A study of the value of a self reported family history of pregnancy hypertension or cardiovascular disease as a predictor in the development of pregnancy-induced hypertension

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Summary

Pregnancy-induced hypertension (PIH) is a common complication affecting approximately 20% of women. Despite improved health of women and the availability of antenatal care, it remains a major cause of maternal mortality and perinatal morbidity and mortality. The condition has been recognised for centuries, however its aetiology remains uncertain. Numerous studies have suggested that familial factors are associated with susceptibility to develop PIH, although the genetic basis of the condition is not clear.
The purpose of this study is to investigate the value of a family history of hypertension in pregnancy or cardiovascular disease, as reported by the woman herself in predicting the development of PIH.

The sample consisted of 1181 primigravid women who booked for antenatal care, within the first trimester of pregnancy, at Glasgow Royal Maternity Hospital. Following return of a self report questionnaire and collection of data on pregnancy outcome, complete data was available for 955 women.

This study used a prospective cohort design. A simple questionnaire was developed asking about family history of pregnancy hypertension in mothers, sisters, aunts and grandmothers. Additional questions were asked about the occurrence of cardiovascular disease (hypertension, heart disease and stroke) in close family members.

As the purpose of the study was to assess the value of information provided by the women themselves in predicting PIH no attempt was made to verify information given, by tracing case records of family members. Case

records of all women entered into the study were followed up for outcome of pregnancy.

Data were analysed for overall incidence of PIH and in particular for incidence in groups of women who reported either positive or negative family history of hypertension in pregnancy or cardiovascular disease.

The study found that the incidence of a reported family history of pregnancy hypertension was high (35.7%). The incidence of reported family history of cardiovascular disease was also high (49.1%). In contrast the incidence of PIH, in particular severe disease, within women in the study was low (14% for all PIH, 1.4% for severe).

The odds ratio for development of mild PIH and for PIH requiring therapy were significantly increased in women who reported that a member of their family had been affected by pregnancy hypertension compared to those who reported that they had no such history (1.56 and 2.0 respectively). However the odds ratio was not significantly increased for women who developed moderate and severe disease.

The questionnaire also identified a group of women who reported that they had no family history of disease. The incidence of PIH amongst these women was significantly lower than that in women who reported that they had a family history of either pregnancy hypertension or cardiovascular disease (11.1% versus 15%). Women who reported that they had a sister who had been affected had a particularly high incidence of PIH (28.5%) When this group was compared to the women who reported no family history the odds ratio was significantly increased for development of all types of PIH. However in the more clinically meaningful comparison with

the study group as a whole the odds ratio was only significantly increased in relation to mild disease.

The study investigated the affect of a reported family history of cardiovascular disease on development of PIH. In comparison with the group of women who reported no history, women who gave a family history of essential hypertension had an increased odds ratio for development of PIH, in particular mild disease (odds ratio 1.97). Those who gave a family history of cardiac disease had an increased odds ratio (2.27) for moderate and severe disease.

Information provided by women themselves on family history of pregnancy hypertension and cardiovascular disease did identify risk groups for subsequent development of PIH. In a clinical setting this information may be of value as part of an assessment of individual women's risk of developing PIH and in planning antenatal care. However, even within the highest risk group the incidence of severe PIH remained low, most women remaining normal throughout pregnancy. Correspondingly within the lowest risk group, although the incidence of severe disease was low it did occur in some women. Based on the data of this study it would appear that information on family history of pregnancy hypertension or cardiovascular disease, provided by the woman herself would not be of clinical value as a screening test for predicting the development of PIH. The questionnaire was acceptable to most women within the study, and may be useful in identifying affected family groups for further research into the genetic basis of PIH.

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Abbreviations

CL	confidence limits
CVD	cardiovascular disease
GGHB	Greater Glasgow Health Board
GRMH	Glasgow Royal Maternity Hospital
IUGR	intrauterine growth retardation
Mod	moderate pregnancy-induced hypertension
NS	not statistically significant
OR	odds ratio
PIH	pregnancy-induced hypertension
Pop	population
SCBU	special care baby unit
SD	standard deviation
Sev	severe pregnancy-induced hypertension

Chapter One

Introduction

1.1 The problem of pregnancy-induced hypertension (PIH) and purpose of research

1.1.1 A woman's experience of PIH

> *"I developed pre-eclampsia at thirty weeks and at thirty-one weeks I had an emergency section as my blood pressure was so high they thought I was going to die. Do you know, I went to my doctor at thirty weeks and he said I had mild toxaemia and to go home and put my feet up. The following week my blood pressure was 150/110 they suggested I stay in hospital, I came back in the evening and went into a coma. I looked like I had been pumped up with a bicycle pump I was so swollen, the whole thing was a nightmare. My son weighed three pounds two ounces, he lived for three days."*
>
> (Anon; 1990)

The effects of hypertension in pregnancy have been recognised since the time of ancient Greece. Numerous terms have been used to identify the condition, however, its aetiology remains largely unknown today.

PIH, despite improvements in ante natal and intrapartum care, continues to be one of the main causes of maternal mortality and is a major cause of perinatal morbidity and mortality (Chamberlain et al, 1978; MacGillivray, 1983).

1.1.2 Prediction of PIH

PIH is a condition which primarily affects primigravid women, as such it cannot be predicted on the basis of past history of the disease. It occurs in the second half of pregnancy and onset is often severe and without warning.

A successful screening test would improve the targeting of monitoring for women at risk of developing the disorder and give opportunity for prophylaxis, should this be successfully developed, or of early treatment. For this reason many screening tests for PIH have been developed, but none have as yet been shown to be practical, effective and cost effective.

1.1.3 Familial tendency to PIH

It is thought that PIH occurs in susceptible women and several researchers have suggested that there is a familial tendency in its development. Chesley, Cosgrove and Annitto (1968) brought together a number of reports, the earliest dating from the end of the last century which describe families where numerous members have been affected by eclampsia and pre-eclampsia. Many of these descriptive studies have relied at least in part, on anecdotal information and in addition, have included both primigravid and parous women and so may include those with essential hypertension as well as PIH and eclampsia. Chesley, Cosgrove and Annitto (1961, 1968, 1976) reported the systematic follow-up, using medical records, of the families of a group of women who had survived eclampsia between 1931 and 1951. They reported an increase in the incidence of both eclampsia and pre-eclampsia in the sisters and daughters of the index cases compared to the general population. Subsequent studies have attempted to determine to genetic basis of PIH and eclampsia (Cooper and Liston, 1979; Chesley and Cooper, 1986; Kilpatrick, 1987; Cooper et al, 1988; Arngrimsson et al, 1990), although it remains unclear whether the genetic model is dependent on maternal genotype or on maternal-fetal genetic interaction. All these studies agree however, that the predisposition to PIH is heritable and this gives the possibility that knowledge of a woman's family history may be of use in predicting women at risk of developing PIH.

1.1.4 Purpose of research

This thesis describes a study carried out at Glasgow Royal Maternity Hospital. The aim of this study was to test the value of the knowledge of a family history of hypertension in pregnancy or cardiovascular disease, as reported by the woman herself, as a predictor of the development of PIH.

The Royal Maternity Hospital serves the north and east of the city of Glasgow. This area has a more transient population, than that studied in Iceland by Arngrimsson et al (1990). It is difficult to trace the obstetric case records of the family members of many women who are cared for at Glasgow Royal Maternity Hospital. This is due partly to the frequent surname changes of many families, the wide dispersal of family members, the closure of small maternity homes within the city over the past 20 years, and the distribution or destruction of case records from these homes. To attempt to obtain information on family history by tracing old medical records is time consuming and often fruitless. The principle of a screening test is that it is simple and cost effective to apply to a large population with the aim of detecting the small number who will be at high risk of being affected by the condition. We therefore sought to find out what information women themselves could give about their family history and to evaluate its usefulness in predicting their risk of developing PIH. We did this by means of self completed questionnaire. The aim was to develop a family history questionnaire which was easy to administer and complete, and to test this as a screening test for susceptibility to the development of PIH.

1.2 Aim of research

To determine whether family history of hypertension in pregnancy or cardiovascular disease, as reported by the woman herself, is a predictor in the development of PIH.

1.3 Objectives of research

i) To determine the self reported incidence of hypertension in pregnancy in the family history of the study group.

ii) To determine the incidence of PIH and pre-eclampsia in the study group.

iii) To determine whether a self reported family history of hypertension in pregnancy predicts women at risk of PIH.

iv) To determine the self reported incidence of cardiovascular disease in the family history of the study group.

v) To determine if a self reported history of cardiovascular disease predicts women at risk of PIH.

vi) To determine whether absence of a self reported family history of hypertensive disease selects a group at low risk for the development of PIH.

vii) To determine if a self completion questionnaire is a feasible tool for gaining information on the family history of women booking at an ante natal clinic.

1.4 Literature review

1.4.1 History of Pre-eclampsia.

The effects of pre-eclampsia have been recognised for centuries. As knowledge of the condition has grown its various signs have been attributed to various diseases, in particular; epilepsy, renal disease and essential hypertension.

1.4.2 Epilepsy

From the earliest times it has been known that convulsions may affect women in pregnancy. Chesley (1978) reviewed the earliest history of eclampsia and the development of medical understanding of the condition, the following summary is based largely on this work. In his review Chesley suggests that the Greeks, prior to Hippocrates time may have recognised pre-eclampsia, in that a pregnant woman suffering drowsy headaches with heaviness was considered liable to suffer fits.

Hippocrates in his Aphorisms (Sec, vi, No 30) wrote that

> *"it proves fatal to a woman in the state of pregnancy if she be seized with any of the acute diseases"*

Six centuries later Gallen commenting on these aphorisms writes that epilepsy, apoplexy, convulsions and tetanus are especially lethal.

Gabelchoverus in 1596 noted pregnancy to be one of four causes of epilepsy. A century later Mauriceau attributed convulsions in pregnancy to an excess of heated blood, irritation of the uterine cervix or to noxious vapours arising from the uterus when the fetus had died. He recognised that primigravid women were at far greater risk of convulsions than multiparas, a factor considered of importance today.

1.4.3 Eclampsia

It was not until the 18th century that it was appreciated that eclampsia and epilepsy were different diseases. De Sauvages in 1739 differentiated epilepsy, a chronic condition, from convulsions of acute causes which he termed eclampsia. One of these being described as Eclampsia parturientium. Eclampsia continued to be used as a generic term for convulsions of various causes. This persisted until the early 1960's when all but the obstetric definition was dropped (Chesley, 1978).

1.4.4 Renal disease

In 1843, Lever found that women with eclampsia had proteinuria and for many years renal disease was thought to be the cause of eclampsia. Lever acknowledged that eclampsia was different from renal disease in that proteinuria resolved after delivery. With the development of methods of assessing renal function, and the renal histology studies of Sheehan in 1950 it was demonstrated that renal lesions were present only when a patient had proteinuria. This is a late manifestation of the disease and therefore it was apparent that renal disease was not a primary cause of the condition.

1.4.5 Hypertension

The development of blood pressure recording techniques in the late nineteenth and early twentieth centuries led to the discovery that hypertension is associated with eclampsia (Cook and Briggs, 1903) and the term pre-eclampsia was introduced to describe the condition of hypertension prior to a convulsion occurring.

Primary or essential hypertension was differentiated from renal hypertension in 1896 and was termed "senile plethora" (Ballantyne, 1885).

This was considered to be a disease of the elderly and therefore could not present in a woman of childbearing age. It was not until the 1940's (Chesley, 1980) that essential hypertension was accepted as a possible cause of hypertension in pregnancy.

Chesley et al (1976) followed the medical histories of a group of women who had suffered from eclampsia. This study covering a period of over 40 years demonstrated that there was a hypertensive condition, specific to pregnancy which resolved at the end of the pregnancy and carried no long term sequalae.

1.4.6 Types of Hypertension.

At the present time it appears that here are two main types of hypertension which affect women in pregnancy (Wallenburg, 1989; Walker, 1991).

i) Pregnancy occurring in women with pre-existing chronic (essential) hypertension, renal disease or other hypertensive disease diagnosed prior to pregnancy. This may be detected in the first trimester of pregnancy or when hypertension persists following delivery.

ii) Hypertension which occurs for the first time during the second half of pregnancy, labour or puerperium and which resolves when the pregnancy is over. This condition occurs predominantly, but not exclusively in primigravida. There are various terms for this condition, but the most commonly used are pregnancy - induced hypertension (PIH) and pre-eclampsia. (Greer, 1992)

1.4.7 Defining signs

Since the aetiology of PIH and pre-eclampsia is unknown, the definition and diagnosis are based on the three classical clinical signs, hypertension, proteinuria and oedema.

i) Hypertension

During the first trimester of a healthy pregnancy there is a 40% increase in maternal blood volume and increased cardiac output which will be maintained throughout the pregnancy. In order to compensate for this there is normally vasodilation and therefore decreased peripheral vascular resistance. There is a decrease in arterial blood pressure which is greatest during mid pregnancy after which the blood pressure tends to rise again toward the non pregnant level approaching term (MacGillivray, Rose and Rowe, 1969; Page and Christianson, 1976). In PIH the blood pressure increases as a result of an increased systemic vascular resistance in the presence of the increased cardiac output which has occurred in the first trimester of pregnancy. Hypertension is not the disorder in itself, but rather an indication of an underlying circulatory disturbance (Wallenburg, 1989), and as such, may be used as a marker of risk. The traditional dividing line between normal and abnormal blood pressure in pregnancy is a diastolic blood pressure of 90mmHg (Greer, 1992) using Korotkoff phase IV as the measure of diastolic pressure. Although, for some women, towards term this may not reflect a particularly substantial rise in blood pressure from their pre-pregnancy level. Studies have shown, however, that there is an increased perinatal mortality rate where the mothers blood pressure rises above 90mmHg (Page and Christianson, 1976).

ii) Proteinuria

In pregnancy, proteinuria is considered abnormal when it reaches a level greater than 300mg in 24 hours. The absence of proteinuria does not always ensure that PIH will be mild, as severe PIH may occur in the absence of proteinuria and the correlation between the level of blood pressure and the occurrence of proteinuria is low (McEwan, 1987). Where it is present however, proteinuria is a sign of severe disease and is associated with an increase in perinatal mortality (MacGillivray, 1958; Friedman and Neff, 1976).

iii) Oedema

Although oedema is one of the classic signs of pre-eclampsia it also frequently occurs in normotensive pregnancies (Robertson, 1971). In the absence of hypertension and proteinuria it is not associated with poor perinatal outcome. Oedema does occur in about 85% of women with pre-eclampsia (Thomson, Hytten and Billewicz, 1967). Unlike hypertension and proteinuria however, oedema is not a marker of disease severity. Interestingly, oedema in pre-eclampsia is associated with a lower perinatal mortality rate than pre-eclampsia with no oedema so called *'dry pre-eclampsia'* (Vosburgh, 1976), and is of no value as a defining sign of PIH.

1.4.8 Definition

Nelson's definition (1955) of pre-eclampsia has traditionally been widely accepted as follows:

Mild pre-eclampsia; a diastolic blood pressure of 90mmHg or over, on two occasions at least 24 hours apart, occurring for the first time after twenty-six weeks gestation, where there is no evidence of pre-existing hypertensive disease.

Severe pre-eclampsia; in addition to raised blood pressure as described there is proteinuria of at least 0.3g/litre in twenty-four hours.

A similar definition accepted by the International Society for the Study of Hypertension in Pregnancy uses the term PIH which may be mild, moderate or severe.

