The SIP Study:
Stress Immunity and Preterm Birth

Does the maternal response to stress determine the risk of preterm delivery in women at high risk of preterm labour?

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy by:

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University of Liverpool

Faculty of Medicine

DECLARATION

This thesis is the result of my own work. The material contained in the thesis has not been presented, nor is currently being presented, either wholly or in part for any other degree or other qualification.

The research was carried out in the Liverpool Women's Hospital. All recruitment of women, collection, preparation and coding of maternal serum samples was carried out by the researcher.

All interviewing, transcribing and coding of maternal psychological tests was carried out by the researcher.

All laboratory work was carried out in collaboration with the staff in the Division of Reproductive and Perinatal Medicine, University of Liverpool. The researcher worked in the laboratory on a weekly basis after each clinic centrifuging, coding, freezing and storing serum samples. She spent a further two days at the conclusion of the study, carrying out the basic ELISA assay with the final serum samples under the supervision of laboratory staff.

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Lorna Wood

Stress, Immunity and Preterm Birth

The SIP Study

"On her frights and griefs
Which never tender lady has borne greater,
She is something before her time delivered."

Furness H H., (ed) (1964) The Winter's Tale:
Shakespeare W (1564-1616) Dover, New York, USA

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For my family, friends and colleagues who have encouraged and supported me throughout.

The SIP Study: Stress Immunity and Preterm Birth.
Wood L.

Background: Exposure to stress during pregnancy is associated with preterm birth.
Study1. Objectives: This prospective observational midwifery study investigated whether maternal immune response to stress determines the risk of premature delivery in women with a history of idiopathic preterm labour.
Methods: The study measured maternal immune response and psychological stress at two gestations in pregnancy. 200 maternal serum samples and psychological scores were collected at 20 wks and 151 serum samples and scores at 28 wks gestation. The HPA axis was assessed by measuring Cortisol, Corticotrophin Releasing Hormone (CRH), Corticotrophin Releasing Hormone Binding Protein (CRH-BP), Granulocyte Colony Stimulating Factor (GCS-F), Adrenocorticotropic Hormone (ACTH) in maternal serum. Stress was investigated using the Hospital Anxiety Score (HADS) and the List of Threatening Experiences Questionnaire (LTE-Q).
Results: The most statistically significant result in the SIP study was those women with a history of previous preterm births between 24 - 36 wks were more likely to deliver preterm again ($\rho = 0.008$). There was no correlation between any markers of stress elicited by stress questionnaires and biological markers of stress (HPA axis). Five variables were identified for the logistic regression model: life events at 20 wks ($\rho = 0.150$), previous births at 24 – 37 weeks ($\rho = 0.008$), previous births < 24 wks ($\rho = 0.01$), CRH at 20 wks ($\rho = 0.62$), cervical suture in situ ($\rho = 0.05$).
Conclusion: Neither immune response nor psychological scores were associated with the outcome of recurrent premature labour. The study failed to detect a biological response to maternal stress supporting the theory that there may be a 'damping down' effect in pregnancy, with placental CRH production overriding the effects of maternal stress.
Study 2. Objectives: A cross-sectional study compared anxiety scores in 50 low risk women (CG) with the participants from the SIP study (PTL).
Results: The results of the cross-sectional study found that anxiety levels in the PTL group were significantly higher ($\rho = 0.0006$) than women in the CG.
Study 3. Objectives: This study explored women's responses to LTE-Q as a qualitative midwifery study from the main study participants.
Methods: The primary aim was to explore the answers women gave to LTE-Q using "think-aloud" technique. The secondary aim was to explore causation by determining whether women related stressful life events to their previous preterm birth experiences. The data were managed manually and answers subjected to framework analysis to develop insights from the perspective of those involved in a particular lived experience allowing the participants' framework of meaning to be explored.
Results: 200 semi-structured interviews using LTE-Q were conducted at 20 weeks. 52 women (26%) were identified from those responses. Several categories emerged; pregnancy as an illness, injury or assault, physiological imaging, inability to heal, pre-occupied with suffering child, existing day to day, relationship overshadowed by loss, resignation of relationship, instability of relationship.
Three themes emerged in relation to the word damage; Damaged Self (DS), Damaged Child (DC) and Damaged Relationship (DR).
Conclusion: A temporal relationship was found supporting the perception of an association between stressful life events and previous preterm births. Many women used their previous preterm birth experiences to frame their answers to LTE-Q.

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Chapter 1

1 THE SIP STUDY

1.1 Introduction

This thesis presents the SIP Study: Stress, Immunity and Preterm Birth. This midwifery study explored the association between maternal stress, maternal immune response and the outcome of preterm birth in women with a history of idiopathic premature delivery.

The SIP Observational Study was designed to determine whether stress is a mediating factor in recurrent spontaneous preterm labour. The SIP Qualitative Study is a qualitative analysis of the responses given to a life events questionnaire.

This thesis describes multiple methodological approaches to the problems of elucidating the relationship between maternal stress and spontaneous preterm labour. These include a quantitative prospective observational study and a meta-synthesis of the literature reviewed. Originally the life events questionnaire was intended as part of the quantitative observational midwifery study only, however, LW realised that the interesting responses given by women within the answers to the questionnaire would be explored in greater depth within a qualitative study. The women's responses do not form the main focus of this thesis as, fundamentally this is an observational study, nevertheless, data gained from the qualitative study is described and analysed thematically within the thesis. The SIP study therefore has been conducted in two parts.

