depressive and bipolar disorders in Hungary: Results from a national epidemiologic survey. Journal of Affective Disorders, **50**, 153-162.

Takahashi, L. K., Baker, E. W., and Kalin, N. H. (1990) Ontogeny of behavioral and hormonal response to stress in prenatally stressed male rat pups. Physiology and Behaviour, **47**, 357-364.

Takahashi, L. K. and Kalin, N. H. (1991) Early development and temporal characteristics of stress-induced secretion of pituitary-adrenal hormones in prenatally stressed pups. Brain Research, **558**, 75-78.

Takahashi, S. H., Yamane, H., Kondo, H., *et al* (1974) CSF monoamine metabolites in alcoholism: A comparative study with depression. Folia Psychiatric Neurology in Japan, **28**, 347-354.

Takei, N., O'Callaghan, E., Sham, P., *et al* (1993) Does prenatal influenza divert susceptible females from later affective psychosis to schizophrenia. Acta Psychiatrica Scandinavica, **88**, 328-336.

Taylor, M. A., Abrams, R., and Hayman, M. A. (1980) The classification of affective disorders: A reassessment of the unipolar-bipolar dichotomy: A clinical, laboratory, and a family study. Journal of Affective Disorders, **2**, 95-109.

Taylor, M. A. and Abrams, R. (1981) Early- and late-onset bipolar illness. Archives of General Psychiatry, **38**, 58-61.

Taylor, M. A., Berenbaum, S. A., Jampala, V. C., *et al* (1993) Are schizophrenia and affective disorder related? Preliminary data from a family study. American Journal of Psychiatry, **150**, 278-285.

Teixeira, J. M. A., Fisk, N. M., and Glover, V. (1999) Associations between maternal anxiety in pregnancy and increased uterine artery resistance index. cohort based study. British Medical Journal, **318**, 153-157.

Tek, C., Kirkpatrick, B., Kelly, C., *et al* (2001) Summer birth and deficit schizophrenia in Nithsdale, Scotland. Journal of Nervous & Mental Disease, **189**, 613-617.

Tohen, M., Waternaux, C. S., and Tsaung, M. (1990) Outcome in mania: A four-year prospective follow-up of 75 patients utilizing survival analysis. Archives of General Psychiatry, **47**, 1106-1111.

Tohen, M., Goodwin, F. K. (1995) Epidemiology of bipolar disorder. In Textbook in Psychiatric Epidemiology (eds M. T. Tsuang & M. Tohen), London.

Tomeo, C. A., Rich-Edwards, J. W., Michels, K. B., *et al* (1999) Reproducibility and validity of maternal recall of pregnancy-related events. Epidemiology, **10**, 774-777.

Torgersen, S. (1986) Genetic factors in moderately severe and mild affective illness. Archives of General Psychiatry, 43, 222-226.

Torrey, E. F. (1999) Epidemiological comparisons of schizophrenia and bipolar disorder. Schizophrenia Research, **39**, 101-160.

Torrey, E. F., Rawlings, R., and Yolken, R. H. (2000) The antecedents of psychoses: a case-control study of selected risk factors. Schizophrenia Research, **46**, 17-23.

Towbin, A. (1998) Brain damage in the newborn and its neurological sequels: pathological and clinical correlation. Danvers, Mass: PRM publications.

Traskman, L., Asberg, M., Bertilsson, L., *et al* (1981) Monoamine metabolites in CSF and suicidal behavior. Archives of General Psychiatry, **38**, 631-636.

Tsuang, M., Faraone, S. V., and Fleming, J. A. (1985) Familial transmission of major affective disorders: Is there evidence supporting the distinction between unipolar and bipolar disorders? British Journal of Psychiatry, **146**, 268-271.

Tsuang, M. T., Winokur, G., and Crowe, R. R. (1980) Morbid risks of schizophrenia and affective disorders among first degree relatives of patients

with schizophrenia, mania, depression and surgical conditions. British Journal of Psychiatry, **137**, 497-504.

Vaillancourt, C., Berger, N., and Boksa, P. (1999) Effects of vaginal birth versus caesarean section birth with general anaesthesia on blood gases and brain energy metabolism in neonatal rats. Experimental Neurology, **160**, 142-150.

van Deventer, S. J. H., Buller, H. R., Cate, J. W., *et al* (1990) Experimentally induced endotomemia in humans . Analysis of cytokine release and coagulation, fibrinolytic and complementary pathways. Blood, **76**, 2520-2526.

van Gorp, W., Altshulser, L., Theberg, D., *et al* (1998) Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. Archives of General Psychiatry, **55**, 41-46.

Van Praag, H. M. and Korf, J. (1971) Endogenous depression with and without disturbances in 5-hydroxytryptamine metabolism: A biochemical classification? Psychopharmacologia, **19**, 148-152.

Verdoux, H. and Bourgeois, M. A. (1993)a. A comparative study of obstetric history in schizophrenics, bipolar patients and normal subjects. Schizophrenia Research, **9**, 67-69.

Verdoux, H. and Bourgeois, M. A (1993)b. Obstetrical complications and schizophrenia. Comparative study of obstetric antecedents in schizophrenia and bipolar patients. Encephale, **19**, 313-320.

Vestergaard, P., Sorensen, T., Hoppe, E., *et al* (1978) Biogenic amine metabolites in cerebrospinal fluid of patients with affective disorders. Acta Psychiatrica Scandinavica, **58**, 88-96.