PIH is diagnosed where a diastolic blood pressure of 90mmHg or greater, occurs in a previously normotensive woman after the 20th week of pregnancy, two consecutive recordings having been obtained at least four hours apart (Davey and MacGillivray, 1986). Many authors classify mild and moderate PIH together, however they are differentiated clinically. Moderate hypertension may be indicative of disease progression and treatment may be commenced where PIH is classed as moderate. Collins and Wallenburg (1989) define moderate PIH as a systolic blood pressure greater than 140mmHg or diastolic blood pressure greater than 90mmHg on two occasions before 28 weeks gestation, or a systolic blood pressure greater than 150mmHg or diastolic blood pressure greater than 95mmHg between 28 and 36 weeks gestation. Severe disease may be diagnosed where the diastolic blood pressure is persistently elevated to above 110mmHg. The term pre-eclampsia is only used where there is PIH with the addition of proteinuria greater than 300mg in 24 hours (Davey and MacGillivray, 1986).

In practice, the clinical picture is often unclear. Many women will have their blood pressure recorded for the first time in pregnancy and, due to the physiological drop in blood pressure during the mid trimester of pregnancy (MacGillivray, Rose and Rowe, 1969; Christianson, 1976; Chesley 1978) essential hypertension may be misdiagnosed as PIH when the blood pressure rises to the pre-pregnancy level towards term.

In addition, a woman who has essential hypertension may develop superimposed PIH, described as an exacerbation of hypertension or the development of proteinuria or raised uric acid levels (Walker, 1992a) Accurate diagnosis of PIH and pre-eclampsia is complex and may often only be made in retrospect.

1.4.9 The importance of classification

Accurate classification of the disorder is of primary importance where a distinct group is required for study or in order to compare research findings (Baker and Broughton Pipkin, 1993).

Nelson (1955) stresses the importance of adherence to simple criteria which may be applied rigidly in any investigation into the epidemiology of pre-eclampsia,

> *'so that there is no temptation for the investigator to use his "judgement". The latter may change during the course of the enquiry and lead to inconsistencies of diagnosis and grading.'*

For this reason aetiological studies on hypertension in pregnancy, which are confined to proteinuric hypertension presenting for the first time in a primigravid pregnancy, will give the most clearly distinct study group.

1.4.10 Incidence

The incidence of hypertensive disorders in pregnancy varies between countries, racial groups (Tunbridge and Donnai, 1983) and clinical centres. This may be explained partly by the wide variation in health care available to women in different areas, and partly to the lack of conformity in the terminology and definitions used to classify the hypertensive disorders in pregnancy (Greer, 1992).

A study of primigravid women in Aberdeen during the years 1948-1955 (MacGillivray, 1958) investigated the incidence of pre-eclampsia in the first and second pregnancies of the same women. Using Nelson's definition of pre-eclampsia, this study reported an incidence in the first pregnancy of 18.4% for mild pre-eclampsia and 5.8% for severe pre-eclampsia.
Where the first pregnancy was normotensive, only 3.1% of women developed mild pre-eclampsia and 0.1% severe pre-eclampsia, in their second pregnancy. This study concludes that pre-eclampsia is primarily a disease of the first pregnancy and that a normal first pregnancy protects the woman from pre-eclampsia in subsequent pregnancies.

A second study carried out in Aberdeen which studied a total population of pregnant women between 1967 to 1978 (Campbell and MacGillivray, 1985) reported a higher incidence of mild pre-eclampsia, 26.3% and a similar incidence 5.6% for severe pre-eclampsia in primigravidae. The authors suggest that this increased incidence of mild pre-eclampsia could reflect the greater availability of blood pressure tests at this time. This study found that considering all second pregnancies there was an incidence of 17% mild pre-eclampsia and 1.9% severe pre-eclampsia.

Further investigating the incidence of pre-eclampsia in the second pregnancy according to the presence and degree of the disease in the first pregnancy, it was found that women who had proteinuric pre-eclampsia in their first pregnancy had an increased risk of both mild and severe disease in a second pregnancy, 30.1% mild, 7.5% severe. Only 2% of women who had mild pre-eclampsia in their first pregnancy developed severe pre-eclampsia in their second pregnancy, although 29% of women within this group developed mild pre-eclampsia in their second pregnancy. Where a woman has a normotensive first pregnancy the incidence of both mild and

severe pre-eclampsia in a second pregnancy is low, 9.3% and 0.7% respectively.

More recent studies in European and American populations have reported a lower incidence of pre-eclampsia than that reported in the Aberdeen studies (Alderman, Sperling and Daling, 1986; Kilpatrick et al, 1989). The incidence reported in these studies has been between two and three per cent. The reason for the apparent reduction in pre-eclampsia is not entirely clear, however, Kilpatrick et al (1989) suggest that one factor may be the reliance on current hospital records, which may have reduced diagnostic error.

1.4.11 Maternal risk of PIH

i) Maternal death

There has been a fall in the number of deaths attributable to PIH and eclampsia compared to 30 years ago, however, they remain the major cause of maternal death in the United Kingdom (Department of Health, 1989). Pulmonary oedema, cerebral vascular accident and cerebral oedema are the commonest causes of death (Turnbull et al, 1989). Death associated with PIH and eclampsia may also be caused by liver damage, disseminated intravascular coagulation or renal failure.

ii) Eclampsia

Eclampsia is identified by grand mal seizures in the absence of epilepsy or other cause of convulsions. The terms pre-eclampsia and eclampsia imply that there is an inevitable progression from the other, however, many women will be asymptomatic prior to the onset of convulsions. About 50% of cases of eclampsia occur antenatally during the second half of pregnancy,

25% of cases will occur during labour and the remaining 25% will occur during the puerperium (Villar and Sibai, 1988).

Hypertension and proteinuria are usually associated with eclampsia although the hypertension may not be severe and proteinuria is absent in 20 to 40% of cases (Walker, 1992a; Villar and Sibai, 1988). The most common prodromal symptoms are headache, epigastric pain and visual disturbance (Sibai, El-Nazir and Gonzalez-Ruiz, 1986). Of women who develop eclampsia the main cause of death is cerebral haemorrhage although most eclamptic women present with no evidence of hypertension prior to the convulsion (Walker, 1992b).

iii)Abruption

Traditionally PIH has been associated with an increased risk of placental abruption. Fifty years ago 75% of cases of abruption were associated with hypertension (Munro Kerr, 1933). Although more recent studies have shown that two thirds of cases of abruption occur in normotensive pregnancies (Chamberlain, 1981), the risk of abruption is still almost three times greater in severe PIH than in normotensive pregnancies (Sibai et al, 1986).

iv) Essential hypertension

Studies such as that by Chesley et al, (1976) and Fisher et al (1981) followed up, over a lengthy period, groups of women who had developed eclampsia or PIH and reported the incidence of essential hypertension in later life was no greater than would be found in the general population.

For several groups, however there does appear to be an increased incidence of hypertension in later life, these are women who develop severe PIH or eclampsia particularly where this presents prior to 30 weeks gestation,

those who have hypertension in several pregnancies (Sibai et al, 1986) and women who have mild PIH (Greer, 1992). It may be that these women have a tendency to essential hypertension which is first manifest during pregnancy.

1.4.12 Risk to the fetus from PIH

Proteinuria in association with hypertension and eclampsia, gives an increased perinatal mortality rate of 33.7/1000 compared with 19.2/1000 in normotensive pregnancies (Chamberlain et al, 1978). Severe PIH and eclampsia are also associated with intrauterine growth retardation (IUGR) and intrauterine asphyxia (Moore and Redman, 1983). The baby who is not affected by intrauterine growth retardation is still at risk from prematurity where delivery is carried out in the mother's interest regardless of gestation. In the longer term there is an association between severe pre-eclampsia and neurodevelopmental disability (Taylor, 1988).

1.4.13 Pathology

The maternal circulatory changes which occur during pregnancy are not completely understood. They are associated with the interaction of fetal and maternal tissue which leads to the vascular adaptations to pregnancy occurring in the uteroplacental bed. It is not clear why in PIH there is failure to develop the normal circulatory adaptation to pregnancy. Cooper, Brennecke and Wilton (1993) summarise the pathology of PIH as follows. They suggest that it may originate from a genetic defect which causes dysfunction in the maternal immunological adaptation to the presence of the fetus, leading to exposure of the trophoblast to a damaging maternal immunological reaction in the developing placental site. There is failure of trophoblast invasion of maternal placental bed spiral arteries, with placental bed vascular atherosis which results in placental tissue ischaemia. This is

followed by release of a toxic factor and consequential generalised maternal vascular endothelial cell dysfunction.

There is a reduction in the production of vasodilator substances from the maternal endothelium, such as prostacyclin and an increase in vasoconstrictors such as endothelin. This paracrine imbalance contributes to vasospasm and an exaggerated response to angiotensin II. In addition reduced placental perfusion leads to the formation of microthrombi as well as platelet consumption in the mother, and a chronic form of low grade disseminated intravascular coagulation. Increased platelet consumption is associated with an increase in production of thromboxane A_2 which is a vasoconstrictor. Tissue hypoxia from vasoconstriction, decreased tissue perfusion due to oedema and hypovolemia causes dysfunction of kidney, liver, brain and placenta as well as other organs. This gives rise to the characteristic signs of PIH, namely hypertension, proteinuria, IUGR and in the most severe cases, epigastric pain and eclampsia.

1.4.14 Management of PIH

Until recently any pregnant woman presenting with a diastolic blood pressure of 90mmHg or above would invariably be admitted to hospital for periods of bed rest. Midwifery textbooks contained detailed instructions for the care of the woman with pre-eclampsia including nursing in a darkened room and earplugs to reduce disturbance to the woman caused by noise (Myles, 1975). Today however the focus of management of PIH is the assessment of disease severity and the assessment of fetal well-being. The maternal condition is assessed using serial blood pressure measurement, full blood and platelet count together with measurement of plasma urea and electrolytes, urate and liver function tests.

Fetal well-being is assessed by ultrasound estimation of growth, fetal heart rate monitoring and biophysical profile as well as Doppler ultrasound assessment of umbilical blood flow (Greer, 1992). Treatment aims to protect the mother from the effect of hypertension and to prolong the pregnancy allowing the fetus to mature and thereby reducing perinatal morbidity and mortality. There is agreement that antihypertensive therapy should be used where hypertension is severe i.e., diastolic blood pressure over 110mmHg, however, treatment is less well accepted in mild and moderate disease where the risk to the mother comes from the potential for disease progression rather than from hypertension itself. The aim of treatment in mild and moderate disease is to reduce disease progression and to allow women to remain at home (Walker, 1987).

Within the Glasgow Royal Maternity Hospital a stepwise approach to the use of anti hypertensive therapy is used for both essential hypertension and PIH (Greer, 1992). This systematic approach to treatment involves the use of a first line therapy such as methyldopa or an adrenocepter antagonist such as labetalol or atenolol. Second and if necessary third line therapy is used to gain, and maintain control of the woman's blood pressure. Second line therapy usually takes the form of a vasodilator such as hydralazine or nifedipine and third line therapy, methyldopa or an adrenocepter antagonist depending on the first line agent. Delivery will be carried out when an adequate gestation is reached or there are signs of fetal distress or deterioration in the condition of the mother.

1.4.15 Prophylaxis

Two therapies have been postulated to be effective in reducing the incidence of PIH; these are low-dose aspirin (Wallenburg et al, 1986) and fish oil (Secher and Olsen, 1990). Aspirin suppresses the synthesis of

thromboxane (Collins and Wallenburg, 1989) resulting in less platelet aggregation which may benefit placental perfusion. Several small, controlled trials had suggested that aspirin reduced the incidence of proteinuric hypertension as well as IUGR.

A trial was designed to investigate the benefits and risks of low dose aspirin, the collaborative low dose aspirin study in pregnancy (CLASP, 1994), in which 9354 women were randomly allocated to receive either 60mg aspirin daily or placebo. The sample size was theoretically large enough to detect differences in rates of stillbirths and neonatal deaths between the two groups. The results of the CLASP study showed that aspirin did appear to be of benefit in preventing or delaying the need for delivery in early onset pre-eclampsia. However, in contrast to the findings of other small controlled studies the CLASP study found only a small reduction in the incidence of proteinuric pre-eclampsia, it showed no difference in gestation at delivery between the groups and did not affect intrauterine growth retardation, stillbirth or neonatal death. The results showed no significant increase in incidence of abruption or in bleeding during epidural anaesthesia and no increased morbidity in the neonate.

The results of another large randomised controlled trial carried out by Sibai et al (1993), which included over 3000 women found no benefit of aspirin in preventing pre-eclampsia, however this study found a significant increase in the incidence of ante-partum haemorrhage in women who had received aspirin. The authors of the CLASP trial conclude that available evidence does not support the routine prophylactic or therapeutic use of anti-platelet therapy in pregnancy amongst all women thought to be at risk of developing pre-eclampsia. Where there is an established increased risk of severe pre-eclampsia, for example, in women who have a history of

severe pre-eclampsia there may be benefit from aspirin as prophylaxis in subsequent pregnancies.

1.4.15 Role of antenatal care

One of the challenges for those providing antenatal care is to differentiate between those women who will require medical intervention and monitoring in pregnancy, the "high risk" pregnancy, and the large numbers of women whose pregnancies will progress with the minimum of intervention.

The present system of antenatal care has been routinely offered to all pregnant women since 1928 (Ministry of Health, 1929). It is largely directed towards the detection of PIH by regular measurement of blood pressure and urinalysis for proteinuria. However these signs are a late manifestation of the disease, usually appearing in the late second or the third trimester of pregnancy and as described above (1.4.11), women presenting with cerebral haemorrhage or eclampsia have frequently had no previous evidence of hypertension. The success of routine antenatal care in prediction or early detection of these disorders is poor. The converse situation is also problematic. Many women present with a diastolic blood pressure of 90 mmHg in late pregnancy, they are asymptomatic and, in the absence of proteinuria there is low risk to mother or fetus, however a single diastolic blood pressure recording of 90mmHg often marks an action line for admission and increased monitoring. Hall, Chng and MacGillivray, (1980) suggest that as a diastolic blood pressure of 90 mmHg at 38 to 40 weeks gestation is within normal limits there is over diagnosis of pre-eclampsia at term. This study analysed the rate at which asymptomatic antenatal problems are diagnosed, missed or over diagnosed and reported

that the productivity of routine antenatal care in respect of prediction and detection of obstetric problems including pre-eclampsia is extremely low.

1.4.16 Prediction of risk of PIH

PIH is a disease which primarily affects primigravid women. Once a woman has had a pregnancy complicated by PIH the risk in subsequent pregnancies can be predicted. Prediction of risk in primigravidae would allow the possibility of prevention or of early detection and treatment of the disease.

In the context of health care, Hennekins and Burning (1987) define screening as follows;

> *"screening refers to the application of a test to people who are as yet asymptomatic for the purpose of classifying them with respect to their likelihood of having a particular disease."*

They further identify criteria for conditions appropriate for screening tests.

i) The disease should be serious.

ii) The screening test should be cost-effective in terms of cost of applying the test in relation to benefit gained in prediction or early diagnosis.

iii) The treatment given before symptoms appear should be more effective than treatment given once symptoms have developed.

iv) The prevalence of the detectable pre clinical disease should be sufficiently high within the target population in order to justify the costs of the screening programme relative to cases detected.

PIH would appear to be a potentially suitable disease for a screening test. It is a serious condition, responsible for a high proportion of maternal and fetal mortality and morbidity. It is a common condition in pregnancy with

approximately 15% of primigravid women being affected, 6% developing severe disease (MacGillivray, 1958).

In order to be of value a screening test must meet the following criteria; (Mohide and Grant, 1989). A suitable test should be valid, in terms of sensitivity, specificity and reproducibility. The sensitivity of a test is an index of its ability to correctly identify the presence of the condition, specificity refers to its ability to correctly exclude the condition when it is absent. The reproducibility of a test refers to the consistency of results if repeated tests are carried out on the same individual.

In addition to these characteristics a test should ideally be inexpensive to administer and acceptable to the population to be screened. Many potential screening tests for PIH have been identified, most are based on the principle that the underlying changes may be detected at a stage prior to the development of the clinical signs. A few of these tests are described below however as yet no effective and acceptable screening test has been developed.