1.2 Background to the research

At present there is a wealth of information regarding stress and its effect on pregnancy in both human and animal literature. However, reviewing the literature highlighted the problems these studies have in identifying which stressors are important, what the evidence is for association and which underlying mechanisms are key in the manifestation of pregnancy complications. Moreover there is a scant amount of midwifery literature that focuses on women with a history of premature birth in relation to those mediating mechanisms and

future pregnancy outcomes. Although the published literature goes some way to understand this complex phenomenon, there is a significant lack of midwifery information focussing on understanding whether women with a history of preterm birth and stressful life events are more likely to experience a preterm birth in a subsequent pregnancy. It is against this background that the research question evolved.

1.3 The role of the researcher

The area that the author (LW) has researched was identified through her role as a specialist midwife interested in women who had experienced both miscarriage and premature birth. Her initial involvement was in the setting up of the preterm labour antenatal clinic with an obstetrician who specialised in this condition (SQ). The researcher had previously been involved with several research projects, the most recent being recruitment of women with a twin pregnancy for both the CRH (corticotrophin releasing hormone) Study (n=100) and the Stress (Does social stress cause preterm birth?) Study (n=100). In both of these studies LW had the responsibility for recruiting women, data collection, venepuncture and laboratory preparation and coding before storing maternal plasma for CRH analysis. In the latter Stress Study she worked with the psychiatrist and obstetrician (DO) on the research team, who had a special interest in the psychoneurophysiology of preterm labour. It was during this time that the researcher became aware of the dearth of midwifery research into the relationship between stress during pregnancy and pregnancy outcome and particularly preterm birth.

The rationale for the study therefore stems from a professional midwifery standpoint of questioning whether emotional stress, can predispose to a premature delivery.

1.4 Outline of the thesis

The thesis consists of 10 chapters.

The opening chapter provides an introduction to the SIP Study and the context in which the researcher undertook the study. Chapter 2 presents a comprehensive overview of preterm birth, stress and the psychoneuroimmunological influence associated with premature labour. The aim of this chapter is to identify the underlying influences maternal stress and maternal

immune response may have on the outcome of a premature delivery and to set in context the rationale for the study. The chapter concludes with the background to the current study. The protocol for the systematic review of quantitative literature is presented in Chapter 3, with Chapter 4 providing a critical review and meta-synthesis of the literature pertaining to observational studies using Bradford-Hill criteria. Chapter 5 presents the study design and rationale for selection of the multi-method approach while Chapter 6 presents the results of the quantitative analysis for the observational study and includes the results for a small cross sectional anxiety study.

Chapter 7 begins with the rational for the qualitative study and the research methodology used including a critique of the research tool as the point of departure and an examination of 'think-aloud technique', continuing with the protocol and systematic review of qualitative literature in Chapter 8. Findings from the study are represented as quotes from the responses given to the LTE-Q and are linked with examples supporting these findings from the literature review and are presented in Chapter 9. Finally, Chapter 10 is an overview of the SIP Study in its entirety.

Therefore the study has been conducted using a mixed methods approach, employing both quantitative and qualitative methods. The main emphasis concentrates on the quantitative analysis through observational methodology, however, the researcher considers the additional qualitative data has enhanced the study, and enabled a greater exploration of the research question. The complimentary methods have been based on using the strengths of one method to enhance the performance of the other.

The observational study is the main focus of this thesis, using quantitative methodology. Within this approach the researcher proceeds from theory identified in a hypothesis to the empirical data collection and its analysis. The process enables the researcher to support or reject the initial hypothesis or theory.

The qualitative study uses qualitative methodology. Qualitative research begins by accepting there is a range of different ways of making sense of the world and is concerned with

discovering the meanings seen by those who are being researched and with understanding their views of the world rather than that of the researchers. Working as a clinical midwife within the preterm labour clinic made it impossible for the researcher to be value free or remain neutral when studying a topic with which she was so familiar and involved.

The thesis has been written reflecting the conduct of this midwifery study. Throughout the thesis the methods used will be presented in the order in which the study was conducted.

Chapter 2

2 STRESS AND PRETERM BIRTH

2.1 Introduction

The aim of this chapter is to set in context the focus for the study by addressing the physiological, immunological and psychological evidence associated with the complex phenomena of premature labour and birth. The chapter begins by providing a background to preterm birth through the definition, incidence, aetiology and contributing factors and goes on to discuss the prediction and prevention of premature labour. A description of the risks to the baby from a premature delivery is given and the definition of stress, anxiety and depression is presented which is central to the association examined in this thesis. The pathophysiology of psychosocial stress and its role in premature labour is discussed with a description of the normal physiological response to stress, infection and inflammation bringing into context hormonal changes which occur in the non-pregnant state.

The chapter continues with an outline of the maternal immune response during pregnancy and labour with a brief explanation of the hypothalamic-pituitary-adrenal (HPA) axis of interest, thereby presenting the rationale for the investigation of these hormones within the conduct of the study. The concept of psychoneuroimmunological influence and preterm birth is discussed with a brief overview of the epidemiological, animal and immunological evidence endorsing the view that stress and maternal immune response are associated in the aetiology of preterm labour and birth. The chapter concludes with an introduction to the background of the SIP Study "stress, immunity and preterm birth", which is the focus of this thesis.

2.2 Preterm birth

Term and preterm parturition are fundamentally the same process except for the gestational age at which they occur. In contemporary terms preterm birth (PTB) is recognised as a public health problem world-wide (Peltier 2000).