Vocisano, C., Klein, D. N., Keefe, R., *et al* (1996) Demographics, family history, premorbid functioning, developmental characteristics and course of patients with deteriorated affective disorders. American Journal of Psychiatry, **53**, 248-255.

Wadhwa, P. D., Sandman, C. A., and Porto, M. (1992) The association between prenatal stress and infant birth weight and gestation age at birth. American Journal of Obstetrics and Gynaecology, **169**, 858-865.

Wadhwa, P. D., Sandman, C. A., Porto, M., *et al* (1993) The association between prenatal stress and infant birth weight and gestational age at birth. Amercian Journal of Obstetrics and Gynaecology, **169**, 858-865.

Wadhwa, P. D., Porto, M., Garite, T. J., *et al* (1998) Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. Amercian Journal of Obstetrics and Gynaecology, **179**, 1079-1085.

Waters, B., Marcenko-Bouer, I., and Smiley, D. (1982) Paranatal complications are not associated with affective disorder in the offspring of bipolar manic depressives. Neuropsychobiology, **8**, 1-9.

Waters, B., Marchenko, I., and Smiley, D. (1983) Affective disorder, paranatal and educational factors in the offspring of bipolar manic depressives. Canadian Journal of Psychiatry, **28**, 527-531.

Watson, J. B., Mednick, S., Huttunen, M., *et al* (1999) Prenatal teratogens and the development of adult mental illness. Development and Psychopathology, **11**, 457-466.

Wehr, T. A., Goodwin, F. K. (1983) Biological rhythms in manic depressive illness. In Circadian rhythms in psychiatry. (eds T. A. Wehr & F. K. Goodwin), pp. 129-184.

Weinstock, M., Matlina, E., Maor, G. I., *et al* (1992) Prenatal stress selectively alters the reactivity of the hypothalamic-pituitary adrenal system in the female rat. Brain Research, **595**, 195-200.

Weinstock, M. (2001) Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Progress in Neurobiology, **65**, 427-451.

Weissman, M. M., Bruce, M. L., Leaf, P. J., *et al* (1991) Affective disorders. In Psychiatric Disorders in America (eds L. N. Robbins & D. A. Regier), pp. 53-80. New York.

Weissman, M. M., Bland, R. C., and Canino, G. J. (1996) Cross national epidemiology of major depression and bipolar disorder. Journal of the American Medical Association, **276**, 293-299.

Wells, J. E., Bushnell, J. A., Hornblow, A. R., *et al* (1989) Christchurch psychiatric epidemiology study: Methodology and lifetime prevalence for specific psychiatric disorders. Australian and New Zealand Journal of Psychiatry, **23**, 315-326.

Westergaard, T., Mortensen, P. B., Pedersen, C. B., *et al* (1999) Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. Archives of General Psychiatry, **56**, 993-998.

Wilcox, J. A. (1986) Perinatal distress and infectious disease as a risk factor for catatonia. Psychopathology, **19**, 196-199.

Wittchen, H. U., Essau, C. A., von zerssen, D., et al (1992) Lifetime and six-month prevalence of mental disorders in the Munich follow-up study. European Archives of Psychiatry and Clinical neuroscience, 241, 247-258.

Woods, B. T., Yurgelun-Todd, D., Mikulis, D., *et al* (1995) Age related MRI abnormalities in bipolar illness: a clinical study. Biological Psychiatry, **38**, 846-847.

Yoon, B. (1997) Experimentally induced intrauterine infection causes fetal brain white matter lesions in rabbits. American Journal of Obstetrics and Gynaecology, **177**, 797-802.

Zambrana, R. E., Dunkel-Schetter, C., and Collins, N. L. (1999) Mediators of ethnic-associated differences in infant weight. Journal of Urban Health, **76**, 102-116.

Zipursky, R. B., Seeman, M. V., Bury, A., *et al* (1997) Deficits in gray matter volume are present in schizophrenia but not bipolar disorder. Schizophrenia Research, **26**, 85-92.

Zornberg, G., Buka, S. L., and Tsuang, M. T. (2000) Hypoxic-Ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psychoses: A 19-year longitudinal study. American Journal of Psychiatry, **157**, 196-202.

APPENDICES

APPENDIX 1.

DSM-IV criteria for hypomania

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) Inflated self-esteem or grandiosity

(2) Decreased need for sleep (e.g. feels rested after only 3 hours of sleep)

(3) More talkative than usual or pressure to keep talking

(4) Flight of ideas or subjective experience that thoughts are racing

(5) Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)

(6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

(7) Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., the person engages in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalisation, and there are no psychotic features.

F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

DSM-IV criteria for mania

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalisation is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) Inflated self-esteem or grandiosity

(2) Decreased need for sleep (e.g. feels rested after only 3 hours of sleep)

(3) More talkative than usual or pressure to keep talking

(4) Flight of ideas or subjective experience that thoughts are racing

(5) Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)

(6) Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation

(7) Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalisation to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism).

DSM-IV criteria for major depression

A. Five (or more) of the following symptoms have been present during the same 2-week period and represents a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.

Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.

Insomnia or Hypersomnia nearly every day

Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

Fatigue or loss of energy nearly every day

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation

Appendix 2: Terms used for literature search in systematic review.