1.4.17 Mid-trimester blood pressure

The use of blood pressure recording as a means of predicting women at risk of developing PIH is attractive in that it is non invasive and is a test already carried out on all pregnant women who receive antenatal care. However there has been differing findings in studies testing the value of mid-trimester blood pressure as a predictor of PIH. A prospective study of women of mixed parity by Page and Christianson (1976) suggested that mid trimester mean arterial blood pressure would predict the later development of PIH. They found that when the average mid trimester mean arterial pressure was 90mmHg or greater there was a significantly increased frequency of PIH

and pre-eclampsia. Subsequent studies by Moutquin et al (1985) found that a mid trimester mean arterial pressure of 90mmHg gave a sensitivity of only 68% a specificity of 75% and a positive predictive value of 14% for the development of pre-eclampsia.

1.4.18 The Roll-over test

Gant et al (1974) developed the roll over test which was carried out between 28 and 32 weeks gestation. The women had their blood pressure recorded while lying on the left side and after turning onto their back. A positive test was noted where the diastolic blood pressure rose by more than 20mmHg. In this study 15 out of the 16 women with a positive test subsequently developed PIH. The appeal of this test would be that it is simple to apply and non invasive, however, subsequent investigators have been unable to reproduce the high sensitivity and specificity achieved by Gant et al (1974). In another study using the roll-over test Turnbridge and Donnai (1983) reported a false negative rate of 19% and a false positive rate of 80%, this test has not been shown to be of benefit in predicting PIH.

1.4.19 Angiotensin II infusion

In 1968, Talledo et al reported that, compared to normotensive pregnant women, pre-eclamptic women showed increased sensitivity to intravenous infusion of angiotensin II. Subsequently in 1973, Gant et al used this increased sensitivity in order to predict the development of PIH in a group of 192 young primigravid women. The results of this study showed that 91% of the women with a negative test remained normotensive throughout pregnancy and, conversely only 9% of women with a negative test subsequently developed PIH. Over 77% of women who had a positive test between 28 and 32 weeks gestation subsequently developed PIH.

The results of other studies into the predictive value of angeotensin II infusion are varied. Oney and Kaulhausen (1982) reported a high predictive value of a negative test but found a false positive rate of approximately 50%. Morris et al (1978) found a false positive rate of 93% and a false negative rate of 17%. Although sensitivity to angiotensin II infusion may be a relatively successful predictor of the development of PIH it is a time consuming and invasive test and as such is unsuitable for use as a screening test in the clinical situation.

Measurement of platelet angiotensin II binding may prove to be an effective proxy for angiotensin II infusion. In several studies relating to platelet angiotensin II binding Baker, Broughton Pipkin and Symonds (1989, 1991a, 1991b 1992) have reported that in normotensive primigravid women platelet angiotensin II binding falls between five and ten weeks gestation paralleling the reduced sensitivity to angiotensin II. Higher levels of platelet angiotensin II have been found in women with PIH compared to normotensive primigravid women, their hypothesis was that the difference in levels of binding between normotensive and PIH would manifest before clinical development of the disease.

In a small prospective study Baker et al (1992) measured platelet angiotensin II binding and sensitivity to angiotensin II infusion in 34 primigravid women. They reported that there was correlation between platelet angiotensin II binding and sensitivity to angiotensin II infusion. In relation to its potential value as a predictor of PIH they found that this test provided correct classification of 77% of women in the study. It appears therefore that platelet angiotensin II binding measurement may prove to be a successful screening test however larger studies would be required in order to verify the results demonstrated above.

1.4.20 Familial tendency to eclampsia and pre-eclampsia

Since the end of the nineteenth century there have been a number of documented reports of families where several generations have been affected by eclampsia and pre-eclampsia. A summary of these reports has been drawn together by Chesley et al (1968). One such report is that by Brocklehurst and Ross (1960) who describe a closely inbred family in which there were 11 cases of eclampsia in eight women over four generations.

There appears to be a familial tendency to develop PIH and eclampsia, although the nature of this inheritance is not clear. A woman's susceptibility to develop PIH will only be tested if she becomes pregnant and therefore the development of the condition could potentially be determined by maternal genotype alone, fetal genotype alone or by a maternal - fetal genotype by genotype interaction.

A number of studies have been carried out which investigate family pedigrees and the development of PIH and pre-eclampsia. In identifying familial patterns of disease development the more recent studies attempt to identify possible genetic models. In a prospective study which covered a period of fifty years Chesley traced the families of a group of eclamptic women between 1931 and 1951 (Chesley et al, 1961, 1968; Chesley and Cooper, 1986). The lengthy time period and numerous hospitals from which data was collected means that terminology and criteria for classification may differ from that used in subsequent studies. Chesley et al (1961, 1968) collected data on sisters, daughters, granddaughters and daughters-in-law of the index cases. In the first report of this series he found that 37% of sisters of eclamptic women had toxaemia in their first pregnancies and, in subsequent reports, that a diagnosis of pre-eclampsia or

eclampsia could be made in the first viable pregnancy of 26.2% of daughters and 16.2% of granddaughters. In the first pregnancies of daughters-in-law only 6.1% were diagnosed as having pre-eclampsia an incidence similar to that of the general hospital population.

In a study based in Aberdeen Maternity Hospital, Adams and Finlayson (1961) compared the incidence of pre-eclampsia in the sisters of women affected by pre-eclampsia, using Nelson's definition of pre-eclampsia, and in normotensive women. They found a higher incidence of pre-eclampsia in sisters of affected women, 13.8% compared to 4.5% amongst the sisters of normotensive women.

Cooper and Liston (1979) carried out a genetic analysis of the data of Chesley, and combined their own data with that of Adams and Finlayson (both had been collected from Aberdeen Maternity Hospital and used Nelson's definition of pre-eclampsia). The combined data showed that the incidence of severe pre-eclampsia in sisters of severely pre-eclamptic index cases was 15.9% and the incidence in mothers was 22.8%.

Sutherland et al (1981) compared the incidence of pre-eclampsia in the mothers and mothers-in-law of pre-eclamptic women and normotensive controls. They found that the incidence in mothers of controls and mothers-in-law of pre-eclamptic women were similar 3% and 4%. Whereas the incidence in mothers of pre-eclamptic women was higher namely 14%.

A study carried out in Iceland (Arngrimsson et al, 1990) investigated three and four generations of families of women with either eclampsia or pre-eclampsia. Comparing the incidence of pre-eclampsia and eclampsia in daughters and daughters-in-law of index cases they found similar increased

incidence as previous studies, 23% in daughters of index cases compared to 10% in daughters-in-law. They also found a higher incidence in grand daughters compared to grand daughters-in-law but this difference was not significant.

By comparing the occurrence of disease in relatives of affected women with expected incidence in a postulated genetic model it is possible to develop a hypothesis for the genetic basis for pre-eclampsia and eclampsia. Cooper et al (1993) have overviewed data from the reports described above and have summarised the evidence for two possible genetic models, consistent with the pedigree studies. The simple recessive model with the genes acting in the mother fits with the data of Chesley et al (1986), Cooper and Liston (1979), Sutherland et al (1981) and Adams and Finlayson (1961).

The Icelandic data (Arngrimsson et al, 1990) fits either the simple recessive model or a dominant gene model with 50% penetrance again acting in the mother. Small studies carried out on the incidence of pre-eclampsia in twin pairs (Thornton and Onwude, 1991) have demonstrated discordance which would appear to be incompatible with the simple recessive model. A study by Cooper et al (1988) found an increased prevalence of eclampsia in daughters born of an eclamptic pregnancy compared to a non eclamptic pregnancy which they suggest indicates an influence of the fetal genotype in susceptibility to eclampsia.

That studies have consistently found a reduced incidence of pre-eclampsia and eclampsia in relations by marriage argues against the maternal-fetal genotype by genotype interaction. This is not conclusive however, as a condition which is heritable, but only manifest in pregnancy, may not, by its

occurrence in both mother and daughter show in which generation genes responsible are acting.

The conclusions of Cooper et al (1988) are supported by studies which have suggested a major histocompatability complex in the genetic mechanism of PIH and pre-eclampsia (Redman et al, 1978; Kilpatrick, 1987; Kilpatrick et al, 1987). The data of Kilpatrick et al (1987) shows that an increased incidence of HLA DR4 has been found in pre-eclamptic women and their babies. In a further study (Kilpatrick et al, 1989), the frequency of HLA DR4 was increased in pre-eclamptic sisters of pre-eclamptic women, compared to pre-eclamptic sisters of normotensive women. The association with HLA DR4 suggests a possible abnormal immune response related to HLA DR4 gene or a genetic link between HLA DR4 and the presumed gene for susceptibility to pre-eclampsia and eclampsia.

Ward et al (1993) found a significant association between pre-eclampsia and the angiotensinogen gene which has been localised to chromosome 1q. The results of this study were supported by Arngrimsson et al (1993) who also suggest that molecular variation in the angiotensinogen gene, or a closely linked gene on chromosome 1q may predispose to pre-eclampsia.

Until the causative gene or genes are conclusively identified at the molecular level the genetic basis of PIH cannot be certain, and based on family pedigree studies, there is as yet no consensus on the probable genetic model responsible for its occurrence. However it appears clear that there is an inherited component in susceptibility to PIH and pre-eclampsia. Data from the studies reviewed while reporting differing incidence of disease amongst family members agree that the incidence of pre-eclampsia and

eclampsia is higher in the mothers, daughters, sisters and granddaughters of index women than in either mothers or daughters-in-law, or in the families of normotensive women. Use of this information in a clinical setting may identify a group of women who are at an increased risk of developing PIH and pre-eclampsia.

Chapter Two

Research Method

2.1 Study design

This study used a prospective cohort design.

2.2 Setting

The study was carried out within the Glasgow Royal Maternity Hospital. This teaching hospital primarily serves the north and east of Glasgow although women from all areas of Glasgow attend the hospital. Approximately 4000 women were delivered each year during the period in which this research was carried out.

2.3 Time frame

The initial time frame for this study was a period of 26 months. 14 months was designated as the recruitment period, a further six months was required for the last women recruited to complete their pregnancies. The final six months was required for case record data extraction. A further six months extension to the study was required for data analysis.

2.4 Funding

The study was funded for a period of two years by the Chest Heart and Stroke Association of Scotland.

2.5 Sample size

The calculation for sample size, Table 2.1, is based on the following assumptions, as from the literature reviewed in chapter one (MacGillivray, 1958; Cooper and Liston, 1979; Chesley et al, 1962).

Table 2.1. Power calculation of comparison of assumed outcome of pregnancy between the positive and negative family history groups.

	will develop PIH	will not develop PIH	
positive family history of pregnancy hypertension	75	225	300
negative family history of pregnancy hypertension	75	625	700
	150	850	1000

Odds ratio = 2.778 (1.949 - 3.960 95% confidence interval)

The incidence of PIH within the general population is approximately 15%. The expected family history of PIH will be 30%. The incidence of pre-eclampsia in daughters whose mother had pre-eclampsia is approximately 25% and therefore approximately 25% of women who have a positive family history will develop the condition.

Based on these assumptions, a sample size of 1000 primigravid women will show an odds ratio of more than two for the development of mild or severe PIH, in those with a family history of hypertension in pregnancy, compared to those with no such family history (80% power, 95% confidence limit.). In order to compensate for an assumed non response rate of approximately 15%, an additional 15% was added to the calculated required sample size. A sample of 1150 women was therefore required for the study.

2.6 Development of Research Tools

2.6.1 Aim

The aim in developing the research tool was to develop a method of collecting information, as reported by the women themselves, on family history of hypertension in pregnancy and cardiovascular disease.

2.6.2 Survey design

A survey design was chosen as the appropriate method of obtaining information on the prevalence, distribution and interrelationship of variables, namely, family history of pregnancy hypertension and cardiovascular disease within the study sample (Seaman, 1987).

Self report surveys may take the form of personal interviews or written questionnaires. Both methods may be used for obtaining information on respondents such as their attitudes, beliefs and social behaviour as well as more specific information such as that on health or employment. Using a personal interview, the researcher will meet each subject and will ask a previously developed set of questions. This method allows the interviewer to re-word questions not initially understood, and to probe for more detailed responses where necessary, thereby providing detailed information of a high quality. The disadvantage of this method is that it requires a lot of time both from the interviewer and the respondent and is therefore costly and impractical to apply to a large study sample.

Questionnaires are self administered, the respondent reading the question and giving a written response. The information gained from a questionnaire will usually be more superficial than that obtained from an interview however, they have the advantage of being simple and inexpensive to administer to a large study population. In using a questionnaire, the researcher assumes a certain level of literacy on the part of the respondent and the questionnaire must be carefully developed in order to be understood by the respondents in the absence of the researcher.

In this study, the survey was to be applied to a large study population, as a screening test, the requirements of which are discussed in chapter one (Mohide and Grant, 1989). A postal questionnaire was chosen as the most appropriate research tool for this study. This was economical to apply to the study population and allowed the women to find out information from family members before responding to questions.

2.6.3 Questionnaire design

A questionnaire comprises three parts; the covering letter, instructions and the questions (Seaman, 1987).

i) The covering letter explains to the recipient, who is carrying out the research, its purpose and importance. It should give assurance of confidentiality in handling and reporting of information received.

ii) The instructions should be simple and understandable, they explain how responses should be made and how the questionnaire is to be returned.

iii) Two forms of questions may be used in questionnaires, open ended questions allow the respondents to answer in their own words while closed-ended, standardised or structured questions provide a fixed set of responses from which the subject must choose the most appropriate response.

Closed ended questionnaires may vary in complexity from the most simple; Yes, No Don't know responses to scaled responses such as the Likert-scale (Likert, 1935) where each question is in the form of a statement either negatively or positively worded and has a five point response scale from strongly agree to strongly disagree for each question.

Open ended questions may provide the opportunity for an individual response to questions however, these may be difficult to categorise and, as subjects are frequently unwilling to write a detailed response questionnaires, may be incompletely filled in. Closed-ended questionnaires may be less threatening to subjects, they may be quickly completed and, more reliably interpreted due to the standardised responses. The disadvantage of closed ended questionnaires is that they oblige respondents to choose one of the predetermined responses and so may be insufficiently specific (Polit and Hungler, 1985).

In developing the questionnaire the researcher must decide what data is required, information which would be desirable must be weighed up with what may be practical to collect. Questions should be clear, simple, unambiguous and avoid jargon or complex terminology (Burns & Grove, 1987).

2.6.4 Developing the questionnaire

Individual interviews were carried out with 10 primigravid women attending the ante-natal booking clinic. The women were given an explanation of the study and asked to participate, all gave consent. They were then asked about their own history of hypertension as well as their knowledge of their family history of hypertension in pregnancy and cardiovascular disease. A detailed record of the family history was completed during the interview by the researcher.

Eight women had knowledge of the histories of their immediate families, that is, mother, fathers, sisters and brothers; six reported that they would be able to find out about the history of grandparents, aunts and uncles. Two reported that they would be able to obtain some, though not all of this information. Two women had knowledge only of cardiovascular disease in their immediate family but reported that they would be willing to enquire about history of hypertension in pregnancy.

Results of these interviews suggested that women knew, or would be willing and able to find out, information about their own family history of pregnancy hypertension and cardiovascular disease.

A questionnaire was compiled based on these interviews. (Appendix 1) The aim of this questionnaire was that it would allow the researcher to develop a

detailed family tree for each of the respondents. The questionnaire comprised instructions for completion and a set of open ended questions about family history of pregnancy hypertension and cardiovascular disease in relation to the following family members; siblings, parents, maternal aunts and uncles and maternal grandparents. Women were asked to give dates of birth of family members in order to determine birth order of pregnancies affected by hypertension. A covering letter explaining the nature and purpose of the study and assuring respondents of the confidentiality of their responses was included.

2.6.5 Pilot study of questionnaire

A consecutive sample of 10 primigravid women attending the ante natal booking clinic were given an explanation of the study and asked to participate. The women were asked to take the questionnaire and to find out as much as possible about their family history before completing and returning the questionnaire. A stamped addressed envelope was provided.