The incidence of preterm delivery has remained constant between 5 and 10% and has not decreased over the past 20 to 30 years (Campbell and Lees 2000, Challis and Smith 2001, Terizdou and Bennett 2002). In England and Wales nearly 8% (1 in 13) of live births are premature (< 37 weeks) and 94% of singleton babies born extremely preterm (between 24 and 28 weeks) are of very low birth weight (VLBW) weighing less than 1500 grams. This compares to less than 1% of babies born at term with VLBW. Preterm births between 22 and 27 weeks occur in 6% of pregnancies, with just under 1% before 22 weeks and 93% occurring after 28 weeks (ONS 2007). In the UK 1.3% of all deliveries (approximately 10,000 births per year) occurred before 32 weeks with 75% of neonatal deaths and the majority of neonatal intensive care admissions from these very premature babies (Kashan et al., 2008a).

Currently, there are no effective medical interventions to predict or prevent premature labour, largely because its pathogenesis is poorly understood and is probably the final common pathway of a number of pregnancy complications involving health of the cervix, myometrium, fetus, fetal membranes and the placenta. The aetiology of preterm delivery (PTD) is thought to be heterogeneous and although a number of causes have been identified within the medical model including; multiple pregnancy, antepartum haemorrhage, intrauterine growth restriction, cervical incompetence, chorio-amnionitis, congenital uterine anomaly, diabetes mellitus, polyhydramnios and pyelonephritis, in the majority of cases no identifiable cause is found (Chamberlain 1995, Peltier 2003, Green et al., 2005). The assumption that there may be an association between psychological and social stressors is grounded in evidence from both epidemiological work and animal studies.

In the past all babies born at less than 2500 grams were considered to be premature. Today with more accurate methods of gestational dating these babies have been identified as small for gestational age. Nevertheless, about 70% of preterm babies are born with a low birth weight of less than 2500 grams. This is widely recognised to be associated with increased infant morbidity and mortality and an important predictor of future health problems, regardless of whether it is caused by poor intrauterine growth or preterm birth (Terzidou and Bennett 2002, Peltier 2003, Halbreich 2005). The health conditions of low birth weight and

prematurity are nonetheless not interchangeable with preterm low birth weight the second leading cause of infant death and a major cause of disability (Mattison et al., 2001, Green et al., 2005).

The emotional impact of PTD on the family is enormous. In some cases babies are admitted to hospital far from the family home for a prolonged period of time. Parents and siblings may suffer considerable anxiety, with doubts about survival and complete recovery. The impact of PTB is measured medically in the associated mortality and morbidity of the syndrome and financially in terms of the economic cost to health service providers. However, the actual social and emotional costs are immeasurable emphasising the importance of addressing preterm birth within midwifery research and practice.

2.2.1 Definition

Preterm birth (PTB) is defined by the World Health Organisation as delivery of an infant before 37 completed weeks gestation or less than 259 days from the first day of the last menstrual cycle with the lower limit of definition on a continuum with spontaneous abortion, however this varies from country to country (Enkin et al., 2000, Mattison et al., 2001, Peltier 2003). Before 24 weeks the birth is termed as a miscarriage with no set lower limit to this definition, but 24 weeks gestation is widely accepted (Chamberlain 1995, Campbell and Lees 2000). Preterm labour (PTL) is defined clinically as progressive cervical dilatation and or effacement with regular uterine contraction between 24 and 37 weeks gestation, with or without rupture of the membranes (Enkin et al., 2000).

The actual date of conception is unknown apart from those pregnancies arising from medically assisted techniques. The use of the last day of the menstrual period is based on the assumption that a woman's menstrual cycle is always 28 days, she ovulates mid-cycle and is sure of these dates. The estimated date of confinement (EDC) therefore is calculated from this information. Ultrasound biometry is an accurate way of predicting the EDC, however it is not available to large numbers of women in developing countries and the accuracy of the dating scan will be influenced by the attendance of women for antenatal care in early pregnancy.

Prematurity is the major cause of neonatal morbidity and mortality, accounting for 65% of neonatal deaths (< 28 days of life) and 50% of childhood neurological disabilities. It involves admission to neonatal intensive care, severe morbidity in the first weeks of life, prolonged hospital stay after birth and readmission to hospital in the first year of life (Campbell & Lees 2000, Green et al., 2005). Preterm prelabour rupture of membranes (PPROM) and spontaneous preterm labour (PTL) account for approximately 70% of preterm deliveries (Terizdou and Bennett 2002), with massive expenditure of neonatal resources in terms of nursing time, skill mix, staffing, equipment and drugs.

2.2.2 Aetiology

The aetiology of premature labour is multifactorial. Approximately 30% are described as iatrogenic, induced by obstetricians for maternal or fetal indications such as hypertensive disorders of pregnancy, intrauterine fetal growth restriction, congenital abnormalities and medical disorders of pregnancy. The remainder are defined as idiopathic, where no known cause is found (Chamberlain 1995, Steer and Flint 1999, Campbell and Lees 2000, Green et al., 2005). The aetiology of PTL is often considered in two aspects; laboratory studies undertaken to understand the biochemistry of parturition, and clinical or epidemiological studies which aim to identify factors associated with prematurity, in order to recognise those at risk.

2.3 Contributing factors

Factors associated with PTB can be divided into three groups: sociobiological variables, past obstetric history and complication of the current pregnancy (Goldenberg et al., 2003) however PTB is pathological with multiple aetiologies and should be considered as a syndrome (Goldenberg et al., 2008).

2.3.1 Sociobiological variables

Sociobiological variables are thought to be associated with maternal lifestyle in terms of social support, economic deprivation, smoking, alcohol, drug use, age, race and ethnicity with considerable variations within and across populations. The link between socio-economic status (SES) and pregnancy outcomes have long been recognised, with women in the lower

socio-economic group and unsupported mothers identified to be more at risk (Mattison et al., 2001, Steer and Flint 2004, Green et al., 2005). Unsurprisingly preterm births are reported to be higher in inner city areas and lower in more affluent areas (Wadhwa et al., 2001, Alderdice and Lynn 2009).