Terms used for obstetric complications

prenatal care

Birth injury

child birth

labour complications

labor complications

prenatal exposure

prenatal exposure delayed effects

obstetric surgical procedures

prenatal development stages

prenatal exposure

perinatal period

postnatal period

obstetrics gynaecology

neonatal

neonates

newborn infants

neonatal development

birth trauma

fetal complications

gestational infection

delivery complications

prenatal risk factors

perinatal risk factors

maternal infection

pregnancy complications

maternal influenza

maternal exposure

fetal hypoxia

low birth weight

premature birth

Terms used for bipolar affective disorder

bipolar disorder
bipolar depression
affective psychosis
bipolar manic disorder
manic-depressive psychosis
manic depressive mania
manic state
manic depressive
mania
manic depression
mood disorders
psychotic mania

Appendix 3: Description of methodological limitations of Kendell et al (1996)

Kendell et al (1996 & 2000) compared the obstetric information recorded on SMR2 for individuals with schizophrenia identified from SMR4 and controls matched on the same six variables as the present study. The results from the 1996 study suggested that OCs were significantly more common amongst individuals with schizophrenia, however the results obtained from the same database in 2000 showed no difference between the two groups. In order to explain this difference the authors retraced and compared each step of the methodology used in both studies. It was discovered that in the 1996 study the controls were the first subject in SMR2 who matched each proband on the requisite matching variables whereas in the 2000 study the proband's control was the closest matching subject on the SMR2 database. The authors found that if the order of SMR2, which reflected the order in which SMR2 forms were returned, was unchanged, the incidence of OCs in the controls was low and the results obtained were as reported in 1996. By comparison if SMR2 was reorganised so that for each obstetric unit all subjects appeared in order of the date of delivery and then case-control matching was carried out, the incidence of complications in the controls was far higher and all the significant proband-control differences disappeared or in some cases were reversed. To explain this finding the authors assumed that SMR2 forms for uncomplicated births were completed, returned to the ISD and entered into SMR2 soon after the delivery, whereas the SMR2 forms of complicated deliveries were returned to ISD much later, possibly because the mother and/or baby remained in hospital longer after delivery. Kendell et al (2000) supported this assumption by comparing the lengths of stay in the obstetric unit for the controls selected in the 1996 study with the average length of stay for all other potential matched controls. Three times as many of the selected controls had a shorter stay in the obstetric unit compared to the average for the other potential controls. Kendell et al (2000) concluded that uncomplicated deliveries tend to precede complicated deliveries in SMR2 and therefore selecting the next matched control in SMR2 rather than the best matching control in SMR2 results in an exaggeration of the difference between cases and controls and thus increases the probability of a type II error.

Appendix 4. Format of the SPSS SMR2 database.

Variable name	Label	Values
Total number	Total number of previous pregnancies (exclude present pregnancy)	0-8 9=9 or more
Spontaneous abortions	Number of previous pregnancies leading to spontaneous abortion	0-8 9=9 or more
Still births	Number of previous pregnancies leading to still birth	0-8 9=9 or more
Caesarean	Previous caesarean section carried out	1=No 2=Yes 9=Other/Not known
Rhesus iso- immunisation	Previous rhesus iso-immunisation	1=No 2=Yes 9=Other/Not known
Eclampsia	Previous eclampsia, severe pre-eclampsia or hypertension	1=No 2=Yes 9=Other/Not known
Antepartum haemorrhage	Previous antepartum haemorrhage	1=No 2=Yes 9=Other/Not known
Multiple births	Previous multiple births	1=No 2=Yes 9=Other/Not known

Variable name	Label	Values
Post partum hemorrhage	Previous post-partum haemorrhage or retained placenta	1=No 2=Yes 9=Other/Not known
Other significant history	Any other previous obstetric history	1=No 2=Yes 9=Other/Not known
Rhesus antibodies	Baby has rhesus antibodies	1=No 2=Yes 9=Not known
Parity	Derived from total previous pregnancies less previous abortions	
Blood transfusion	Blood Transfusion during this pregnancy	1=No 2=Yes
X-ray this pregnancy	X-ray examination during this pregnancy	1=None 2=Abdominal 3=Chest 4=Pelvic 9=Multiple
Method of induction		1=None 2=A.R.M. 3=Oxytocics 4=A.R.M. and Oxytocics 9=Other

Presentation at delivery	Position of baby at delivery	1= Occiput 2=Brow 3=Face 4=Breech 5=Shoulder 9=Other
Total duration of labour	Length of labour in hours	
Mode of delivery	Delivery type	0=Spontaneous 1=Manipulation without instruments 2=Forceps mid and high 3=Forceps low 4=Forceps unspecified 5=Vacuum extractor 6=Caesarean section 8=Other surgical or instrumental 9=Unspecified
Other obstetric procedure	Other procedure relating to obstetrics	1=None 2=Manual removal of placenta 3= Episiotomy 9=Other

Outcome of pregnancy	Outcome of baby	0=Stillbirth 1=Baby discharged alive to care of parent 2=Baby transferred from maternity nursery to care elsewhere in same hospital 3=Baby transferred from maternity nursery to care in other hospital 4=Baby discharged to other non-hospital care 5=Baby died before discharge or transfer within 24 hrs of birth 6=Baby died before discharge or transfer within 1-6 days of birth 7=Baby died before discharge or transfer in 7 days and over after birth 8=Baby temporarily detained in hospital
Sex	Sex of baby	1=Male 2=Female
Birth weight	Weight of baby at birth (gms)	
Estimated gestation		
Diagnoses	Space for 3 ICD-8 diagnoses	
Age in days		
Maternal date of birth	Date of birth of mother	
Date of birth	Date of birth of baby	Date in format ccyymmdd
Date of delivery	Date of delivery of baby	Date in format ccyymmdd

Appendix 5. References for the studies and obstetric complication summary scales included in the literature scale.