The results of this study were poor, nine women initially agreed to participate, however, only four questionnaires were returned, three of which were incomplete. This indicated that women were not willing, or were unable to complete such a large and detailed family history questionnaire.

2.6.6 Developing the second questionnaire

Following the pilot study a second questionnaire was developed (Appendix 2). The aim in developing this questionnaire was that it would provide only the essential information on family history of pregnancy hypertension and cardiovascular disease and would be easily understood and completed by the sample of women required for this study. Two essential features were

identified. Firstly, the questionnaire would be short, no more than one side of an A4 sheet. Secondly, questions would be simple to understand and to answer. In order to meet these requirements questions were restricted to history of hypertension in the woman herself and in the pregnancies of close family members i.e. mother, sisters, aunts, and grandmothers. A set of questions were included about family history of cardiovascular disease in close family members these were specified as siblings, parents aunts and uncles and grandparents. Cardiovascular disease was identified as 'stroke', 'heart disease' and 'high blood pressure'.

A set of 11 questions were developed. Wording of the questions was based on the initial interviews with women in the hospital ante natal clinic. Terms identified as being commonly used and understood by most women, for example, 'high blood pressure' and 'stroke', were used. Each question was closed-ended and had the same pre-determined set of responses, these were; Yes, No and Don't Know (Burns & Grove, 1987)

2.6.7 Pilot study of second questionnaire.

A consecutive sample of ten primigravid women attending the ante natal booking clinic were given an explanation of the study and asked to complete the questionnaire, while waiting at the clinic but without assistance from the researcher. They were then individually interviewed and the responses discussed. All the women agreed to participate in the study. All reported that they found that the questionnaire simple to understand and to complete.

Discussion with the women confirmed that the responses to the questionnaire gave a true reflection of the women's knowledge of their family history of hypertension.

Based on these interviews a covering letter was developed explaining the purpose of the research study. In explaining why the woman had been asked to participate in the study the letter stressed the value of each woman's response in increasing our understanding of hypertension in pregnancy. The letter outlined the nature of the questionnaire and explained simply which family members should be included in responses The letter explained that responses returned would be treated confidentially. A contact telephone number for the researcher was included for women who wished to obtain further information about the study. Simple instructions for completion of the questionnaire were included on the questionnaire itself.

The results of the pilot study suggested that the questionnaire would appear to identify women with both positive and negative history of hypertension in pregnancy and cardiovascular disease based on information given by the woman herself. Its simple closed-ended construction makes it acceptable to the study population and thus potentially suitable for use as a screening test. The disadvantage of this questionnaire is that it is not specific. In relation to pregnancy hypertension, the questionnaire may identify that a woman has a sister who had hypertension in pregnancy, but would not identify how many sisters she had or how many were affected. Similarly, affected aunts and grandmothers may have been either maternal or paternal. In relation to cardiovascular disease it might be identified that a member of the family had heart disease but not who was affected nor how many family members were affected. However this is a pragmatic study which aims to demonstrate whether information readily available from women attending an ante natal clinic will be of value in predicting those at risk of developing PIH. The

questionnaire gives sufficient information to identify women with positive and negative family histories of pregnancy hypertension and cardiovascular disease.

2.7 Study entry

The study aimed to recruit a consecutive sample of women booking for maternity care at the ante natal clinic at Glasgow Royal Maternity Hospital.

2.7.1 Criteria

Eligibility for the study was based on the following criteria;

i) Primigravid

As a diagnosis of pre eclampsia in multiparous women is not reliable only primigravid women were included in this study.

ii) Booking within the first trimester of pregnancy

As discussed in chapter one, recording the blood pressure in the first trimester of pregnancy, prior to the physiological drop in blood pressure which occurs in the second trimester, gives an accurate base line, on which a later rise in blood pressure may be compared. A woman with essential hypertension, whose blood pressure is recorded for the first time in the second trimester may appear to have normal blood pressure. When her blood pressure rises in the third trimester, to her normal level, a mistaken diagnosis of PIH or pre-eclampsia may be made. (MacGillivray et al, 1969; Friedman and Neff, 1976; Chesley, 1978) For this reason women who attended the ante natal clinic for the first time after the first trimester were excluded from the study.

iii) Ethnic background.

Only women from northern European Caucasian background were included in the study. This excludes variations in blood pressure distributions found in people of different racial groups (Turnbridge and Donnai, 1983).

2.7.2 Method of recruitment

There were three stages in recruitment to the study;

i) Review of case records

Case records of all women booking at the ante natal clinic were reviewed, potentially eligible cases were identified. A study questionnaire, introductory letter and stamped addressed envelope were placed in the case record.

ii) Exclusion

Women booking at the ante natal clinic had their case history taken by the clinic midwife. Those women who did not meet the study entry criteria, as described above, were excluded from the study.

iii) Consent gaining

The clinic midwife gave each eligible women an explanation of the nature and purpose of the study and asked if she would be willing to participate and give permission for information for the study to be abstracted from her case records following delivery. Women consenting to join the study were given the questionnaire, covering letter and stamped addressed envelope. They were asked to find out as much as possible about their family history before returning the questionnaire.

2.7.3 Documentation

An index card was prepared for each woman following study entry. This card contained the name, address, hospital unit number and date of study entry for each woman. The date of questionnaire return was entered on the card, this record allowed the identification of women whose questionnaires had not been returned prior to sending questionnaire reminders.

2.7.4 Questionnaire reminder

A letter of reminder including a second questionnaire and stamped addressed envelope was sent to all women who had not returned their questionnaire within one month. Prior to reminders being sent case records were reviewed to confirm the woman's address and to exclude women who had miscarried subsequent to study entry. Women who did not respond to the second questionnaire were considered non-respondents and were not further followed up.

2.8 Study measures of outcome

The first measure of outcome in this study was the woman's family history of hypertension in pregnancy and cardiovascular disease, as reported by the woman herself. The method of data collection for this was self report questionnaire. The second measure of outcome for the study was the outcome of pregnancy of the women within the study group. The method of data collection for this was retrospective case record review. A data collection form (Appendix 3) was completed for each woman at the end of pregnancy, recording the following information:

i) Identifying information; name and case record number.

ii) Demographic details; postcode, age. This information gives a brief description of the sample. Use of the postcode designated deprivation category (Carstairs and Morris, 1991) allows the study group to be compared with the general population within the catchment area of Glasgow Royal Maternity Hospital.

iii) Baseline recordings; gestation and blood pressure at booking. This information is required in order to make an accurate retrospective diagnosis of development of PIH (mild, moderate or severe) and essential hypertension (MacGillivray et al, 1969; Friedman and Neff, 1976; Chesley, 1978).

iv) Pregnancy outcome; gestation at delivery, birthweight, mode of delivery and requirement for admission to special care baby unit. This information was used to compare study groups.

v) Pregnancy complications; diagnosis of PIH or essential hypertension if recorded in the case record, highest recorded blood pressure, degree of proteinuria and blood test results. In addition any daycare attendance or admissions for PIH were recorded as well as any antihypertensive therapy required.

Development of PIH formed the main study outcome for comparison of women identified by the questionnaire as having a either a negative or positive family history of pregnancy hypertension or cardiovascular disease. Further information on pregnancy outcome was collected for women who developed hypertension. This formed part of an audit within Glasgow Royal Maternity

Hospital on the outcome of all pregnancies of women who developed hypertension, and is not reported in this study.

2.8.1 Questionnaire non respondents

The family history of women who did not return their questionnaire is unknown however these women did give consent to study entry and data extraction from case records. Therefore this group may be compared with the main group for pregnancy outcome.

2.9 Analysis

All data were entered on database dBase IV (Borland international, inc. California), and analysed using SPSS (SPSS inc. Chicago). Data were analysed for the overall incidence of PIH, and the incidence in groups of women who reported either a positive or negative family history of hypertension in pregnancy or cardiovascular disease. Data were analysed using 2 x 2 contingency tables which gave incidence, sensitivity and specificity as well as positive and negative predictive values and odds ratio for the development of PIH in positive and negative family history groups.

Sensitivity is defined as an index of a test's ability to detect the condition when it is present. Specificity is defined as a test's ability to correctly exclude a condition when it is absent. The positive predictive value refers to the proportion of women who have a positive test and who actually have the condition. The negative predictive value refers to the proportion who have a negative test and do not develop the condition. The odds ratio is the ratio of women who have a particular test result among those who have the condition,

to individuals who have the same test results but do not have the condition (Mohide and Grant, 1989). Statistical significance between groups was analysed using Pearson Chi square test.

2.10 Definition of terms.

2.10.1 Family history

Studies reviewed in chapter one define family history as being of three generations, grandmother, mother, aunts, daughters and sisters (Chesley et al, 1968; Cooper et al, 1988). Mothers-in-law and sisters-in-law have not been included in this study as the incidence of pre-eclampsia in these relatives of women with pre-eclampsia is low (Cooper and Liston, 1979; Sutherland et al, 1981; Chesley and Cooper, 1986).

Male relatives; father, uncles and brothers were included as this study investigates the possible link between family history of cardiovascular disease and the development of PIH (Adams and Finlayson, 1961). For this study, family history is defined as relating to parents siblings, aunts, uncles and grandparents of the study members.

3.10.2 Pregnancy Hypertension and Cardiovascular disease

The purpose of the study was to evaluate information on family history as reported by the women themselves therefore, no attempt was made to verify information by tracing the medical records of family members. Pregnancy hypertension for this study is defined as, hypertension occurring in the pregnancy of a family

member, as reported by the woman herself. Cardiovascular disease is defined as hypertension not confined to pregnancy (referred to as high blood pressure) cardiac disease (described as heart disease) or cerebro-vascular accident (referred to as stroke).

2.10.3 Pregnancy-induced hypertension.

PIH occurs in a woman who is normotensive prior to pregnancy and throughout the first 20 weeks of pregnancy, who then develops hypertension. The condition may be defined as mild, moderate or severe. Hypertension is defined as a diastolic blood pressure of 90mmHg or greater on two consecutive occasions at least four hours apart. In the absence of proteinuria this is classified as mild or moderate PIH. Moderate PIH was diagnosed where the systolic blood pressure was greater than 140mmHg or the diastolic blood pressure greater than 90mmHg on two occasions before 28 weeks gestation, or greater than 150mmHg systolic or greater than 95mmHg diastolic between 28 and 36 weeks gestation (Collins and Wallenburg, 1986). The presence of significant proteinuria, that is proteinuria greater than 300 mg in 24 hour urine collection, or greater than two pluses on Multistix-S.G (Ames) urine test, or a diastolic blood pressure persistently greater than 110mmHg was required for the disorder to be classed as severe PIH (Davey and MacGillivray, 1986).

2.10.4 Eclampsia

Eclampsia is characterised by grand mal seizures, in the second half of pregnancy, not attributable to epilepsy or to any convulsive problem. Eclampsia is usually associated with hypertension but may occur in women where no hypertension has been identified (Greer, 1992).

2.10.5 Essential Hypertension

Essential or chronic hypertension is defined as hypertension, that is, a diastolic blood pressure of 90mmHg or more, which pre-dates pregnancy, occurs prior to the 20th week of pregnancy or persists after the pregnancy is completed (Walker, 1991). As described in chapter one this condition may easily be confused with PIH where a pregnant woman does not have her blood pressure recorded in the first trimester of pregnancy. A woman with previously observed essential hypertension may develop superimposed PIH diagnosed where there is exacerbation of hypertension the development of proteinuria and a rising plasma urate level.

2.10.6 Antihypertensive treatment

For this study a woman was classified as having had treatment where she was prescribed regular antihypertensive therapy (discussed in chapter one), as recorded in the case record. This did not include women prescribed one dose of antihypertensive treatment.

In order to obtain the most accurate classification all of the above definitions were applied by the researcher on retrospective case record review.

CHAPTER THREE

RESULTS

3.1 Sample Description

3.1.1 Study entry

A total of 1287 consecutive women were initially identified as being potentially eligible for study entry after screening of case records prior to the antenatal booking visit. Twenty eight (2.1%) women failed to attend for their hospital booking appointment. A further 46 (3.5%) women were excluded from the study for clinical reasons namely; 15 who were identified by ultrasound scan as having a non continuing pregnancy, one ectopic pregnancy and 30 women who, following history taking and ultrasound scan were found to be over 12 weeks gestation and therefore were not eligible for the study. Following the exclusion procedure 1213 women were eligible to join the study. Thirty two women did not agree to participate and 1181 were initially entered into the study (97.3% consent).

3.1.2 *Area of residence, deprivation category*

Table 3.1 compares deprivation categories by area of residence between women entered into the study and the general population within the catchment area of the Glasgow Royal Maternity Hospital. There was no statistically significant difference between the groups for any of the deprivation categories. This suggests that the study sample was representative of the general population of women who attend the Glasgow Royal Maternity Hospital.

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Table 3.1 compares deprivation categories by area of residence between women entered into the study and the general population within the catchment area of the Glasgow Royal Maternity Hospital. There was no statistically significant difference between the groups for any of the deprivation categories. This suggests that the study sample was representative of the general population of women who attend the Glasgow Royal Maternity Hospital.

Table 3.1 Deprivation categories, by area of residence, of women in the study (n=1181) compared to the population (pop) within the catchment area of the Glasgow Royal Maternity Hospital (GRMH)

Deprivation Category (by postcode)	Number Study pop	%	GRMH area pop	%	difference between groups
1-3	242	20.4	282,697	28.6	ns*
4-5	306	25.9	215,382	21.8	ns
6-7	610	51.6	488,925	49.5	ns
Not available	23	1.9	214	0.02	ns
Total	1181	99.8	987,218	99.9	ns

*difference between groups is not significantly (ns) different

3.1.3 *Reminders*

There were 503 women who did not initially return the questionnaire. Case records of these women were reviewed four weeks after study entry, prior to sending the questionnaire reminder. Twenty six women had miscarried between 12 and 16 weeks and 11 had moved from the area or transferred to another hospital for antenatal care. These women were not sent questionnaire reminders and were excluded from the main analysis. After questionnaire reminders had been sent to the remaining 466 women 1042 questionnaires were ultimately returned (91% response). Data on pregnancy outcome was collected for women who did not return the questionnaire and is discussed in chapter 3.3.9.

3.1.4 *Data collection*

Review of the returned questionnaires revealed that 28 questionnaires contained insufficient information for analyses, including two women who wrote explaining that as they had been adopted they had no knowledge of their family history. The remaining 1014 questionnaires were complete. Retrospective case record review was the method of data collection for pregnancy outcome. Following case record review data was incomplete in 26 cases. These included; missing case records (n=10), case records containing missing information sufficient to require exclusion of the women from the study (n=2) and women who had transferred care or moved outwith the area prior to delivery (n=14). This left 988 cases where there was complete data for both questionnaire and pregnancy outcome.

3.1.5 Identification of high risk factors

The aim of this study was to investigate the risk conferred by a family history of hypertension (identified by self report) on apparently normal pregnant women, therefore women who had identifiable high risk factors for development of PIH either from their past history, or at the outset of pregnancy were excluded from the main analysis of data on family history, although data on pregnancy outcome is

presented for these women. Thirteen women who had twin pregnancies within the initial study group were excluded because of the increased incidence of PIH in twin pregnancies (MacGillivray, 1958). As PIH occurs exclusively in the second half of pregnancy women who miscarry will not be tested for their potential of developing PIH therefore 20 women who had returned completed questionnaires but who had subsequently miscarried were also excluded from further analyses. Exclusion of these groups left data for 955 singleton pregnancies. Sixty five women had essential hypertension, either diagnosed for the first time in early pregnancy or identified by past history. Pre-existing hypertension is a known risk factor for the development of superimposed PIH and therefore data for family history of these women was analysed separately from the main group, although data for pregnancy outcome is presented alongside that of the main study group. Thus the total of singleton pregnancies which had progressed to at least 24 weeks gestation, in women who were normotensive at outset of pregnancy was 890, this group formed the main study sample.