The relationship between lifestyle and adverse birth outcome can be explained indirectly through health behaviour during pregnancy, linking stress to a greater use of alcohol, drugs and poor nutrition (Lobel et al., 1992, Dunkel-Schetter et al., 2001). Moreover an inter-pregnancy interval of less than three months and lack of antenatal care are both associated with premature birth. Smoking in pregnancy is known to have a wide sociological divide and is recognised within the medical model to have a propensity to the development of placenta praevia, preterm rupture of membranes and abruptio placentae, which are all known precursors of preterm labour (Hall et al., 1997, Goldenberg et al., 2008).

Women with a low body mass index (BMI<19) have been found to be more at risk (Dayan et al., 2002) as well as teenagers aged 15 and younger relating the outcome of PTB to both physical immaturity and possibly poor nutrition. The increasing number of births to women older than 35 years and the use of fertility treatments has also had an impact on multiple birth rates resulting in more premature deliveries overall (Mattison et al., 2001, Green et al., 2005).

Studies in America exploring the association with race and ethnicity have found PTL more common in Afro-American women than in white women however there is difficulty in distinguishing genetic variation from social deprivation including access to antenatal care and behavioural risks as these women no longer constitute a homogenous group (Hall et al., 1997, Goldenberg et al., 2003). PTB also differs among racial groups, with the most persistent disparities occurring between non-Hispanic white and non-Hispanic black groups. Native American women have intermediate rates, with Asian rates the lowest of all these groups. Nonetheless, socioeconomic factors within different populations of women in the same country continue be the main underlying cause rather than actual racial differences (Meis et al., 2000, Wadhwa et al., 2001, Green et al., 2005). Different aspects of SES such as education, unemployment or annual income, may impact on how well women actually cope

with stress. Other environmental stresses such as war and conflict are nevertheless important but have a less well understood role in this common complex disorder.

2.3.1.1 Maternal stress

The timing of maternal exposure to stress may be crucial with pre-pregnancy and first trimester exposure increasing the risk of problems of premature birth and low birth weight and these effects possibly mediated by an alteration in the uterine environment in early fetal-placental development.

Historically research in this area has been limited by variations in measuring stress during pregnancy and small sample sizes. Nonetheless studies with large samples and validated psychological tools have reported positive associations with preterm birth, particularly with maternal stress and locus of control in women's (n=739) lives (Misra et al., 2001), with stressful life events, anxiety and low economic status in women (n=130) during the 6 months prior to conception or during the first trimester (Lobel et al., 1992), with women (n=465) and pregnancy desirability (Berkowitz et al., 1983) and in women (n=8711) with self-reported stressful jobs (Henrickson et al., 1994). Moreover, women in the USA with depression, low self esteem, low pregnancy desirability and low income (n=120) have been found to have twice the rate of PTB (22.7%) than the national average of 11.6% (Jesse et al., 2003).

As part of the Preterm Prediction Study (n=2593), Copper et al investigated maternal stress and anxiety at specific gestations throughout pregnancy and found that only stress was significantly associated with spontaneous PTB and low birth weight, reporting a 16% increased risk amongst women who perceived their life to have been stressful (Copper et al., 1996). An increased risk was also found in relation to maternal stress, as a consequence of severe life events in a large cohort of women (n=1962) with perceived racial discrimination and pregnancy related anxiety, although depression had no significant association with PTB (Dole et al., 2003). However other studies have questioned this association. Peacock et al., (1995) found no significant association between anxiety and PTL, Perkin et al., (1993) no significant association between depression and anxiety and PTB concluding that the evidence from normal pregnancies that progress to term, that this may be a consequence of PTL and

not a causative agent. Messer et al., (2005) found no association between pregnancy intendedness as a source of increased stress. There are several potential explanations for such conflicting conclusions, including sample size and poor definitions of stressors which may influence the results found.

The stress of war has a different impact on different people and at different times, with PTB rates during the Yom Kippur war in 1973 lower than in the year after the war (Omer et al., 1986) however, more recently, the influence of war on PTB in Bosnia showed an increase during the war (1992 to 1995) and immediately after (1996 to 2003) to 16.6% compared to pre-war period (1988) of 9.1%. In the post-war period in 2003 there was a decline to 9.5%. The perinatal and maternal mortality rate inevitably changed with the majority of causes identified as associated with eclampsia, sepsis, embolism and shell injuries with problems of suboptimal antenatal care, health care infrastructure collapse and material damage to almost all health facilities (Fatusic et al., 2005).

Alternatively pregnancy outcomes in the USA after the terrorist attack of September 11th (9/11) found contrasting results. In Boston women (n=606) exposed to 9/11 had a reduced risk of PTD compared to women (n=1184) who had delivered before 9/11 (Rich-Edwards et al., 2005). In New York the risk of low birth weight (< 2.500g) and PTB (< 37 weeks), one week after 9/11 compared to three weeks before found no immediate change in either. Months after 9/11 the levels of post traumatic stress (PTS) in New York City however was higher than anywhere else in the USA and in particular amongst women. This study found that these events were associated with immediate rise in very low birth weight (< 2000g) babies and a slight decrease in PTD rates (Eskenazi et al., 2007), supporting the assumption that there may be an association between the actual timing of stress and its influence on birth outcome.