OBSTETRIC EVENT	Which studies/ summary scales have considered this an obstetric complication.
Previous spontaneous abortion	• Parnas (1982) scale: **Previous fetal loss** • Kinney et al (1993 & 1998): **More than one** prior miscarriage
Previous stillbirth	• Parnas (1982) scale: Previous fetal loss
Parity ≥ 4	• Kinney et al (1993 & 1998): **Parity > 4** • Mortensen et al (unpublished): **looked at parity 0, 1-2; 3+** • Cannon et al (2002): **Parity 4+**
Rhesus antibodies this pregnancy	• Cannon et al (2002) • Definite complication in Lewis and Murray scale
Induced labour NOS	• McNeill- Sjostrom (1995) rating scale
Labour induced using oxytocics	• Kinney et al (1993 and 1998) • McNeil-Sjostrom (1995) rating scale
Labour induced using ARM or oxytocics	• Kinney et al (1993 and 1998) • McNeil-Sjostrom (1995) rating scale
Face presentation	• Definite complication in Lewis and Murray scale: **Abnormal presentation** • McNeil-Sjostrom (1995) rating scale • Parnas et al (1982) scale: **bad fetal position**
Brow presentation	• Parnas et al (1982) scale: **bad fetal position** • Definite complication in Lewis and Murray scale: **Abnormal presentation**
Shoulder presentation	• Parnas et al (1982) scale – **bad fetal position** • Definite complication in Lewis and Murray scale: **Abnormal presentation**

Breech presentation	• Parnas et al (1982) scale – bad fetal position • Vocisano et al (1996) • Kinney et al (1993 & 1998) • Mortensen et al (unpublished) • Definite complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
Labour >24 hours	• Parnas et al (1982) scale • Kinney et al (1993 and 1998): **labour prolonged and gave 16-24 hours for multiparous** • McNeil-Sjostrom (1995) rating scale: **labour more than 16 hours for a nullparious women and a labour > 10 hours for a women with a parity of 1+ is an obstetric complication** • Equivocal obstetric complication in Lewis and Murray scale
Labour < 3 hours	• Kinney et al (1993 and 1998): **Labour < 2 hours** • Definite complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
Forceps delivery	• Parnas et al (1982) scale • Kinney et al (1993 and 1998) • Cannon et al (2002) • **High or difficult forceps** considered a Definite complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale

Delivery by c-section	• Parnas et al (1982) scale • Kinney et al (1993 & 1998) • Mortensen et al (unpublished) • Cannon et al (2002) • Definite complication in Lewis and Murray scale but only if complicated or emergency if NOS then Equivocal obstetric complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
Vacuum extraction	• McNeil-Sjostrom (1995) rating scale
manipulation without instruments	• McNeil-Sjostrom (1995) rating scale
Surgical/ instrumental manipulation NOS	• McNeil-Sjostrom (1995) rating scale
Birth weight < 2500 grams	• Vocisano et al (1996) • Cannon et al (2002) • Mortensen et al (unpublished) • Equivocal obstetric complication in Lewis and Murray scale
Birth weight > or equal to 4000 grams	• Cannon et al (2002) • Vocisano et al (1996): birth weight > 3500 grams • Mortensen et al (unpublished)
Gestation age >42 weeks.	• Cannon et al (2002) • Definite complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
GA ≤ 36 weeks	• Vocisano et al (1996) • Cannon et al (2002) • Definite complication in Lewis and Murray scale

	• McNeil-Sjostrom (1995) rating scale

ICD-8 CODES	
Diabetes	• Cannon et al (2002): Maternal diabetes • McNeil-Sjostrom (1995) rating scale
Anaemia	• Kinney et al (1993 & 1998)
Placenta abnormalities	• Parnas et al (1982) scale: **Placental defects** • Cannon et al (2002) • McNeil-Sjostrom (1995) rating scale
Threatened spontaneous abortion	• Definite complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
Haemorrhage	• Cannon et al (2002): **Antepartum haemorrhage** • Kinney et al (1993 & 1998): **bleeding/spotting** • Definite complication in the Lewis and Murray scale.
Malposition of fetus in uterus	• McNeil-Sjostrom (1995) rating scale
Hydramnios	• McNeil-Sjostrom (1995) rating scale
Pre-eclampsia	• Kinney et al (1993 and 1998) • Equivocal obstetric complication in the Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
Eclampsia	• Parnas et al (1982) scale • Cannon et al (2002) • Severe pre-eclampsia which may be defined as eclampsia and is a Definite complication in Lewis and Murray scale but only if severe and leading to early induction or hospitalisation • McNeil-Sjostrom (1995) rating scale