3.1.6 *Maternal age*

The mean age of women in the study group was 25 years (SD 4.5)

3.2 Results of the family history questionnaire

3.2.1 Personal history

In relation to personal history of hypertension 62 women reported that they had a history of high blood pressure, either currently or in episodes in their past history. Retrospective case record review confirmed that each of these women had a documented medical history of hypertension. As described above, data on these women and an additional three women, who were first identified as having essential hypertension during the first half of pregnancy, are analysed separately from data for the main sample.

Eighty-seven women reported a history of renal problems. Retrospective review of case records of these women revealed in each case that the women's history was confined to episodes of either cystitis or urinary tract infection. These women had no hypertension at booking and had no evidence of renal impairment and were therefore included within the main analyses, although they were also identified within the study group for identification of risk of PIH.

3.2.2 Family history of hypertension in pregnancy

Within the main study sample of 890 women 318 women gave a history of someone in their family with pregnancy hypertension (table 3.2), 561 had no family history of pregnancy hypertension and 11 women did not know their family history. The incidence of pregnancy hypertension in the family history of the study group was therefore 35.7%. This question identified our first potential high and low risk groups (318 with positive family history (high risk) / 561 with no family history of pregnancy hypertension (low risk)).

One hundred and eighty-four women reported that their mothers had hypertension while pregnant, 58 did not know whether their mothers had been affected and the

remaining women (n=648) reported that their mothers had not had hypertension in pregnancy. In relation to sisters and aunts, women were first asked if they had a sister or aunt who had been pregnant, then whether they had been affected by hypertension in pregnancy. Under half the respondents (n=377) had a sister who had been pregnant, of these 84 reported that they had a sister with an affected pregnancy. Most women had an aunt who had been pregnant (n=762) and of these 113 reported that they had an aunt who had an affected pregnancy. Seventy women reported that they had a grandmother who had a pregnancy affected by hypertension. As would be expected, in giving information on family history of pregnancy hypertension women had most information on closer relatives. Only ten women who had a sister who had been pregnant did not know if a pregnancy had been affected by hypertension, although seven women did not know if they had a sister who had been pregnant. Fifty eight women did not know if their mothers pregnancies had been affected. However in relation to aunts and grandmothers more women were unable to give information. Of the women who had an aunt who had been pregnant 168 did not know whether they had a pregnancy affected by hypertension and 253 women were unable to give information about their grandmothers pregnancies.

Some women had several family members affected by hypertension in pregnancy, 32 women reported that both their mother and a sister had hypertension in pregnancy. Forty-seven women had both mother and an aunt affected. In 18 cases the woman's mother, aunt and grandmother were reported to have had hypertension in pregnancy, one woman reported that three generations of her family (mother, sister, aunt and grandmother) had been affected.

3.2.3 Family history of cardiovascular disease

All respondents were able to give information about their family's history of cardiovascular disease. 437 women reported a positive family history and 453

reported that they had no family history of cardiovascular disease. The incidence of cardiovascular disease in the family history of the study group was therefore 49.1%. In considering specific types of cardiovascular disease (table 3.3) 346 women reported that they had a family history of essential hypertension, 283 of cardiac disease and 192 of stroke although these groups are not exclusive and women may have reported more than one type of cardiovascular disease in her family history.

3.2.4 Negative and Don't know responses

The questionnaire was completed by 351 women who gave completely negative responses, that is, they reported that they had no family history of cardiovascular disease or of hypertension in pregnancy. These women formed our presumed lowest risk group for the development of pregnancy induced hypertension. With the exception of the two women who had been adopted all respondents were able to give at least information about history of cardiovascular disease in their family.

Table 3.2 Results of family history questionnaire (excluding women with essential hypertension and twin pregnancies.) n=890

	YES (%)	NO (%)	Don't know
Family history of cardiovascular disease	437 (49.1)	453 (50.8)	0
Family history of pregnancy hypertension	318 (35.7)	561 (63.0)	11 (1.2)
Mother had pregnancy hypertension	184 (20.6)	648 (72.8)	58 (6.5)
Sister(s) who have been pregnant	377 (42.3)	506 (56.8)	7 (0.78)
Sister(s) had pregnancy hypertension	84 (22.2)*	283 (75.0)	10 (2.6)
Aunt(s) who have been pregnant	762 (85.6)	119 (13.3)	9 (1.0)
Aunt(s) had pregnancy hypertension	113 (14.8)**	481 (63.1)	168 (22.0)
Grandmother(s) had pregnancy hypertension	70 (7.8)	567 (64)	253 (28)

* % of sisters who have been pregnant
** % of aunts who have been pregnant

Table 3.3 Self reported family history of cardiovascular disease

	number	%
All cardiovascular disease	437	49.1
Essential hypertension	346	38.8
Cardiac disease	283	31.7
Stroke	192	21.5

3.3 Pregnancy Outcome

3.3.1 Incidence of hypertension

Within the initial study population of 955 complete cases of singleton pregnancies where pregnancy reached at least 20 weeks, 134 (14.0%) women subsequently developed PIH (table 3.4). Sixty five women had essential hypertension (6.8%), of these women 27 (41.5%) developed superimposed PIH. The remaining 756 (79.1%) women had no history of hypertension and were normotensive throughout their pregnancy.

Within the sample of women who had singleton pregnancies and excluding women with essential hypertension the incidence of PIH was 15.06%.

Of the 134 women who had PIH, 101 (11.3% of the total sample) were mildly affected, 20 (2.2% of the total sample) had moderate disease and 13 (1.4% of the total sample) developed severe PIH, 42 women (4.7% of the total sample) in this group received antihypertensive therapy, table 3.5.

3.3.2 Gestation at birth

Table 3.6 summarises the obstetric outcome for women within the three groups (normotensive, PIH and essential hypertension). The mean gestation at delivery was 39 completed weeks for both the normal and PIH groups (SD 3 and 2 respectively). For the essential hypertension group the mean gestation of delivery was 38 weeks (SD 5). The difference in gestation at delivery between the groups was not significant.

Table 3.4 Incidence of hypertension in singleton pregnancies
n=955

Diagnosis	%	number
Normotensive	79.1	756
PIH (includes mild, moderate and severe)	14.0	134
Essential hypertension	6.8	65
Total	99.9	955

Table 3.5 Severity of PIH in singleton pregnancies excluding women with essential hypertension
n=134

Degree of PIH	% (of total sample)	number
Mild	11.3	101
Moderate	2.2	20
Severe	1.4	13
Antihypertensive therapy	4.7	42

Table 3.6 Obstetric outcome for singleton pregnancies by hypertension group (n=955)

Obstetric outcome	normotensive n=756	PIH n=134	essential hypertension n=65
Intrauterine death	4 (0.5%)	0	0
Perinatal death	0	2 (1.4%)	1 (1.5%)
Mean (SD) gestation at delivery, in weeks	39 (3)	39 (2)	38 (5)
Preterm delivery (<37 weeks)	79 (10.4%)	16 (11.9%)	5 (7.6%)
Birthweight mean (SD)	3.26kg (0.59)	3.29 (0.62)	3.13 (0.64)
Small for gestational age (<10th percentile)	72 (9.5%)	11 (8.2%)	3 (4.6%)
Admission to SCBU	73 (9.6%)	21 (15.6%)*	7 (10.7%)

* $\chi^2 = 4.36$; $p < 0.05$

The prevalence of preterm delivery, that is delivery prior to 37 weeks gestation, for the whole sample was 10%.

In the normal group 79 (10.4%) women delivered prematurely, there were 16 (11.9%) preterm deliveries in the PIH group and five (7.6%) in the essential hypertension group. There was no statistically significant difference in the number of preterm deliveries between the groups.

3.3.3 Birth weight

Mean birth weight was 3.26kg (SD 0.59) in the normal group, 3.29kg (SD 0.62) in the PIH group and 3.13kg (SD 0.64) in the essential hypertension group. The difference in birth weight between the groups was not statistically significant. The incidence of babies who were small for gestational age, defined as birth weight below the 10th percentile for gestation (Normogram for boys/girls, Medical Research Council, 1979, Edinburgh) was 9% for the group as a whole, 9.5% (n=72) in the normal group, and 8.2% (n=11) in the PIH group. There was no statistically significant difference between these two groups. There were only three babies (4.6%) who were small for gestational age in the essential hypertension group, this was not significantly less than the other two groups.

3.3.4 Admission to Special Care Baby Unit

Within the normal group 73 babies (9.6%) were admitted to the special care baby unit (SCBU). There were seven (10.7%) babies admitted in the essential hypertension group. However 21 babies (15.6%) were admitted in the PIH group and this is a significantly higher number.

3.3.5 Fetal and perinatal loss

In the normal group there were four intrauterine deaths, one of these occurred at 26 weeks and was associated with fetal abnormality, another occurred at 25 weeks following premature rupture of membranes, the remaining two deaths occurred at 26 and 27 weeks and were of unknown cause. In the PIH group there were two perinatal deaths, one of these occurred in a baby delivered at 30 weeks gestation due to severe PIH. This baby died following intraventricular haemorrhage at four days old. The second death occurred in the baby of a woman with mild PIH. The baby was delivered at term and died at one day old, death was due to birth asphyxia. In the essential hypertension group there was one perinatal death. This baby died at six days old due to respiratory distress syndrome after delivery at 29 weeks gestation due to severe superimposed PIH in the mother.

3.3.6 Mode of delivery

Within the normal group 105 women (13.8%) were delivered by caesarean section, 165 (21.8%) had instrumental delivery, either forceps or ventouse and the remainder had spontaneous delivery. In the PIH group 20 women (14.9%) were delivered by caesarean section, 34 (25.3%) had an instrumental delivery. Within the essential hypertension group nine women (13.8%) were delivered by caesarean section and 13 (20%) had instrumental delivery. There was no statistically significant difference between these groups for mode of delivery.

3.3.7 Pregnancy outcome in women with severe PIH

Within the group of 134 women who had PIH there were 13 women who had severe disease. Although this is a small group, morbidity would be expected to be higher in these women and their pregnancy outcome is described in more detail. Within this group there were eight preterm deliveries (61.5%), compared to 11.9% in the PIH group as a whole. Three babies in the severe group were small

for gestational age (23%), two where the birth weight was below the 5th percentile for gestation. Seven babies (53.8%) were admitted to the special care baby unit and as described above there was one perinatal death. These outcomes confirm that development of severe PIH carries considerable risk to the fetus.

3.3.8 Pregnancy outcome for twin pregnancies

Thirteen women had twin pregnancies and were excluded from the analysis of family history data. In this group two women (15.3%) developed mild PIH. Three women (23%) had premature delivery and four babies (30.7%) were small for gestational age. Within this group there were two intrauterine deaths both involved one twin where the other twin survived.

3.3.9 Pregnancy outcome of questionnaire non-respondents

It may be supposed that women who had no family history of pregnancy hypertension would be less interested in the study and therefore less likely to return the questionnaire. As almost 10% of women entered into the study did not respond to the family history questionnaire and, as the overall incidence of PIH amongst the women who returned questionnaires was low (14%), if the incidence of PIH amongst women who did not return the questionnaire was significantly different from that of the main sample this would suggest that the sample was biased by willingness or not to return the questionnaire.

Data on pregnancy outcome was therefore collected for 102 women who did not respond to the family history questionnaire, for comparison with the main study group.

Case records were missing for five women and complete data was available for 97. There was one twin pregnancy within this group. The incidence of PIH (table 3.7) was higher in this group compared to the group who returned questionnaires,

18.7% compared to 14% however this difference was not statistically significant. Only one woman in this group had essential hypertension (1%) compared to 6.8% in the main group. Comparing the degree of hypertension (table 3.8), the incidence of mild PIH was similar in both groups (11.3% in the returned questionnaire group and 11.4% in the non returned group). For moderate PIH the incidence was 5.2% in the non return group compared to 2.2% in the main group. The incidence of severe disease was similar in both groups 2% in the non returned group compared with 1.4% in the main group. Numbers of women who had moderate and severe disease, however were small in the non return group (five and two respectively).

In comparing obstetric outcome of women in this group with that of the main study group (table 3.9) there was no statistically significant difference in any of the outcomes reported although as before, the numbers in the non return group were small for some outcomes. Comparison of the incidence of PIH and obstetric outcome between the women who did return their family history questionnaires and those who did not suggests that although the family histories of the non return group cannot be known the pregnancy outcomes are similar and the sample does not appear to be biased on the basis of non return of the questionnaire.

Table 3.7 Incidence of hypertension in singleton pregnancies of women who did not return family history questionnaires

Diagnosis	%	number
Normotensive	80.2	77
PIH (includes mild, moderate and severe)	18.7	18
Essential hypertension	1	1
Total	99.9	96

Table 3.8 Degree of PIH in singleton pregnancies of women who did not return the family history questionnaire (n=18)

Degree of PIH	% (of total sample)	number
Mild	11.4	11
Moderate	5.2	5
Severe	2.0	2
Antihypertensive therapy	7.2	7

Table 3.9 Obstetric outcome in singleton pregnancies of women who did not return family history questionnaires

Obstetric outcome	normal n=77	PIH n=18	essential hypertension n=1
intrauterine death	1 (1.2%)	0	0
Perinatal death	1 (1.2%)	0	
Mean (SD) gestation at delivery in weeks	39 (2)	39 (2)	40
preterm delivery <37 weeks	6 (7.7%)	2 (11.1%)	0
mean (SD) birthweight	3.16kg (0.61)	3.13 (0.52)	3.80
Small for gestational age (<10th percentile)	8 (10.3%)	3 (16.6%)	0
Admission to SCBU	7 (9%)	2 (11.1%)	0

3.4 Comparison of results of questionnaire and pregnancy outcome with predicted results

Table 3.10 compares the results of the family history questionnaire and pregnancy outcome of respondents with the predicted results (table 2.1). There was a higher than expected number of women who were excluded from the study after study entry, in addition there were 11 women who could not give information about their family history of pregnancy hypertension, therefore there were only 879 women for whom a prediction of risk could be made on the basis of family history. This was lower than the number anticipated in the power calculation. There was a higher than expected reported incidence of pregnancy hypertension in the family histories.

Within the sample, when women who had essential hypertension are excluded the overall incidence of PIH was 15% and this was in keeping with that predicted. Within the group of women who reported a family history of pregnancy hypertension we predicted that approximately 25% of women would develop PIH, however, only 18.8% actually developed the disease (75/300 were predicted, 60/318 developed disease), although this is a lower than predicted incidence the difference was not statistically significant. Within the group who reported no family history of pregnancy hypertension there was a slightly higher than predicted incidence of PIH, 12.8% compared to 10.7% predicted, however this difference is also not statistically significant. Although the overall sample size was lower than predicted, the incidence of disease was similar between that predicted and the study sample. As the number of women who reported a family history of pregnancy hypertension was high, it appears that the study sample size was adequate.

Table 3.10 Comparison of actual pregnancy outcome of positive and negative family history groups with assumed outcome.

	Developed PIH		Did not develop PIH		Total	
	predicted	actual	predicted	actual	predicted	actual
Family history of pregnancy hypertension	75	60	225	258	300	318
No family history of pregnancy hypertension	75	72	625	489	700	561
Total	150	132	850	747	1000	879

difference between groups is not statistically significant

3.5 Prediction of PIH

The questionnaire identified groups of women by family history these are summarised in table 3.11. The study population (n=890) represents the general population although as described above identifiable risk groups for development of PIH have been removed in order that the influence of family history of hypertension may be more clearly identified. Within this study group the of incidence of PIH was 15%. Three family history groups were initially identified these were;

i) Women who reported a family history of pregnancy hypertension.

ii) Women who reported a family history of cardiovascular disease.

iii) Women who had no family history of pregnancy hypertension.