The CESDI Project 27/28 found three areas of notable difference in the characteristics of mothers associated with an increased risk of early PTB (between 27 and 28 weeks) compared to the population of pregnant women in the UK, concurring with other studies in that the

proportion of smokers, multiple pregnancies and ethnicity were clear indicators of a risk for preterm labour and birth (CESDI 2003).

2.3.2 Past history of preterm birth

A past history of spontaneous PTB is the most strongly correlated risk factor for a recurrence with a decrease in the risk with each term birth experienced (Keirse et al., 1978, Terizou and Bennett 2002) with 21% of women likely to experience another in a subsequent pregnancy (Goldenberg et al., 2003). A recent large study in Denmark (between 1978 and 2007) compared the risk in a second pregnancy after the first singleton pregnancy had ended in spontaneous PTD by using a registry-based cohort of births (n=536,419). This study found that compared with a spontaneous first delivery between 32 and 36 weeks there was an increased risk in the second pregnancy from 2.7% (women who had previous delivery at term) to 14.7%. Moreover delivery before 28 weeks increased the risk of a second early delivery to 26% (Lykke et al., 2009).

2.3.3 Complication of the current pregnancy

Major factors with biologic plausibility for preterm labour in a current pregnancy include a prior PTB, cervical, uterine, placental structural or physiological abnormalities, inflammation, infection and uterine stretch from polyhydramnious or multiple pregnancies (Green et al., 2005). Nearly all higher order multiples will deliver preterm with the combined twin and higher order births comprising of a preterm risk of 15 to 20%. 60% of twins will deliver preterm with 40% of these deliveries as a result of spontaneous labour or PROM under 37 weeks gestation and the remainder planned deliveries due fetal or maternal problems (Goldenberg et al., 2008).

Antepartum haemorrhage is a major factor in spontaneous complicated PTB constituting up to 20% of cases and tends to recur in subsequent pregnancies (Chamberlain 1995, Green et al., 2000, Mattison et al., 2001, Steer and Flint 2004). Bleeding in the first and second trimester not associated with placenta praevia or abruption is also associated with a subsequent PTB (Goldenberg et al., 2008). However lack of antenatal care and late booking are also associated with both low birth weight and PTB (Hall et al., 1997). Identifying the

components of antenatal care that act in preventing PTL however is difficult. Nevertheless women in the lowest socio-economic groups seem to derive the most benefit from midwifery support and antenatal care, acknowledging the importance of the public health and educational role inherent within midwifery.

Infection stimulates a cascade of immunological effects with the ascent of any organism through the cervical mucus plug into the uterus initiating an inflammatory response from the placenta, fetal membranes and maternal deciduas. This leads to the release of cytokines and the stimulation of prostaglandin products which produces cervical ripening and uterine contractions (Steer and Flint 2004, Green et al., 2005). An inflammatory process anywhere in the body particularly in the urogenital tract is a major risk factor for preterm delivery with diagnosis of chorioamnionitis a recognised cause of preterm labour with intact membranes and systemic infections like urinary tract infections and pylonephritis identified as underlying causes (Chamberlain 1995, Campbell and Lees 2000, Mattison et al., 2001, Wadhwa et al., 2001, Peltier 2003).

Bacterial vaginosis is the most common lower genital tract infection with ranges between 15 to 40% higher amongst socially disadvantaged women. This infection however is not consistent throughout pregnancy and is usually associated with early PTB (< 28 weeks) presenting less frequently later in pregnancy (Wadhwa et al., 2001). In one study women who screened positive for Chlamydia at 24 weeks gestation, were found to have a three-fold increased risk of a subsequent spontaneous preterm birth and were also found to have a shortened cervix on ultrasound and a positive screen for bacterial vaginosis (Andrews et al., 2000).

Periodontal disease characterised by a low grade infection of the gums has been proposed as a confounding marker for preterm birth although data on the association is sparse and inconsistent at the current time (Klebanoff and Searle 2006). However there is evidence of an association between periodontal disease and low birth weight and PTD within economically disadvantaged populations (Xiong et al., 2006).

Women who present in PTL therefore, cannot be classified as one entity. Preterm premature rupture of membranes (PPROM) and those with intact membranes are associated with different exposures. This etiologic heterogeneity may explain the difficulties encountered in the prevention of PTB and the prediction of PTL. Therefore, within midwifery practice women more likely to present in PTL can in some ways be identified as those women with biological plausibility, emotional and sociological variables as contributing factors. Women identified as high risk from a physical perspective are offered medical screening and close surveillance within specialist obstetric antenatal care. However within midwifery, women recognised as high risk from a psychosocial perspective do not have a psychological screening test for stress, anxiety or depression during pregnancy apart from the routine mental health questions asked within the antenatal booking history.

2.3.4 Prediction and prevention of premature labour

Identifying women at risk of premature labour is the first step in preventing this complex disorder of pregnancy. Within the medical model, historically, documentation of changes in the cervix was undertaken by digital examination and this was the main diagnostic test used in obstetrics and midwifery. However, in the past decade ultrasound assessment of cervical length and the use of biochemical tests have been key in understanding normal and preterm labour. Cervical length (CL) measured by transvaginal ultrasound (TVU), being the main diagnostic tool used in the assessment of an imminent premature delivery (Terizdou and Bennett 2002, Goldenberg et al., 2005).

A recent Cochrane review assessed whether knowledge of changes in the cervix can prevent preterm birth by looking at the effectiveness of the antenatal management of preterm labour based on ultrasound of CL. Within the 5 trials reviewed with women (n=507), there was insufficient evidence to recommend routine screening of both symptomatic and asymptomatic pregnant women with TVU of CL and concluded that there is a non-significant association between knowledge of TVU and CL results and a lower incidence of PTB (Berghella et al., 2009). It remains unclear therefore whether this screening test is effective as a preventative tool. The review however recommends future research on specific groups of women and a clear protocol for management for evaluation and replication of findings.