Delivery complicated by fetopelvic disproportion	• Parnas et al (1982) scale: Narrow pelvis
Rubella unrelated to pregnancy	• Kinney et al (1993 & 1998) • Definite complication in Lewis and Murray scale
Syphilis	• Definite complication in Lewis and Murray scale • McNeil-Sjostrom (1995) rating scale
Hypoxia or anoxia caused by fetal distress	• Cannon et al (2002); • Parnas et al (1982) scale: **Asphyxiation**. • McNeil-Sjostrom (1995) rating scale
Cord prolapse	• McNeil-Sjostrom (1995) rating scale
Haemolytic disease of the newborn with rhesus incompatibility	• McNeil-Sjostrom (1995) rating scale
Glycosuria	• Cannon et al (2002)
Delivery complicated by postpartum haemorrhage	• Parnas et al (1982) scale: **bleeding after delivery** • Kinney et al (1993 and 1998): **Excessive** bleeding after delivery
Delivery complicated by prolonged labour	• See labour > 24 hours

- Browne et al (2000) used the Lewis & Murray (1987) scale
- Camberwell Collaborative Psychosis Study (unpublished) and Stober et al (1997) used the Lewis et al (1989) rating scale
- Gunduz et al (unpublished) used the McNeil-Sjostrom (1995) rating scale
- Browne et al (2000), Verdoux and Bourgeois (1993a) and Schwarzkopf et al (1989) used the Parnas et al (1982) scale

Appendix 6: Definitions of SMR2 variables considered an obstetric complication and the risks they pose to the fetus.

MOTHERS REPRODUCTIVE HISTORY

PREVIOUS SPONTANEOUS ABORTION

The spontaneous end of a pregnancy before week 24 is known as a spontaneous abortion

PREVIOUS STILLBIRTH

The delivery of a dead fetus after week 24 of pregnancy is known as a stillbirth.

PREGNANCY COMPLICATIONS

HYDRAMINIOS

Normally, the amount of amniotic fluid surrounding the fetus does not exceed 1.5 litres (3 pints). Hydraminios is an excessive amount of amniotic fluid surrounding the fetus in the uterus.

What are the effects on the fetus?

Excess fluid makes it easier for the fetus to move around in the uterus. For this reason, the fetus may not lie in the normal head-down position at the end of pregnancy. Excessive amounts of fluid also increase the likelihood of a premature labour or of premature rupture of membranes.

RHESUS ANTIBODIES THIS PREGNANCY

One of the systems for classifying blood is the Rhesus (Rh) group. This system classifies blood according to the presence or absence of certain proteins on the surface of red blood cells. About 17 in 20 people in the UK have Rh proteins on the surface of their red blood cells and are Rh positive. The remaining 3 in 20 people do not have these proteins and are therefore Rh negative. Rh incompatibility occurs when a mother is Rh negative and her fetus is Rh positive. The circulatory systems of the mother and the fetus are separate, and the red blood cells do not usually cross from one to the other. However, there are circumstances in which stray red blood cells from the fetus can enter the mother's

circulation. The fetus' blood cells may leak into the mother's system during delivery, miscarriage, or termination of pregnancy. There is also a risk of blood mixing when an amniocentesis test is carried out or after a placental abruption, in which part or the entire placenta detaches from the uterus before delivery. If this occurs the mother's immune system reacts by producing antibodies to destroy the fetal red blood cells in her circulation. In future pregnancies in which the fetus is Rh positive, these antibodies cross the placenta and destroy fetal red blood cells. Untreated, these effects become increasingly severe in each subsequent Rh-incompatible pregnancy.

What are the effects on the fetus?

The fetus may develop swelling and progressive anaemia, in which destruction of the red blood cells leads to low levels of oxygen-carrying pigment in the blood. Rarely, a severely anaemic fetus develops acute heart failure and may die in the uterus. After a Rh-incompatible pregnancy, a baby may be born with severe anaemia. Jaundice in the newborn baby occurs due to build-up of bilirubin, a pigment produced from the destruction of fetal red blood cells. Rarely, severe jaundice may cause brain damage.

If Rh antibodies develop, treatment depends on the amount of antibodies and their effect on the fetus. A sample of the fluid in the uterus is tested for evidence of high bilirubin in the fetus. Additional ultrasound scanning may be used to check whether the fetus is swollen. If antibody levels are low, the pregnancy may continue until labour is induced at 38 weeks; if levels are high, labour may be induced earlier. A fetus that is too immature for delivery may have a blood transfusion of Rh-negative blood into the umbilical cord or abdominal cavity. After birth, the baby may need more transfusions and treatment for jaundice.

DIABETES AND GLYCOSURIA

Normally the hormone insulin enables the body to absorb glucose from the bloodstream. During pregnancy, additional hormones, which have an anti-insulin effect, are produced by the placenta. If the body does not produce enough insulin to counter this effect, the result is high levels of glucose in the blood stream and gestational diabetes. Glycosuria is the term given when there is sugar in the urine the most common cause of which is diabetes.

What are the effects on the fetus?

For most women with gestational diabetes, pregnancy progresses safely to about 40 weeks, and vaginal delivery is possible. However, if diabetes becomes difficult to control, early induction of labour may be necessary. If the fetus is very large, the doctor may carry out a caesarean section to avoid a difficult vaginal delivery. The diabetic mother is predisposed to toxaemia, eclampsia, and infection and increased risk of preterm delivery, delivery by c-section, delivering a large baby, urinary tract infection, and spontaneous abortion. One half of diabetic women experience hypertension. The fetus is at increased risk of congenital abnormalities, stillbirth due to fetal metabolic disturbance, intrauterine death due to hypoxia resulting from an episode of hyperglycaemia (an abnormally high level of sugar/glucose in the blood), and the offspring of mothers with poorly controlled plasma (fluid proportion of the blood) glucose are at increased risk of respiratory distress syndrome.