There was higher than expected incidence of family history both of pregnancy hypertension (35.7%) and of cardiovascular disease (49.1%) and as might be expected, there was considerable overlap between these groups In attempting to identify the value of family history in predicting women at risk of developing PIH, comparison was first made between two simple groups which may be easily identified in the clinical setting. The first group were those who reported that a member of their family (mother, sister, aunt or grandmother) had pregnancy hypertension, the second group comprised women who reported that no member of their family had pregnancy hypertension.

Table 3.11 Summary of incidence of PIH within family history groups

Group	Number	%	All PIH	%	Mild	%	Mod	%	Sev	%	Treatment	%	None	%
Study group	890	100.00	134	15.06	101	11.34	20	2.25	13	1.46	42	4.72	756	84.94
Family history: pregnancy hypertension	318	35.73	60	18.87	46	14.47	9	2.83	5	1.57	21	6.60	258	81.13
Family history: no pregnancy hypertension	561	63.03	72	12.83	55	9.80	10	1.78	7	1.25	19	3.39	489	87.17
Family history: CVD	437	49.10	74	16.93	53	12.13	12	2.75	9	2.06	24	5.49	363	83.07
Completely negative family history	351	39.44	39	11.11	30	8.55	6	1.71	3	0.85	12	3.42	312	88.89
Family History: CVD no Pregnancy Hypertension	211	23.71	34	16.11	26	12.32	4	1.9	4	1.90	7	3.32	177	83.89
Family History: CVD & Pregnancy Hypertension	218	24.49	38	17.43	27	12.38	7	3.2	4	1.83	17	7.79	180	82.19
Family history: Pregnancy Hypertension no CVD	100	11.24	22	22.00	19	19.00	2	2	1	1.00	4	4.00	78	78.00
Mother had pregnancy hypertension	184	20.67	27	14.67	20	10.87	6	3.26	1	0.54	11	5.98	157	85.33
Sister(s) had pregnancy hypertension	84	9.44	24	28.57	18	21.43	3	3.57	3	3.57	8	9.52	60	71.43
Aunt(s) had pregnancy hypertension	113	12.7	20	17.70	17	15.04	1	0.88	2	1.77	6	5.31	93	82.30
Grandmother had pregnancy hypertension	70	7.87	11	15.71	10	14.29	0	0	1	1.43	4	5.71	59	84.29
Family history: CVD														
Essential hypertension	346	38.88	66	19.08	54	15.61	10	2.89	2	0.58	14	4.05	280	80.92
Cardiac disease	283	31.80	49	17.31	33	11.66	9	3.18	7	2.47	16	5.65	234	82.69
Stroke	192	21.57	24	12.50	14	7.29	5	2.6	5	2.60	10	5.21	168	87.50
Personal history: essential hypertension	65	6.81*	27	41.54	14	21.54	7	10.8	6	9.23	14	21.54	38	58.46
Personal history: urinary tract infection	87	9.11*	8	9.20	8	9.20	0	0	0	0.00	1	1.15	79	90.80

* % of singleton pregnancies n=955

The sample was then further divided into more distinct family history groups and these are compared with a presumed lowest risk group of women who gave a family history in which there was apparently no hypertension or cardiovascular disease.

3.5.1 Family history of Pregnancy Hypertension as a predictor of PIH

The presumed high risk group for the development of PIH was identified by the questionnaire as the group of 318 women who gave a family history of pregnancy hypertension. This was compared with a presumed low risk group of 561 women who reported that they had no family history of pregnancy hypertension (table 3.12). Within the group who reported that they had a family history of pregnancy hypertension 60 women subsequently developed PIH (18.8%), compared to 72 women who subsequently developed PIH (12.8%) in the group who reported no such history. This difference is statistically significant. A positive family history of pregnancy hypertension gives an odds ratio (OR) of 1.58 (95% Confidence Limits (CL) 1.08-2.2). This implies that a woman who has a family history of hypertension in pregnancy will have a 58% increased chance of developing PIH compared to women who have no such family history.

Table 3.12 Comparison of the incidence of PIH in women with positive and negative family history of pregnancy hypertension

	Developed PIH	Did not develop PIH	Total
Family history of pregnancy hypertension	60	258	318
No family history of pregnancy hypertension	72	489	561
Total	132	747	879*

*Total does not total 890 because of the occurrence of PIH amongst women who did not know their family history.

	95% confidence interval
Prevalence = 0.15	
Sensitivity = 0.455	0.369 - 0.543
Specificity = 0.655	0.619 - 0.688
Positive Predictive Value = 0.189	
Negative Predictive Value = 0.872	
Odds Ratio = 1.58	1.086 - 2.297
	(χ^2= 5.79; $p < 0.05$)

However the use of family history of pregnancy hypertension only predicted 45% of women who subsequently developed PIH, 55% of women who developed the disease came from the negative family history group.

The same family history groups were again compared for the development of mild, moderate and severe disease. Because of small number of women who developed severe PIH in the sample, the women who developed moderate and severe disease were considered together. In addition as a measure of clinical problem, the women who received treatment for PIH were also assessed as a group. Comparing development of mild disease (table 3.13), it can be seen that a positive family history of pregnancy hypertension did predict for the development of mild PIH giving an OR of 1.56, but not for moderate and severe disease. Table 3.14 compares the occurrence of moderate and severe disease, the results show that although the OR was 1.47, the 95% confidence limits transcended unity, therefore this was not found to be significant. Table 3.15 demonstrates that women who reported a family history of pregnancy hypertension were twice as likely to require treatment because of hypertension in pregnancy than those who reported no family history (OR 2.01, CL 1.06-3.8). It can be seen from the sensitivity that 52% of those requiring therapy were selected by the family history questionnaire.

Table 3.13. Comparison of the occurrence of mild PIH in women with positive and negative family histories.

	Developed mild PIH	Did not develop mild PIH	Total
Family history of Pregnancy hypertension	46	272	318
No family history of pregnancy hypertension	55	506	561
Total	101	778	879

	95% confidence interval
Prevalence = 0.115	
Sensitivity = 0.455	0.400 - 0.611
Specificity = 0.650	0.488 - 0.571
Positive Predictive Value = 0.145	
Negative Predictive Value = 0.902	
Odds Ratio = 1.56	1.00 - 2.41
	(χ^2= 4.33; $p < 0.05$)

Table 3.14 Comparison of the occurrence of moderate/severe PIH in women with positive and negative family histories.

	Developed mod/sev PIH	Did not develop mod/sev PIH	Total
Family history of Pregnancy hypertension	14	304	318
No family history of pregnancy hypertension	17	544	561
Total	31	848	879

	95% confidence interval
Prevalence = 0.035	
Sensitivity = 0.452	0.278 - 0.636
Specificity = 0.642	0.608 - 0.674
Positive Predictive Value = 0.044	
Negative Predictive Value = 0.970	
Odds Ratio = 1.474	0.736 - 3.031 (ns)

Table 3.15 Comparison of the requirement for antihypertensive therapy in women with positive and negative family histories.

	Treatment for PIH	Did not require treatment for PIH	Total
Family history of pregnancy hypertension	21	297	318
No family history of pregnancy hypertension	19	542	561
Total	40	839	879

	95% confidence interval
Prevalence = 0.046	
Sensitivity = 0.525	0.364 - 0.681
Specificity = 0.646	0.612 - 0.678
Positive Predictive Value = 0.066	
Negative Predictive Value = 0.966	
Odds Ratio = 2.017	1.067 - 3.812
	(χ^2 = 4.836; $p < 0.05$)

3.5.2 Identification of distinct family history groups

Four distinct family history groups were identified these were;

i) Women who gave a family history of cardiovascular disease but reported no family history of pregnancy hypertension.

ii) Women who gave a family history of cardiovascular disease and also a family history of pregnancy hypertension.

iii) Women who gave a family history of pregnancy hypertension but no family history of cardiovascular disease.

iv) Women who gave a completely negative family history both of cardiovascular disease and pregnancy hypertension.

3.5.3 Incidence of PIH in the completely negative family history group

The completely negative family history group consists of 351 women who reported that they had negative family histories of both cardiovascular disease and pregnancy hypertension. This completely negative group had the lowest incidence of PIH (11.1%), this was compared with those women who reported either a family history of pregnancy hypertension or cardiovascular disease (Table 3.16) in which the incidence of PIH 15%, this difference between these groups was statistically significant.

Table 3.16 Comparison of the outcome of pregnancy of women with a completely negative family history with that of women with a history of pregnancy hypertension or cardiovascular disease

	developed PIH	did not develop PIH	Total
Family history of pregnancy hypertension or CVD	95	444	539
All negative family history	39	312	351
Total	134	756	890

	95% confidence interval
prevalence = 0.15	0.12 - 0.176
sensitivity = 0.709	0.623-0.782
specificity = 0.413	0.378-0.449
positive predictive value = 0.176	
negative predictive value = 0.889	
Odds ratio = 1.71	1.148 - 2.553 (χ^2= 7.053; p< 0.01)

The all negative group contains only 29.1% of the women who subsequently developed pregnancy induced hypertension. A reported family history of pregnancy hypertension or cardiovascular disease gives a 70% increased OR compared to the completely negative family history group (OR 1.71, CL 1.14-2.55) within this group. The completely negative group is therefore taken as the lowest risk group to compare the relative risks of any positive family history.

3.5.4 Comparison of family history groups with the completely negative family history groups

Table 3.17 summarises the results of the comparisons of each family history group with the completely negative family history group. Compared with the completely negative family history group, a family history of pregnancy hypertension gave a statistically increased OR both for all PIH and for mild PIH. As before, there was an OR of around two for women who required treatment, but this did not reach statistical significance.

As may be expected the negative family history of pregnancy hypertension group was not significantly different from the completely negative family history group. A reported family history of cardiovascular disease did give an increased OR for all PIH and this was significant, but if those who also reported a family history of pregnancy hypertension are removed from this group, the statistical significance is lost There is still a high odds ratio, but only related to the development of mild PIH.

Table 3.17 Odds ratio (OR) for development of PIH compared with the completely negative family group.

	Type	Incidence	OR	Confidence	Limits	χ^2
Family history; pregnancy hypertension	all PIH	18.8	1.86	1.2	2.87	7.962*
	Mild	14.4	1.81	1.11	2.94	5.804**
	Mod/sev	4.4	1.7	0.7	4.1	ns
	Treatment	6.6	1.99	0.96	4.12	ns
Family history; no pregnancy hypertension	all PIH	12.8	1.17	0.77	1.78	ns
	Mild	9.8	1.16	0.71	1.90	ns
	Mod/sev	3.0	1.18	0.52	2.69	ns
	Treatment	3.3	0.99	0.47	2.06	ns
Family history; CVD	all PIH	16.9	1.63	1.07	2.47	5.372**
	Mild	12.1	1.47	0.92	2.36	ns
	Mod/sev	4.81	1.91	0.86	4.24	ns
	Treatment	5.4	1.64	0.8	3.33	ns
Family history; CVD no pregnancy hypertension	all PIH	16.1	1.53	0.93	2.52	ns
	Mild	12.3	1.5	0.86	2.62	ns
	Mod/sev	3.8	1.49	0.56	3.94	ns
	Treatment	3.3	0.96	0.37	2.50	ns
Family history; CVD and pregnancy hypertension	all PIH	17.4	1.69	1.01	2.81	4.58**
	Mild	12.3	1.51	0.84	2.71	ns
	Mod/sev	5	2.02	0.76	5.39	ns
	Treatment	7.7	2.38	1.11	5.10	5.332**
Family history; pregnancy hypertension no CVD	all PIH	22	2.25	1.26	4.02	7.890*
	Mild	19	2.51	1.34	4.68	8.781*
	Mod/sev	3.0	1.17	0.31	4.42	ns
	Treatment	4	1.17	0.37	3.73	ns

* $p < 0.01$; **$p < 0.05$

Where there is a history of both cardiovascular disease and pregnancy hypertension, the OR is 1.69. which is statistically significant for the development of any PIH. The OR is not significant when degrees of PIH are separated although it is significantly increased for those women who required therapy (OR 2.38 CL 1.11-5.10).

If a family history of pregnancy hypertension only is considered, there is a statistically significant OR of over 2, but as before, this is only true for the groups of women who had any PIH and the mild PIH group. The OR was not significantly increased in the moderate/severe or the treatment groups.

3.5.5 History of pregnancy hypertension in specific family members

The questionnaire identified pregnancy hypertension in specific family members (mother, sister, aunt and grandmother) however the numbers in these groups are reduced especially for sisters where only 42% of women had a sister who had been pregnant.. Data for each family member group was compared with the completely negative family history group (table 3.18) and they are significant only for sisters. Within this group the OR was significant for all types of PIH. The most surprising results within this set of data were the negative findings for the family history of pregnancy hypertension in the mothers of women within the study sample. Only the results for the all PIH group have been presented for mothers, aunts and grandmothers as all the rest were similarly negative.

3.5.6. Specific Cardiovascular Disease

The questionnaire identified reported family history of cardiovascular disease separated into essential hypertension, cardiac disease and stroke. As before there is overlap between the groups and numbers are reduced in particular for the group reporting family history of stroke (table 3.3). When data for reported family history of different types of cardiovascular disease history were compared to the completely negative family history group (table 3.18), both family history of essential hypertension and cardiac disease increase the OR of all PIH but family history of stroke did not. The essential hypertension group linked mostly with mild PIH (OR 1.97 CL 1.23-3.17) but cardiac disease links with moderate and severe PIH (OR 2.32, CL 1.01-5.33).

3.5.7 Personal history of essential hypertension

As a comparison, the OR for development of PIH for the 65 women who were known to have essential hypertension were also compared to the completely negative family history group (table 3.18), showing increased OR for all types of PIH but particularly the moderate/severe and treatment groups.

The group of women who reported a history of renal problems were similarly compared, although as described above this group of women did not appear to have renal disease on retrospective case record review. This group did not have an increased OR for development of PIH

Table 3.18. Odds ratio(OR) for development of PIH in family history groups compared to completely negative family history group

	Type	Incidence	OR	Confidence	Limits	χ^2
Mother had pregnancy hypertension	all PIH	14.67	1.37	0.81	2.33	ns
Sister had pregnancy hypertension	all PIH	28.57	3.2	1.79	5.70	16.684*
	Mild	21.43	2.91	1.53	5.54	11.457*
	Mod/sev	7.14	2.92	1.01	8.45	4.268***
	Treatment	9.52	2.97	1.17	7.52	5.759***
Aunt had pregnancy hypertension	all PIH	17.7	1.72	0.95	3.09	ns
Grandmother had pregnancy hypertension	all PIH	15.7	1.49	0.72	3.07	ns
Family history;	all PIH	19.08	1.88	1.23	2.89	8.637**
Essential hypertension	Mild	15.61	1.97	1.23	3.17	8.194**
	Mod/sev	3.46	1.36	0.58	3.28	ns
	Treatment	4.05	1.19	0.54	2.61	ns
Family history;	all PIH	17.31	1.67	1.06	2.63	5.04***
Cardiac disease	Mild	11.66	1.41	0.83	2.37	ns
	Mod/sev	5.65	2.32	1.01	5.33	3.949***
	Treatment	5.65	1.72	0.80	3.71	ns
Family History;	all PIH	12.5	1.14	0.66	1.96	ns
Stroke	Mild	7.29	0.84	0.43	1.62	ns
	Mod/sev	5.2	2.08	0.83	5.23	ns
	Treatment	5.21	1.55	0.65	3.66	ns
Personal history of essential hypertension	all PIH	41.54	5.68	3.13	10.30	38.039*
	Mild	21.54	2.93	1.45	5.91	9.787**
	Mod/sev	20	9.5	3.86	23.33	33.288*
	Treatment	21.54	7.75	3.39	17.70	30.731*
Personal history of urinary tract infection	All PIH	9.2	0.81	0.36	1.80	ns

*p < 0.001; ** p < 0.01; *** p < 0.05

3.5.8 Summary of the comparison of family history groups with the completely negative family history group.

Comparing the OR for development of PIH in women who report differing family histories of pregnancy hypertension and cardiovascular disease with women who report no such history, there appears to be a link between reported family history of pregnancy hypertension and subsequent development of PIH. This is mostly related to women whose sisters have been affected. A family history of essential hypertension appears to be related to mild disease rather than moderate/severe disease. The link between ischaemic heart disease and moderate/severe disease is interesting and merits further study. The findings from the group of women who had essential hypertension confirms the high risk nature of this group.