Fetal fibronectin (FFN) is an extracellular matrix glycoprotein localized at the maternal-fetal interface of the amniotic membranes, between chorion and decidua. The use of tests for fetal fibronectin has been shown to be a strong predictor of preterm birth in all populations studied (Berghella et al., 2009). Therefore both fetal fibronectin and cervical ultrasound undeniably improve the identification of women at risk of a preterm delivery and are now commonly used as the first choice in diagnosis particularly in high risk groups. The Preterm Prediction Study found that a combination of a short cervix, with a previous preterm labour caused by preterm premature rupture of membranes (PPROM) and a positive test result for fetal fibronectin were the most highly associated risk factors for premature delivery caused by PPROM (Mercer et al., 2000).

Several approaches in the prevention of premature birth have been advocated. One approach is the use of progesterone. A Cochrane review recently assessed the benefits and harms of progesterone for high risk women and evaluated 11 trials including women (n=2714) and infants (n=3452). The trials identified included; progesterone versus placebo for women with a past history of spontaneous PTB which found that there was a statistically significant reduction in PTB in the studies reviewed; trials with women with a short cervix by TVU, found a statistically significant reduction in the risk of PTB at less than 34 weeks and also neonatal sepsis; studies with women having a multiple pregnancy, found a significant reduction in the risk of antenatal tocolysis; and women presenting in threatened preterm labour found a reduction in the risk of PTB. However, trials of women with other risk factors related to PTB found there was no statistical difference in the reported outcomes (Dodd et al., 2006). The overall conclusion of this review was that there were some beneficial effects including prolonging the labour, but there was insufficient information about other possible benefits or harms and that further research needs to be undertaken.

Surgical intervention in the prevention of PTB in the form of transvaginal cervical cerclage is a now a common treatment for known cervical incompetence before or during pregnancy for a small proportion of women and depends on clinical assessment and past obstetric history. Transabdominal cerclage is only used in very high risk women with either a history of a previous failed transvaginal cerclage or an absent the intravaginal portion. Moreover, the

benefits must be weighed against the risk of an operative procedure during pregnancy, such as preterm rupture of membranes, haemorrhage, damage to the bowel and the need for the pregnancy to be delivered operatively and intervention should always be avoided in women who are unlikely to benefit (Enkin et al., 2000).

The ORACLE Trials aimed to answer two fundamental questions in the area of preterm birth by trying to resolve the evidence from previous studies, that antibiotics would benefit the neonate after PPROM (Kenyan et al., 2001a). They also aimed to find out if antibiotics were beneficial to women with spontaneous PTL by prolonging the pregnancy. They found that antibiotics prolonged pregnancy in cases of PPROM but not spontaneous PTL without PPROM. Since the trial it is now routine practise to prescribe erythromycin to women with PPROM (Kenyan et al., 2001b) however long term follow up of infants in the ORACLE trial found an increase in cerebral palsy amongst those women prescribed antibiotics to prevent preterm labour (Kenyon et al., 2008). This has raised questions about whether keeping a fetus in a potential unfavourable environment is advisable. Moreover screening and treating women with a history of premature deliveries for infection such as bacterial vaginosis remains controversial in preventing a subsequent preterm birth (Terizdou and Bennett 2002).

Obstetric knowledge supports the use of cervical ultrasound length as having the best potential for identifying women at risk and biochemical testing can help to differentiate between women with a suspected and a true premature labour. Prolonging pregnancy in order to delay delivery of a preterm infant sufficiently to allow the administration of corticosteroids as a reactive model of care continues, through the use of therapeutic interventions.

2.4 Risks of prematurity

Prematurity is a major cause of neonatal mortality and one of the major influences on the chance of survival depends on where the delivery takes place with very preterm babies (under 32 weeks gestation) recovering better if delivered in a tertiary referral centre with neonatal intensive care facilities. Depending on age and maturity, premature babies may experience a wide variety of health problems and there is wide variation in survival rates reported for babies born at 26 weeks from 35% (Costeloe et al., 2000). The risk of death in

the first few weeks of life is due to a multitude of complications associated with immaturity in particular thermal instability, neurological problems, susceptibility to infections, metabolic disturbances, pulmonary diseases, cardiac, renal and haematological problems. Moreover, the mortality rate increases dramatically when babies weigh less than 1000 grams or are born before 28 weeks gestation with rates of disability of 30% and cerebral palsy of 15% (Levene et al., 2006). This variety and severity of problems associated with preterm deliveries, is determined by how mature the organ systems are with survival before 24 weeks gestation especially problematic (Drife and Magowen 2005).

Many preterm babies experience some degree of respiratory distress syndrome (RDS) due to lung immaturity and because the surfactant system is not mature enough to coat the alveolae, inducing collapse of the lungs as the baby exhales. The use of antenatal steroids, improved resuscitation techniques and subsequent management including exogenous surfactant treatment has resulted in the survival of more than half of the babies that are born weighing less than 1000 grams (Elder et al., 1997, Stewart and Roth 1999). However pulmonary disorders such as, broncho-pulmonary dysplasia and respiratory distress syndrome are still common due to inadequate synthesis of surfactant and is a common cause of death in the neonatal period (Greenhough and Roberton 1999).