MATERNAL ANAEMIA

Red blood cells are manufactured in the bone marrow and circulate in the bloodstream for about 120 days before they are broken down in the spleen. In a healthy person, the production and destruction of red blood cells are balanced. Anaemia occurs if this balance is upset, reducing the number of healthy cells, or if the haemoglobin is abnormal. Red blood cells bind with oxygen from the lungs and carry it through the circulation to the body tissues. With anaemia therefore the oxygen-carrying capacity of the blood is reduced, and the tissues of the body may not receive sufficient oxygen.

What are the effects on the fetus?

The rate of stillbirth in infants of anaemic mothers is increased six-fold. Maternal anaemia is also associated with an increased risk of hypoxia, intrauterine growth retardation, premature labour and puerperal sepsis (toxins in the blood or tissues after childbirth).

ANTEPARTUM HAEMORRHAGE

Antepartum haemorrhage is defined as bleeding before the onset of labour. Threatened spontaneous abortion is a form of haemorrhage. In a threatened spontaneous abortion, the fetus is alive and the cervix remains closed. There is some vaginal bleeding, which is usually painless, but the pregnancy often

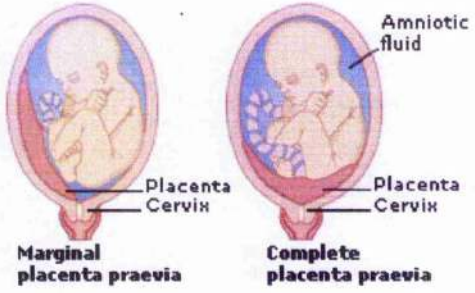
continues to full term.

What are the effects on the fetus?

All antepartum haemorrhage is considered an obstetric complication, as the risk of fetal mortality is high. Threatened spontaneous abortion is the term used to describe the situation where there is unexplained vaginal bleeding during early pregnancy in the presence of a live embryo or fetus. Unlike an inevitable spontaneous abortion the bleeding is not accompanied by uterine pain and ultrasound examination shows the presence of an appropriately sized uterus and fetal heartbeat. Such pregnancies generally continue and produce normal babies. However since the bleeding comes from inside the cervix this is considered an obstetric complication.

PLACENTA PRAEVIA

In some pregnancies, the placenta is implanted lower down in the uterus and closer to the cervix than is normal. Although a placenta that is lying low will usually move upwards gradually as the uterus expands, the placenta may remain in this position and cover some or the entire opening of the cervix. This condition is known as placenta praevia. The severity of this condition is related to how much of the opening of the cervix is covered by the placenta. In marginal placenta praevia, the placenta lies low in the uterus and just reaches the edge of the cervix. When complete placenta praevia occurs, the whole of the cervix is covered.



What are the risks to the fetus?

Symptoms caused by the condition vary, and mild cases may cause no adverse effects. In other cases, intermittent light to heavy vaginal bleeding occurs from week 24 of pregnancy onwards. If bleeding is heavy, the mother may need to have an emergency caesarean section and possibly a blood transfusion to replace

the blood lost. Complete placenta praevia may cause severe bleeding that can be life threatening to the mother and/or fetus. Even if there are no problems, and there is only marginal placenta praevia, the baby is usually delivered by caesarean section at 38 weeks. Thus placenta praevia can result in intrauterine death due to anoxia and the fetus is also at increased risk of prematurity. Fetal abnormalities are twice as common in those with a placenta praevia

PRE-ECLAMPSIA

Pre-eclampsia is a combination of high blood pressure with excessive fluid retention and/or protein in the urine. The cause of pre-eclampsia is not yet understood, but it may be due in part to the mother developing an immune reaction to the fetus. The condition is most likely to develop in a first pregnancy, a subsequent pregnancy with a new father, or a multiple pregnancy. Pre-eclampsia can run in families and is most common in women under the age of 19 or over 35. There is also an increased risk of pre-eclampsia in overweight women and in women who have chronic kidney disease, diabetes, or pre-existing high blood pressure.

What are the risks to the fetus?

Perinatal mortality associated with eclampsia is 400-600 per 1000 births (Llewellyn-Jones, 1982). The risk to the fetus depends on the stage in gestation when the eclampsia occurs. Perinatal mortality is reduced if the eclampsia occurs past 32 weeks and the fits are controlled and delivery is prompt. However, in early gestation perinatal death usually occurs due to hypoxia. The risks of pre-eclampsia to the fetus include asymmetrical growth retardation, placental abruption and pre-term delivery and hypoxia (Chamberlain & Pearce, 1992).

RUBELLA

Rubella, also called German measles, usually causes little more than a mild rash. The disease is caused by the highly contagious rubella virus, which is transmitted through airborne droplets from the coughs and sneezes of infected people. Rubella has become less common in the developed world because of routine childhood immunization.

What are the risks to the fetus?

About 90% of fetuses are affected if rubella occurs in the first 8 weeks of

gestation. About 65-85% of fetuses are affected if infection occurs between 9 and 12 weeks gestation. Damage to the fetus in the first twelve weeks of gestation includes cardiac, eye and ear abnormalities and neurological damage. After the 12th week of gestation an adverse effect on the fetus is less likely; at 13-16 weeks gestation 35% of the fetuses are affected and after this less than 1% are affected. Those that are affected show deafness and mental retardation (Chamberlain & Bowen-Simpkins, 2000). Rubella is also associated with pre-term labour (Chamberlain & Bowen-Simpkins, 2000).