3.6 Comparison of the odds ratio (OR) for family history groups with study population

If knowledge of a woman's family history of pregnancy hypertension or cardiovascular disease is to be of practical value in predicting her risk of developing PIH, risk conferred by such history must be increased in relation to the general population rather than a lowest risk group. In order to test this, the family history groups defined above were compared to the total study group as proxy for the general population in which the incidence of PIH was 15%.

3.6.1 Comparison of OR of family history groups and the study population for the development of any pregnancy-induced hypertension

Comparing the OR of each of the family groups with the total study population for the development of any PIH (table 3.19), the only statistically significant finding was for sisters, and for women who themselves had essential hypertension. A family history of pregnancy hypertension both with and without a family history of cardiovascular disease demonstrate an increase OR although not at a statistically significant level. The completely negative family history group showed a 30% reduction in PIH compared to the study population as a whole although this was not statistically significant.

3.6.2 Comparison of OR of family history groups and the study population for the development of mild PIH

Comparing the same family groups for the development of mild PIH (table 3.20) the OR was only found to be significantly increased for those women who reported that their sisters had been affected, women who reported a family history of pregnancy hypertension but no cardiovascular disease, women who had a family history of essential hypertension and for women who themselves had essential hypertension. Within this group a simple family history of pregnancy hypertension did not increase the OR significantly.

3.6.3 Comparison of OR of family history groups and the study population for the development of moderate/severe PIH

Comparing the same family history groups for the development of moderate and severe PIH (table 3 21), only the women who themselves had essential hypertension showed an increased OR compared to the study sample as a whole.

A reported history of an affected sister did give an increased OR of approaching two however this did not reach statistical significance.

3.6.4 Comparison of OR of family history groups and the study population for the requirement for antihypertensive therapy

Comparing the family history groups for the women who required antihypertensive therapy (table 3.22) as with the moderate and severe groups the only group which demonstrated a statistically increased OR was the group of women who had essential hypertension. There was an OR of over two in the group with a family history of affected sisters however, as before this was not statistically significant.

Table 3.19 Comparison of odds ratio for development of any PIH in family history groups and study population

Group	Number	%	All PIH	%	OR	Confidence	Limits	χ^2
All patients	890	100.00	134	15.06	1	0	0	ns
Family history of pregnancy hypertension	318	35.73	60	18.87	0.76	0.54	1.08	ns
No family history of pregnancy hypertension	561	63.03	72	12.83	0.83	0.61	1.13	ns
Family history; CVD	437	49.10	74	16.93	1.15	0.84	1.57	ns
Completely negative family history	351	39.44	39	11.11	0.7	0.48	1.03	ns
Family history; CVD no pregnancy hypertension	211	23.71	34	16.11	1.08	0.72	1.63	ns
Family history; CVD and pregnancy hypertension	218	24.49	38	17.43	1.19	0.78	1.80	ns
Family history; pregnancy hypertension, no CVD	100	11.24	22	22.00	1.59	0.95	2.64	ns
Mother had pregnancy hypertension,	184	20.67	27	14.67	0.97	0.62	1.52	ns
Sister had pregnancy hypertension	84	9.44	24	28.57	2.26	1.36	3.75	10.316**
Aunt had pregnancy hypertension	113	12.70	20	17.70	1.21	0.72	2.03	ns
Grandmother had pregnancy hypertension	70	7.87	11	15.71	1.05	0.53	2.05	ns
Family History; Essential Hypertension	346	38.88	66	19.08	1.33	0.96	1.84	ns
Family History; Cardiac Disease	283	31.80	49	17.31	1.18	0.82	1.69	ns
Family History; Stroke	192	21.57	24	12.50	0.8	0.50	1.28	ns
Personal history; Essential hypertension	65	6.81	27	41.54	4.01	2.37	6.79	30.309*
Personal history; Urinary tract infection	87	9.11	8	9.20	0.57	0.27	1.21	ns

* $p < 0.001$; ** $p < 0.01$

Table 3.20 Comparison of odds ratio for development of mild PIH in family history groups and study population

Group	Number	%	Mild	%	OR	Confidence	Limits	χ^2
All patients	890	100.00	101	11.34	1			
Family history of pregnancy hypertension	318	35.73	46	14.47	0.76	0.51	1.12	ns
No family history of pregnancy hypertension	561	63.03	55	9.80	0.85	0.59	1.22	ns
Family history of CVD	437	49.10	53	12.13	1.08	0.74	1.56	ns
Completely negative family history;	351	39.44	30	8.55	0.73	0.47	1.14	ns
Family history; CVD no pregnancy hypertension	211	23.71	26	12.32	1.10	0.67	1.78	ns
Family history; CVD and pregnancy hypertension	218	24.49	27	12.38	1.10	0.68	1.77	ns
Family history; pregnancy hypertension, no CVD	100	11.24	19	19.00	1.83	1.03	3.24	4.94**
Mother had pregnancy hypertension	184	20.67	20	10.87	0.95	0.55	1.62	ns
Sister had pregnancy hypertension	84	9.44	18	21.43	2.13	1.17	3.85	7.260*
Aunt had pregnancy hypertension	113	12.70	17	15.04	1.38	0.76	2.48	ns
Grandmother had pregnancy hypertension	70	7.87	10	14.29	1.30	0.61	2.73	ns
Family History; Essential hypertension	346	38.88	54	15.61	1.44	1	2.09	4.12**
Family History; Cardiac disease	283	31.80	33	11.66	1.03	0.66	1.60	ns
Family History; Stroke	192	21.57	14	7.29	0.61	0.33	1.13	ns
Personal history; Essential hypertension	65	6.81	14	21.54	2.14	1.09	4.16	5.93**
Personal history; Urinary tract infection	87	9.11	8	9.20	0.79	0.34	1.75	ns

* p.< 0.01; **p < 0.05

Table 3.21 Comparison of odds ratio for development of moderate/severe PIH in family history groups and study population

Group	Number	%	Mod/sev	%	OR	Confidence	Limits	χ^2
All patients	890	100.00	33	3.71	1			ns
Family history of pregnancy hypertension	318	35.73	14	4.4	1.20	0.60	2.35	ns
No family history of pregnancy hypertension	561	63.03	17	3.00	0.81	0.43	1.52	ns
Family history of CVD	437	49.10	21	4.81	1.31	0.72	2.37	ns
Completely negative family history	351	39.44	9	2.56	0.68	0.30	1.54	ns
Family history; CVD no pregnancy hypertension	211	23.71	8	3.80	1.02	0.46	2.24	ns
Family history; CVD and pregnancy hypertension	218	24.49	11	5.00	1.38	0.64	2.89	ns
Family history; pregnancy hypertension no CVD	100	11.24	3	3.00	0.8	0.24	2.66	ns
Mother had pregnancy hypertension	184	20.67	7	3.80	1.02	0.44	2.35	ns
Sister had pregnancy hypertension	84	9.44	6	7.14	1.99	0.81	4.91	ns
Aunt had pregnancy hypertension	113	12.70	3	2.65	0.7	0.21	2.34	ns
Grandmother had pregnancy hypertension	70	7.87	1	1.43	0.37	0.05	2.79	ns
Family History; Essential Hypertension	346	38.88	12	3.47	0.93	0.45	1.90	ns
Family History; Cardiac Disease	283	31.80	16	5.65	1.56	0.81	2.98	ns
Family History; Stroke	192	21.57	10	5.20	1.43	0.65	3.08	ns
Personal history; Essential hypertension	65	6.81	13	20	5.25	2.13	12.92	16.013*
Personal history; Urinary tract infection	87	9.11	0	0.00	0	0	0	ns

* $p < 0.001$

Table 3.22. Comparison of odds ratio for antihypertensive therapy family history groups and study population

Group	Number	%	Treated	%	OR	Confidence	Limits	χ^2
All patients	890	100	42	4.72	1			
Family history of pregnancy hypertension	318	35.73	21	6.60	1.42	0.83	2.45	ns
No family history of pregnancy hypertension	561	63.03	19	3.39	0.7	0.4	2.23	ns
Family history; CVD	437	49.10	24	5.49	1.17	0.7	1.96	ns
Completely negative family history,	351	39.44	12	3.42	0.71	0.37	1.37	ns
Family history; CVD no pregnancy hypertension	211	23.71	7	3.32	0.69	0.3	1.56	ns
Family history; CVD and pregnancy hypertension	218	24.49	17	7.79	1.71	0.91	3.17	ns
Family history; pregnancy hypertension but no CVD	100	11.24	4	4.00	0.84	0.25	2.52	ns
Mother had pregnancy hypertension	184	20.67	11	5.98	1.28	0.64	2.5	ns
Sister had pregnancy hypertension	84	9.44	8	9.52	2.12	0.96	4.69	ns
Aunt had pregnancy hypertension	113	12.70	6	5.31	1.13	0.47	2.72	ns
Grandmother had pregnancy hypertension	70	7.87	4	5.71	1.22	0.42	3.5	ns
Family History; Essential hypertension	346	38.88	14	4.05	0.85	0.45	1.58	ns
Family History; Cardiac disease	283	31.80	16	5.65	1.21	0.66	2.18	ns
Family History; Stroke	192	21.57	10	5.21	1.02	0.44	1.87	ns
Personal history; Essential hypertension	65	6.81	14	21.54	5.54	2.84	10.8	31.004*
Personal history; Urinary tract infection	87	9.11	1	1.15	0	0	0	ns

* $p < 0.001$

Chapter Four

Discussion

4.1 Validity of data

The purpose of this research was not to determine the value of an accurate family history of pregnancy hypertension in predicting the subsequent development of pregnancy-induced hypertension (PIH) nor to test the accuracy of a woman's knowledge of her family history of the condition. Rather, it was to determine whether information about family history of hypertension in pregnancy or cardiovascular disease which could be provided by the woman herself would be of value as a pragmatic predictor for the development of PIH. In some respects this study has similarities to the retrospective family history studies into of eclampsia and pre-eclampsia which pre-dated Chesley's systematic follow up of women who had eclampsia (described in chapter one), in that it relies on information about family history of hypertension provided by the women themselves, and there was no attempt to verify this information by review of medical records.

Research of familial tendency to PIH from the time of Chesley's studies have used the method of tracing medical records of family members, applying specific diagnostic criteria based on blood pressure, proteinuria and parity, in attempting to obtain an accurate retrospective diagnosis of PIH, pre-eclampsia or eclampsia. Although this method may encounter problems of poor documentation within case records and differing terminology used over time, these studies have provided the most accurate information on the incidence of PIH and eclampsia within families. The main problem in using this methodology is the difficulty in tracing the obstetric case records of various family members. For this method to be used prospectively as a screening test for PIH it would be necessary to

trace the obstetric case records for several family members for each primigravid woman booking at an ante-natal clinic.

This was considered impractical, particularly in the context of the value of such a history as a possible screening technique to identify women at higher risk. This study aimed to adopt a pragmatic approach by asking a series of simple questions about family history of hypertension in pregnancy as well as cardiovascular disease and to test their value in predicting the development of PIH. However, information provided by women about the medical history of family members must be treated with some caution. Although the family history questionnaire appeared to provide accurate information on the woman's knowledge of her family history, it is not possible to know how accurate this information would be in comparison with a review of medical records.

The number of "don't know" responses demonstrates, as might be expected, that women were able to give less information about more distant relatives (aunts and grandmothers) than about close family members (mother and sisters) However, even in relation to close family, the study relies both upon the understanding a family member will have about their own medical history and how accurately they will have passed that information on to the woman answering the questionnaire. Although the questionnaire differentiated between hypertension occurring in pregnancy and outwith pregnancy, it did not differentiate between first and subsequent pregnancies. The question, "did your mother have hypertension in pregnancy?" would therefore be answered in relation to the mothers total pregnancies, not just her first pregnancy. A women replying that a family member had pregnancy hypertension may have been identifying PIH or essential hypertension which also occurred in pregnancy. That there was a higher than anticipated reported incidence of family history of pregnancy

hypertension (36%) suggests that this may have occurred. This is not surprising as in the clinical situation PIH can be difficult to differentiate from essential hypertension.

It must be assumed therefore that within this study a woman reporting a family history of pregnancy hypertension is giving a mixed history of all types of hypertension which may have occurred in the pregnancies of a number of family members.

4.2 Reported Incidence of family history of cardiovascular disease

The reported incidence of cardiovascular disease within the sample was high (49.1%). The area in which the study was based is within the Greater Glasgow Health Board (GGHB) area, and includes several areas of socioeconomic deprivation, where the standardised death rate (for people under 65 years) is twice that of people living in the most socioeconomically advance areas of the city. Within the GGHB population two of the main causes of death in people under 65 years are cardiac disease and stroke. The death rate for these conditions is 14% to 18% above the average for Scotland (GGHB, 1990). It would seen likely therefore, that the high incidence of cardiovascular disease reported in this study reflects a true picture of the incidence of disease within the north and east of Glasgow.

4.3 Incidence of PIH within the study

Within the study group the incidence of PIH was low. Only 15% of women developed any PIH with 11.3% developing mild, 2.2% moderate, and only 1.4% developing severe disease. This incidence is considerably lower than that described in the studies of Campbell and MacGillivray (1985) however, it is more in keeping with the more recent studies (Alderman et al, 1986 and Kilpatrick et al, 1989) described in chapter one,

who reported an incidence of severe PIH of between two and three percent.

In addition, 42 women who had PIH (4.3% of the study population) received anti-hypertensive therapy and it would be reasonable to assume that these women had significant or progressive disease, although they could not be described as having severe PIH on retrospective case record review.

4.4. Prediction of pregnancy-induced hypertension

4.4.1. Family history of pregnancy hypertension

The familial tendency to develop PIH was apparent using the data obtained from the simple family history questionnaire, however, in applying the information as a screening test the data were more equivocal. Over one third of women reported that they had a family history of pregnancy hypertension. These women had an increased incidence of PIH which was significantly higher than the group of women who reported that they had no such family history (18.8% verses 12.8%).

The sensitivity and specificity of this test were not high (45% and 65% respectively), and the positive predictive value of these questions was low (18.9%). Over 80% of women who were predicted positive on the basis of having a reported family history of pregnancy hypertension subsequently remained normotensive throughout their pregnancy (Table 3.12).

Although, in the study group as a whole the incidence of severe PIH was low (1.4%), however, 4.7% of women required antihypertensive therapy and this may indicate that clinically they had significant disease. Women

who reported a family history of pregnancy hypertension were twice as likely to require antihypertensive therapy as those who did not (Table 3.15).

4.4.2 Identification of the lowest risk group

The questionnaire did identify a group of women who were least likely to develop PIH. These were the group of women who reported that they had no family history either of pregnancy hypertension or of CVD. In comparison with this completely negative group, a reported family history of CVD or pregnancy hypertension gave a sensitivity of 70%, specificity of 41% and a negative predictive value of 88%. Although this suggests that the completely negative group of women are at particularly low risk 11% subsequently developed PIH, 3.4% required antihypertensive therapy.

4.4.3 Comparison with other screening tests

In comparing the results of this study with other screening tests for PIH account must be taken of the differing incidence of disease in study populations as well as the divergent results reported for many of the tests by successive studies. A reported family history of pregnancy hypertension, compared to women who reported no such family history provides broadly similar results to other non-invasive screening tests such as the roll-over test and the measurement of mid-trimester blood pressure. The measurement of mid-trimester blood pressure (Moutquin et al, 1985) in predicting pre-eclampsia in a population where the prevalence was 5%, demonstrated a sensitivity of 86% (compared to 45% in the current study), specificity of 50% compared to 65% and a positive predictive value of 10% compared to 18% in the current study. The roll-over test however, gave a sensitivity of only 10% and a specificity of 90% with a prevalence of disease of 19% (Turnbridge and Donnai, 1983).