Prematurity can also lead to bleeding into the cerebral ventricles and the development of periventricular leukomalacia or ventricular dilatation. These complications are associated with major intellectual, emotional and physical disabilities. Babies may suffer long-term neurologic and developmental impairments with mental and cognitive dysfunction (Mattison et al., 2000, Challis and Smith 2001, Halbreich 2005, Green et al., 2005). In addition many infections can become life threatening as the immune system is poorly developed. Cardiac problems can also occur when the ductus arteriosis fails to close at the time of birth which inhibits the development of a mature circulatory system and surgery may be required to remedy the problem (Elder et al., 1997, Levene et al., 2006).

In Western countries up to 85% of neonatal deaths are attributed to prematurity and of those who survive 10% will suffer some form of long-term handicap (Drife and Magowen 2005).

The risk of long term intellectual, emotional or physical disability is directly related to the gestational age of the infant and is difficult to predict the severity of disability at the time of birth (Stewart and Roth 1999).

The EPICure study followed premature babies born under 26 weeks, up to the age of 6 years and reported that 1 in 10 babies had developed a permanent disability such as chronic lung disease, cerebral palsy, blindness or deafness (Marlow et al., 2005). Those babies surviving birth before 26 weeks were suffering from high rates of disability with 22% defined as severely disabled (cerebral palsy but not walking, low cognitive scores, blindness, profound deafness). Moderate disability (defined as cerebral palsy but walking, IQ/cognitive scores in the special needs range, a lesser degree of visual or hearing impairment) was found in 24% of children with 34% having a mild disability (defined as low IQ/ cognitive score, squint, requiring glasses) and 20% had no problems (Marlow et al., 2005). When surviving children born before 26 weeks were re-assessed at age 11 years, they had significantly lower scores for cognitive ability, reading and maths with 13% attending special schools and 57% in mainstream schools had special educational needs (Johnson et al., 2009).

Long term disability as a result of prematurity requires community resources to assist in the achievement of an optimal quality of life for these children, including educational support, social services and respite care for the family and in the future, as adults they may need help with supportive housing and transportation. Finally, families must find ways of coping with the emotional stress of the death of a very premature baby or the uncertainty for their future. Problems with travel to and from hospital and the stress of arranging care for other children are the challenges often faced by parents with prolonged hospitalisation, separating parents from babies in the critical new-born period.

2.5 Stress, anxiety and depression

Within the literature, stress, anxiety and depression often appear synonymous; however they are distinct constructs and should be defined as such. Stress as a response may or may not include anxiety or depression and is embedded in a process which involves interacting with the environment, appraising that interaction and attempting to cope with any problems that

arise. Coping is defined as an attempt to manage situations that are perceived as demanding or exceeding available resources by finding a new way to look at the situation or by using distractions to focus away from the problem (Lazarus and Folkman 1984, Atkinson et al., 1990).

Pregnancy can be a stressful time for women. The sources of stress can be psychological or physical, external or internal in origin and possibly associated with personality traits (Sanderson 2004). The normal worries reported to concern women during pregnancy include changes in physical appearance and physical problems, interpersonal relationships, with fear about giving birth and concerns about parenting (Alderdice and Lynn 2009). Although stress is associated with anxiety and depression it is unknown whether preterm labour is triggered by stress through severe anxiety, depression, life events or a combination of factors.

The majority of women adapt well to pregnancy and most experience no psychological complications. However approximately 25% of women report emotional distress during pregnancy in the form of stress, anxiety or depression (Yali and Lobel 1999). More recently, antenatal anxiety and depression has been recognised as a condition in its own right and is proposed to be as common as postnatal depression affecting between 10% and 15% of women (DOH 1999, Evans et al., 2001, NICE 2007) highlighting the need to be urgently addressed within midwifery.

Midwifery practice is guided by the philosophy that having a baby is a major life event, during which all women should benefit from midwifery care that can be centred around the woman's unique and individual needs and ensuring the services provided to childbearing women and their families are empowering (RCM 2006). Currently the March of Dimes Foundation website explicitly advises women to reduce stress during pregnancy to reduce the risk of preterm birth and gives a number of practical ways of doing this (MOD 2008) however, within midwifery this has yet to be seriously addressed.

2.5.1 Definition of stress

The definition of stress largely depends on the orientation within psychology. The stress concept entered the field of biological sciences in the 1950's through the work of Hans Selye, a Canadian endocrinologist. He pioneered research on the biological effects of exposure to stressful stimuli through the concept of the General Adaptation Syndrome (GAD) and used the term 'stressors' to describe this. This model consisted of describing physiological responses such as enlargement of the adrenal gland, atrophy of the thymus, spleen and other lymphoid tissue and gastric ulceration. This foundational work led to a rich line of research on the biological function of glucocorticoids (Malim and Birch 1996, Neylan1998).

The most popular approach to studying stress is based on the transactional model focussing on the 'perceived' demands of the environment and the 'perceived' ability to cope with these demands, rather than 'actual' demands and 'actual' ability to cope (Atkinson et al., 1990, Malim and Birch 1996). In health psychology, stress is described as a state of challenge or a threat that disrupts the normal rhythm and balance of a person's life. This can include environmental events that are perceived as threatening (stressors) and the persons' reaction to them (stress response) (Sanderson 2004). Some researchers focus on stressors, in particular stress-full life events and the risk of subsequent illness. Others focus on stress responses, trying to identify the cognitive, emotional, physiological and behavioural responses that occur when faced with a demanding or threatening situation (Burns 1988, Atkinson et al., 1990).