Rubella infection has been associated with several neurodevelopmental disorders including schizophrenia.

SYPHILIS

Syphilis is caused by the bacterium *Treponema pallidum*. This organism enters the body through the mucous membranes of the genital area or the skin. Left untreated, the disease may be fatal.

What are the effects on the fetus?

A pregnant woman with syphilis can pass the disease to the fetus, causing it to develop congenital syphilis. However, screening during pregnancy has now made congenital syphilis very rare.

MALPOSITION OF THE FETUS IN THE UTERUS

In most normal pregnancies, the fetus settles into the mother's pelvic cavity from week 36 onwards, ready for labour and birth. About 8 in 10 fetuses settle head downwards, facing the mother's back, with the chin resting on the chest. In this presentation, the fetus is in the optimum position for birth, and a normal vaginal delivery is usually possible. All other fetal positions are considered to be abnormal presentations and may cause problems during labour.

What are the risks to the fetus?

When a fetus is lying in an abnormal position in the uterus, a vaginal delivery may be possible, but the labour may be prolonged. If the fetus becomes stuck, it may need an assisted delivery or caesarean section. If the fetus lies in an abnormal position just before delivery, there may be complications that place both the fetus and mother at risk. A fetus in the normal head-down position

blocks the cervix and prevents the umbilical cord from passing out of the uterus before the fetus. Some abnormal presentations leave space for the cord to drop through the cervix when the membranes surrounding the fetus rupture. When this occurs, the cord may be compressed by the fetus, or, rarely, its blood vessels may go into spasm because of the drop in temperature outside the uterus. As a result, the fetus may be deprived of oxygen. This may cause brain damage or fetal death. An abnormal presentation may also increase the risk of the cervix or vagina being torn during delivery.

LABOUR AND DELIVERY COMPLICATIONS

ASSISTED DELIVERY

Delivery can be assisted either instrumentally or surgically. Instrumental deliveries involve the use of forceps or vacuum extraction. In the case of forceps, large tongs are used to grasp and make traction on the fetal head in a difficult delivery. A vacuum extraction is often used instead of forceps delivery and involves attaching a suction cup to the baby' s head and then gently pulling to help ease the baby from the birth canal. A caesarean section is a surgical procedure where the baby is delivery through the abdomen.

What is the effect on the fetus?

With respect to forceps delivery, incorrect application of the forceps can cause compression of the skull leading to fractures, while to much force can lead to intracranial haemorrhage. With respect to caesarean section, animal studies have shown that rats born by caesarean section display respiratory alterations and low CNS hypoxia during the first twenty-four hours of life (El-Khodor & Boksa, 1997; Vaillancourt et al, 1999). Similar responses have been reported in humans; Hakes et al (1993) reported an increased incidence of respiratory distress in humans born by caesarean section. Furthermore El-Khodor & Boksa (2001) found that dopamine receptor binding was increased in the limbic areas of the brain in rats born by caesarean section compared with rats born vaginally. Rats born by caesarean section also displayed long term changes in the regulation of dopamine following stress compared to vaginally born rats.

INDUCTION OF LABOUR

As the name suggests induction of labour is the act of starting labour. This may be necessary if the health of the mother or the fetus is at risk, if the pregnancy continues beyond the due delivery date or complications, such as poor growth of the baby occur. Oxytocin, which is a uterine stimulant, can be infused into a vein to induce labour or to speed up prolonged labour by increasing the strength, duration, and frequency of contractions.

What are the effects on the fetus?

Prolonged or excessive oxytocin can cause fetal hypoxia by over stimulating the uterus and in rare cases can cause rupture of the uterus (Miller & Callander, 1989).

ABNORMAL PRESENTATION AT DELIVERY

At delivery the fetus should be head down facing the mothers back. All other presentations at delivery are considered abnormal. In a brow presentation, the fetus' head is bent slightly backwards with the brow over the cervix. With shoulder presentation the fetus lies across the uterus with its shoulder over the cervix. A breech presentation is when the buttocks or lower extremities of the baby present at the pelvis. In a face presentation, the neck of the fetus is bent backwards so that the face is positioned over the cervix.

What are the effects on the fetus?

The main risk associated with abnormal presentation of the fetus at delivery is an obstructed labour, which increases the risk of rupture of the membranes. Fetal death is usual from interference of the placenta circulation or cord prolapse. A breech delivery may cause additional problems if the legs and body of the fetus are able to pass through the cervix when it is not completely dilated, but the head becomes stuck. If, in a footling breech, one foot drops through the cervix, this may prompt the mother to try to push too early. The risks of breech presentation during labour include placenta separation, intracranial haemorrhage, cord prolapse and joint dislocation. The fetal loss in uncomplicated breech deliveries varies from 3-12% (Llewellyn-Jones, 1982). The hazards of a breech delivery include cerebral haemorrhage from passing to quickly through the pelvis, asphyxia from passing to slowly, uterine rupture and hypoxia due to increased risk of cord prolapse. Face presentation offers a considerable risk to the fetus,

even when malformed babies are excluded. Amongst normal babies the mortality rate is about 10%. This is due to a higher incidence of operative procedures, to cerebral congestion and hypoxia in labour due to poor venous return to the head and neck.