The results of the family history questionnaire do not compare well to tests such as angiotensin II infusion, which has demonstrated a specificity of 91% (Gant, 1973) This test is invasive and complex to perform however, and so is unsuitable as a screening test for application to the general pregnant population.

4.4.4 Comparison with the study population

Although comparison of positive with negative family history groups forms an interesting statistical comparison, of more relevance in a clinical situation is the comparison of incidence of PIH in a woman who reports a family history of pregnancy hypertension with the incidence in the general population. After exclusion of women who had essential hypertension the incidence in the study population was 15% and this was taken as the background incidence for comparison.

In considering the comparison between family groups and the study population as a whole, identification of OR for development of disease is of more value than specific test indices such as sensitivity, specificity, positive and negative predictive values. This is because the groups are not mutually exclusive, comparison is made between incidence in women with an affected sister and the total study group rather than with women who do not have an affected sister. Although these comparisons give less statistically significant results they were thought to be more clinically meaningful.

When family history groups were compared with the study population only a reported history of pregnancy hypertension in a sister gave a significantly increased odds ratio (OR) for the development of any or mild PIH.

Although there was also an increased OR for the development of moderate/severe PIH where a sister was affected, compared to the study group, this was not significant.

Within this study, a reported family history of a sister who has had hypertension in pregnancy provided the best predictor for the development of PIH. However, less than half of women sampled had a sister who had been pregnant and this restricts its value as a predictor for PIH. Nevertheless, a women who has a sister who has had hypertension in pregnancy appears to be at particular risk of developing PIH.

Twenty per cent of women reported that their mother had an affected pregnancy, this proved to be a poor predictor for the development of PIH. The incidence of any PIH, as well as that of mild, moderate and severe disease was no higher in women who reported that their mother had pregnancy hypertension than in the study population.

How do the results of this study compare with those of other studies?
Chesley et al (1961, 1962, 1968) took a group of eclamptic women as the index cases for a prospective study which investigated the incidence of eclampsia and pre-eclampsia in daughters, daughters-in-law, sisters, granddaughters and granddaughters in law. This study found the highest incidence of severe pre-eclampsia or eclampsia in sisters of index cases (37%) and an increased incidence in daughters compared to daughters in law (26.2% and 6.1% respectively). The data of Chesley et al (1961, 1962, 1968) agrees with that of the current study in that the incidence of PIH where a sister had an affected pregnancy was also high compared to the study population (28.5% and 15% respectively). However in contrast, the current study did not find an increased incidence of PIH in the reported

histories of either mothers or grandmothers when compared to the study population.

Adams and Finlayson (1961) also compared the incidence of pre-eclampsia in sisters of pre-eclamptic index cases, women who developed hypertension which could not be classified as pre-eclampsia and normotensive controls reporting a higher incidence of pre-eclampsia in sisters of who had pre-eclampsia compared to controls (13.8% compared to 4.5%)

Although Chesley et al (1961, 1962, 1968) and Adams and Finlayson (1961) report different incidences of pre-eclampsia in relatives studied, both demonstrated a high incidence of disease in sisters of affected women. The current study also demonstrated an increase of over two-fold in the incidence of severe disease (1.4% in the study population compared to 3.57% where a sister was reportedly affected), although the incidence of severe PIH overall was very low.

Cooper and Liston (1979) analysed the data of Chesley et al (1961, 1962, 1968), combining new data with that of Adams and Finlayson in an attempt to identify the genetic model of inheritance for pre-eclampsia. The combined data found a higher incidence of severe pre-eclampsia amongst mothers of index cases than in sisters (22.8% and 15.9%). Although these results could not conclusively identify the genetic model of inheritance, they confirm the high incidence of pre-eclampsia in both mothers and daughters. As before these data agree with those of the current study in relation to sisters but not for mothers.

Sutherland et al (1981)compared the incidence of pre-eclampsia in mothers and mothers in law of women who had severe pre-eclampsia as index cases

and normotensive women as controls. This study confirmed the results of the previous study finding a higher incidence of pre-eclampsia in mothers of index cases (14%) than in mothers in law of index cases (4%) and mothers and mothers in law of controls (3% and 4% respectively). This was again in contrast to the results of the current study which found no greater incidence of PIH in women who reported that they had an affected mother.

Arngrimsson et al (1990) used as index cases women who had severe pre-eclampsia or eclampsia, tracing medical records of daughters and granddaughters and using daughters-in-law and granddaughters-in-law as controls. This study again confirmed a high incidence of pre-eclampsia in daughters compared with controls (23% compared to 10%). However in relation to granddaughters this study found that there was not a significantly higher incidence of pre-eclampsia compared to controls. This contrasts with data of Chesley et al (1961, 1962, 1968) who found an increased incidence of disease in granddaughters, however it is in agreement with the current study which found that the incidence of PIH in women who reported that they had an affected grandmother was not higher than the study population.

All of these studies agree that there is an increase incidence of pre-eclampsia in mothers or sisters of eclamptic or pre-eclamptic women although the reported incidence varies in each study. Data from the current study concurs with the findings of these studies in relation to sisters, although the magnitude of the increase is much less. This suggests that women were able to provide the most accurate information about their sisters' pregnancies, although even this group will contain all types of hypertension occurring in pregnancy. The contrast between the results of

this study compared to other studies in relation to family history of pregnancy hypertension in mothers suggests that, although the mother is a close relative, the questionnaire did not give sufficient information on the mother's history of pregnancy hypertension.

The study population were primigravid women, their sisters are likely to be of similar ages and may have had only one or two pregnancies, thus a reported history of pregnancy hypertension is likely to relate to hypertension in a first or second pregnancy, and to be true PIH. However, mothers of respondents will be older and presumably have completed their reproductive years. Therefore a woman reporting that her mother had hypertension in pregnancy will be reporting hypertension which may have occurred in any pregnancy. This may include PIH but also gestational hypertension which may indicate a tendency to develop essential hypertension. This may explain the lack of association between reported maternal hypertension and the development of PIH in women.

4.4.5 Mild or severe PIH

Comparison of family history groups with the lowest risk group suggested that there did appear to be a link between a reported family history of pregnancy hypertension and the development of mild PIH. This link was also present in comparison to the study population, where there was an affected sister, and where there was a family history of essential hypertension. Overall the questionnaire did not identify family history groups which would predict the development of moderate and severe disease except in relation to affected sisters where it found an increased incidence of moderate and severe disease, and this was significant in comparison to the lowest risk group. This contrasts with other family history studies cited which have consistently demonstrated a strong familial

link with severe disease. However, the methodology of these studies differ from the current study in that they used, as index cases women who had severe disease (either eclampsia or pre-eclampsia) and trace, either prospectively or retrospectively the incidence of disease in relatives.

These studies used similar numbers of normotensive women, or "in-laws" as controls. The current study in contrast took as its starting point a group of primigravid women, normotensive at outset of pregnancy, and attempted to predict their risk of developing PIH through their reported family history. Most of these women remained normotensive throughout pregnancy only a very small number developing severe PIH (n=13). The lack of predictive value in relation to severe disease may be partly explained by the small number of women in the severe PIH group.

Several studies have suggested that mild and severe PIH are inherited as different entities. Adams and Finlayson (1961) found that sisters tended to develop similar types of hypertension in pregnancy (42.2% developed hypertension and 9.4% pre-eclampsia in the sisters of women with hypertension, compared to 34.4% hypertension and 13.8% pre-eclampsia in the sisters of pre-eclamptic women). Although the incidence of any hypertension was higher in sisters of women who had either hypertension or pre-eclampsia than that of the general population. The authors suggested from this finding that pre-eclampsia and hypertension are independent conditions.

Cooper and Liston (1979) investigated the incidence of mild and severe pre-eclampsia amongst mothers and daughters of mild and severe index cases. They found the incidence of mild disease was highest in relatives of

mildly affected index cases, although only in the data of Adams and Finlayson (1961) was this statistically significant.

Sutherland et al (1981), compared the incidence of mild pre-eclampsia in the mothers and mothers-in-law of index cases who had severe pre-eclampsia and normotensive controls. Their results showed that although there was a higher incidence of mild pre-eclampsia in the relatives of the index cases compared to the controls, this was not statistically significant. The authors support the previous studies in suggesting that mild and severe disease are different pathological entities, inherited differently.

Although any hypertension which occurred in the pregnancies of women responding to this questionnaire was clearly defined, the reported family history of pregnancy hypertension within this study will have included both mild and severe disease. Therefore the types of pregnancy hypertension present in the family history of women who subsequently developed either mild or severe PIH cannot be differentiated.

There is a higher incidence in the general population of mild than severe disease and therefore, correspondingly, there must be a higher incidence of a history of mild disease, which is thought to have a tendency to predispose to later development of essential hypertension, or to reveal a latent tendency to develop hypertension which may only manifest in later life.

That the questionnaire was more successful in predicting the development of mild PIH probably reflects a familial tendency to develop mild disease and the larger number of women who will have a family history of mild, compared to severe, PIH.

It must be assumed that the questionnaire did not elicit sufficiently specific information on type of pregnancy hypertension within the family history in order to predict the very small number of women who developed severe PIH within this study.

The results suggest that there is a familial tendency to develop both mild and severe PIH however, from this data it is not possible to say whether or not they are independent entities.

4.4.6 Influence of Cardiovascular disease

This study suggests that there is influence of a family history of cardiovascular disease on the development of PIH, although as discussed the study was carried out in an area where there is a particularly high incidence of cardiovascular disease in the general population and this may have influenced the results.

The data were separated into groups of women who reported family history of both pregnancy hypertension and cardiovascular disease, pregnancy hypertension alone and cardiovascular disease alone. Where only cardiovascular disease was reported there was no increased OR for the development of either mild or moderate\severe disease.

The group who reported a history of pregnancy hypertension alone had a significantly increased OR but solely for development of mild PIH (tables 3.17 and 3.20). Only where there was also a reported family history of cardiovascular disease was there an increased OR for the development of moderate\severe disease although this was not statistically significant (Table 3.17).

In considering the influence of specific cardiovascular disease the data suggest that a reported family history of essential hypertension is related to the development of mild disease (tables 3.18 and 3.20). Where there is a reported history of cardiac disease however, there is a significantly increased OR for the development of moderate\severe disease (table 3.18). Other studies have investigated the influence of family history of essential hypertension on incidence of PIH but not that of other cardiovascular disease.

Chesley et al (1968; 1986) compared the incidence of pre-eclampsia in the sisters and daughters of eclamptic index cases and found that it was not affected by whether or not the index women subsequently developed essential hypertension. The authors conclude that familial incidence of pre-eclampsia is independent from the tendency to develop essential hypertension. Adams and Finlayson (1961), measured the blood pressure of mothers of women who had pre-eclampsia and of siblings of women who had previously had pre-eclampsia and normotensive controls. They found, in contrast to the previous study that there was a greater incidence of hypertension in later life in mothers and in siblings of women who had pre-eclampsia than in those of the control group. This paper concluded that pre-eclampsia does not cause hypertension in later life but develops in women with an inherited hypertensive tendency.

The current study suggests that there is a link between a family history of essential hypertension and the development of mild PIH but in the development of moderate and severe disease there is influence of a family history of cardiac disease. The absence of an increase of severe disease in women who reported only a family history of pregnancy hypertension, and the increased OR for development of moderate\severe disease in the group

with both cardiovascular disease and pregnancy hypertension, could suggest that although a family history of pregnancy hypertension is important in the development of any PIH there is influence from a family history of cardiovascular disease in the development of more significant disease.

4.5 Essential hypertension

Investigating the outcome of pregnancy in women who had essential hypertension was not a primary objective of the study, however the questionnaire highlighted a group of women who either had essential hypertension or who gave a history of hypertension. This study confirmed that these women were at particular risk of subsequently developing superimposed PIH. This group had the highest incidence of severe disease (9.23%) within the study and 21.5% required antihypertensive therapy.

A woman who gives a history of hypertension should be considered at high risk of developing PIH, even where her blood pressure is normal at the time of booking, especially where no first trimester blood pressure is available.

4.6 Conclusion

The high response rate to the questionnaire used in this study shows that it is feasible to obtain simple family history information from pregnant women who attend an ante natal clinic. Women were not, however, prepared to answer a very detailed questionnaire, the pilot study of a larger, more complex family history questionnaire was unsuccessful.

It must also be acknowledged that the information obtained by this method is limited, the responses may give an account of a woman's understanding

of her families history in relation to hypertensive disorders generally but it should not be presumed to separate specific types of hypertension which may occur in pregnancy.

The questionnaire did highlight both higher and lower risk family history groups for the subsequent development of PIH. The highest risk group was that where a sister had been affected. In this group the incidence of all types of PIH were highest of all family history groups. Although, the number of women who had a sister who had been pregnant and therefore, had opportunity to be tested for the development of PIH was low.

The lowest risk group identified was the women who reported that they had neither family history of pregnancy hypertension nor cardiovascular disease and these women had the lowest incidence of PIH within this study. Although these higher and lower risk groups were identified, within the highest risk group the incidence of severe disease remained low and most women remained normal throughout pregnancy. Within the lowest risk group although the incidence of PIH especially severe disease was low it did occur in some women. Based on these data the family history did not appear to be of value in the clinical setting as a screening test in predicting the development of PIH.

Should pregnant women be asked routinely about their family history of hypertension in pregnancy? In spite of the disappointing results of this study in relation to prediction of PIH this would appear to be good practice, as women both at increased or reduced risk may be identified in this way. In addition, it may be of value to ask about family history of cardiovascular disease, in particular heart disease as this appears to have some impact on the development of severe PIH. This information may be

of clinical value as part of risk analysis for individual women at outset of pregnancy.

A woman who reports that she has a sister who has been affected by hypertension in pregnancy may warrant additional attention to blood pressure around the end of the second trimester of pregnancy. However, information on family history of pregnancy hypertension or cardiovascular disease which may be provided by the women themselves does not justify altering clinical practice, toward the broad groups of women identified, either to increase monitoring for the highest risk group or to decrease vigilance toward the lowest risk group.

This study did confirm the need for particularly careful monitoring of women who present with essential hypertension or give a past history of hypertension, as these women were clearly at risk of developing severe superimposed PIH (9.2% of women in this group developed severe PIH).

Numerous studies concur that there is a strong familial tendency in the development of PIH, however, it is not, at present, feasible to utilise this information as a screening test at least partly because women do not have sufficient information about their family history.

Although it is good practice to routinely enquire about family history, this study highlights the importance of ensuring that women who develop PIH have accurate information about their condition which may be passed on to relatives if required.

At present the only economical, feasible screening available for PIH is the routine antenatal measurement of blood pressure which has been offered to women since 1928. If the gene or genes responsible for development of

PIH were identified this may provide the basis for cost effective screening for PIH. There is a need to develop linkage studies between disease genes and marker genes. These studies require family histories of at least two generations with affected women. Although this questionnaire did not in itself prove of value as a screening test for the development of PIH its particular strength was its simplicity. It was economical to apply to a large study population, it was non invasive and acceptable to most women. A simple family history questionnaire may be a useful preliminary contact in identifying families in which women have been affected by PIH. These families could then be targeted for more detailed examination in pedigree studies.

The data highlighted several questions about the aetiology of PIH. It would be interesting to further investigate the postulated familial tendency to develop similar types of hypertension in pregnancy.

Further study is required into the apparent influence of cardiovascular disease in the development of PIH. In particular, the connection between a family history of essential hypertension and the development of mild disease. In addition, further study is warranted into the apparent link between a family history of cardiac disease and the development of severe PIH.

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