LABOUR >24 HOURS

Labour is the period when the fetus, placenta and membranes are expelled through the birth canal. A labour lasting more than 24 hours is considered a long labour whilst a labour less than 3 hours is considered a short labour.

What are the effects on the fetus?

The fetus often becomes distressed during a prolonged labour and is at risk of hypoxia. Delivery within 1 or 2 hours puts the fetus at risk of cerebral damage.

DELIVERY COMPLICATED BY FETOPELVIC DISPROPORTION

Disproportion between the size of the fetus and the size of the birth canal is often referred to as Dystocia.

What are the effects on the fetus?

Dystocia can cause fetal injury such as cranial trauma, intracerebral damage and at times spinal injury as the head is forced through the birth canal (Towbin, 1998). Vaginal delivery may be difficult for large babies if the mothers pelvis is small and thus require the use of forceps or caesarean section which are considered an obstetric complication.

HYPOXIA OR ANOXIA CAUSED BY FETAL DISTRESS

Hypoxia is abnormal reduction of oxygen in the body tissues i.e. oxygen deficiency. Anoxia is a total lack of oxygen.

What are the effects on the fetus?

Hypoxia/ anoxia, through a series of events, can result in structural and biochemical brain abnormalities.

CORD PROLAPSE

The umbilical cord carries oxygenated blood from the placenta to the fetus. During delivery the cord may become compressed between the head and the pelvic bone. This is called cord prolapse.

What are the effects on the fetus?

Obstruction of the cord will restrict the oxygen supply to the fetus. Towbin (1998) estimates that after 6-10 minutes of this the fetus will suffer hypoxic cerebral damage

NEONATAL COMPLICATIONS

HAEMOLYTIC DISEASE IN THE NEWBORN WITH RHESUS INCOMPATIBILITY

A condition resulting from incompatibility of the maternal and fetal blood cell groups and which the fetal red blood cells are destroyed by transplancetal passage of the mothers antibodies e.g. due to previous rhesus incompatibility the mother has produced antibodies which have crossed the placenta and effected the integrity of the baby's red blood cells. The infant has therefore been born with haemolytic anaemia and jaundice. The term haemolytic refer diseases characterised by a shortened life span of the red blood cells.

What are the effects on the fetus?

Haemolytic disease in the newborn with rhesus incompatibility is a very serious disease. Over and above the complications associated with rhesus antibodies, the newborn may have high levels of bilirubin (a bile product produced from the breakdown of the red blood cell pigment haemoglobin) in the blood stream, which can cause brain damage.

BIRTH WEIGHT <2500 GRAMS

An infant with a birth weight less than 2500 grams is considered to be small.

What is the effect on the fetus?

Increased risk of infection. Increased risk of the failure of the lungs to expand and therefore an increased risk of hypoxia.

BIRTH WEIGHT MORE THAN OR EQUAL TO 4000 GRAMS

An infant with a birth weight of 4000 grams or more is considered to be large.

What is the effect on the fetus?

Large fetuses are more prone to hyperinsulinaemia (excessively high blood

insulin levels). This in turn can result in sudden uncontrolled hypoglycaemia (an abnormally diminished volume of glucose in the blood) immediately after or during birth. There is a recognized association between hypoglycaemia and neurological dysfunction (Stenninger et al, 1998). Furthermore, the delivery of a large baby may be complicated by dystocia. Dystocia can cause fetal injury such as cranial trauma, intracerebral damage and at times spinal injury as the head is forced through the birth canal (Towbin, 1998). Large babies also have decreased liqour volumes, which can result in intrauterine trauma

GESTATION AGE

Forty weeks is considered term. Thus 42 weeks gestation is beyond term and is considered post term. Pre-term delivery is defined as a delivery that commences more than 21 days before term, therefore before 37 weeks of gestation

What is the effect on the fetus?

The placenta function may become inadequate after term as the uterine blood flow diminishes and degenerative changes progress with a large fetus that is still growing. Furthermore during labour the risk of fetal distress and fetal death is increased as the skull is more ossified so moulding less easy.

The main risk of pre-term labour is fetal mortality. Between 1993 and 1995, only 28% of babies born at 24-25 weeks gestation survived, the remaining 42% were stillborn and 30% died within the first year of life. At 28-29 weeks gestation the survival rate increased to 72%, with 13% stillborn and 15% dying in infancy and at 32-33 weeks increased again to 95%, with only 4% still born and 1% dying within the first year of life. By comparison at 34-35 weeks gestation 97% survived and 2.5% and 0.5% respectively were stillborn or died within the first year of life (Chamberlain & Bowen-Simpkins, 2000). Secondly, the immature fetus is at risk of cerebral haemorrhage because the fragile cranial bones provide insufficient protection for the brain during labour. The brain itself is more susceptible to hypoxic damage and there are inefficient clotting mechanisms. However, in well-equipped special care units, especially where there is an intensive care unit, two-thirds of babies born after 28 weeks of gestation survive without neurological damage (Chamberlain & Bowen- Simpkin, 2000). Furthermore, surfactant, which permits the pulmonary tissue to expand during

inspiration and prevents the air sacs from collapsing and sticking together after each breathe, is largely produced after the 35th week of gestation. Therefore the pre-term baby is also at risk of postnatal respiratory problems, which may cause hypoxia. The birth weight of the pre-term baby is usually 2500 grams or less (Llewellyn-Jones, 1982) and therefore the pre-term baby is predisposed to all the complications associated with low birth weight.