There are differences in the reaction to stressors and experiencing an event is interpreted in a unique way with respect to personal goals and well-being, with the outcome of appraisal being negative or positive. This cognitive appraisal has two parts, the appraisal process and the resulting belief contributing to the overall emotional experience. Inability to deal with stress can lead to an array of psychosomatic disorders and stress may or may not be complicated to include anxiety or depression (Malim and Birch 1996).

There is a great deal of evidence linking the pathophysiology of psychosocial stress with an increased vulnerability to affective and anxiety disorders. Stressful life events often precede

the onset of depression and stress has been associated with the severity of the illness (Dunner et al., 1979, Brown et al., 1987, Hammen et al., 1992).

2.5.2 Definition of anxiety

In general terms anxiety is a state of apprehension, tension and worry, a distressing emotion which may have no specific cause, unlike fear and may be maintained for some time. Anxiety states are often learned by classical conditioning and are considered abnormal when occurring in situations that most people handle without difficulty. Anxiety is defined as a response to a perceived threat, with actual physical symptoms such as a racing heart or psychological reactions in the inability to concentrate or make decisions (Lazarus and Folkman 1984, Sanderson 2004). There is little evidence as to why some individuals become chronically anxious and it is likely that there is both an environmental and genetic influence associated with stress vulnerability (Lau et al 2006).

Anxiety disorders are a group of mental disorders characterised by intense anxiety or by maladaptive behaviour designed to relieve anxiety. They include a group of disorders in which anxiety is either the main symptom (generalised anxiety and panic disorders) or is experienced when the individual attempts to control certain maladaptive behaviours (phobic and obsessive-compulsive disorders). Post-traumatic stress disorder involves anxiety following a traumatic event (Sanderson 2004).

Anxiety does not occur as a single phenomenon, its various forms of manifestation can be categorised under two different headings of trait anxiety and state anxiety.

Trait anxiety:

This is a relatively stable aspect of the personality and is influenced by biological and genetic factors (Lau et al 2006). It is a pre-set level of anxiety experienced by an individual who has the tendency to be more anxious and to react less appropriately to anxiety provoking stimuli. Individuals who present with trait anxiety (A-Trait) will tend to have an attitude reflecting their perception of certain environmental stimuli and situations as dangerous or threatening. In practice, this anxious perceptive style will eventually become pervasive, extending to and

influencing other areas of experience and in effect becoming a characteristic of the personality (Endler et al 1975).

State anxiety:

This is a more developed form of anxiety and is the anxiety state (A-State) we experience when something causes us to feel appropriately and temporarily anxious and this anxiety then retreats until we feel 'normal' again. State anxiety is largely influenced by environmental factors (Lau et al 2006). Individuals with state anxiety are more likely to react to a large number of stimuli and will tend to worry in situations with low anxiety-generating potential, such as normal day-to-day activities (Endler et al 1975).

Theories of anxiety disorders tend to focus on internal conflicts, learned responses to external events, maladaptive cognitions and biological factors (Atkinson et al., 1990, Sanderson 2004). From a behavioural perspective, anxiety can be triggered more by specific external events (A-State), than by internal conflicts. Avoidance of the stimulus is a method used to reduce anxiety however this means the source of the anxiety is never fully explored or conquered. Prolonged anxiety or depression can lead to a state of stress, which is a recognisable physiological condition (Sanderson 2004). Stressful life events involving physical or social threat may reflect sources of individual specific environmental experiences common to both state and trait anxiety (Lau et al 2006).

The most widely used measurement of State and Trait Anxiety is Charles Spielberger's State-Trait Anxiety Inventory for Adults (STAI). The State-Trait Anxiety Inventory was developed as a research tool for the study of anxiety. According to Spielberger state anxiety reflects a "transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity. Trait anxiety denotes relatively stable individual differences in anxiety proneness and refers to a general tendency to respond with anxiety to perceived threats in the environment (Spielberger et al 1995)."

Within the SIP study an alternative tool was used to identify and measure psychological morbidity, the Hospital Anxiety and Depression Scale (HADS), which assesses state anxiety and general depression scores (Zigmond and Snaith 1983). The SIP study was measuring life stresses therefore HADS was used in order to give an accurate measure of state anxiety (A-State) and a separate measure of depression (dysthymia) with a classification of severity within the scoring system and is used in midwifery and other research to measure psychological morbidity.

2.5.3 Definition of depression

Depression is a normal reaction to life stresses and is characterized by a disorder of mood. There is a general recognition of four sets of symptoms involving emotional, cognitive, motivational and physical symptoms. Not all need to be present in depression. A mood disorder is characterized by sadness and dejection, decreased motivation and interest in life, negative thoughts (for example feelings of helplessness, inadequacy and low self-esteem) and such physical symptoms as sleep pattern disturbances, loss of appetite and fatigue (Burns 1988, Malim and Birch 1996).

Depression can be a debilitating disorder and tends to recur, however in the general population most depressive episodes are of a relatively short duration and individuals generally recover with or without treatment. However, in the group with depression lasting more than a year, about 10% will not recover and will remain chronically depressed (Atkinson et al., 1990) posing significant risks for women in this group who may be pregnant.

Depressive disorders have different classifications, with manic depression (bipolar disorder), major depression, atypical depression, psychotic depression and dysthymia.

Manic depression (bipolar disorder):

This is characterized by cycling mood changes with severe highs (mania) and severe lows (depression), often with periods of normal mood in between. Sometimes the mood switches are dramatic and rapid, but usually they are gradual. Within the depressed cycle, an

individual can have any or all of the symptoms of depression and in the manic cycle, the individual may be overactive, over talkative, and have a great deal of energy. Mania often affects thinking, judgment, and social behaviour in ways that cause serious problems and embarrassment. Between 5 – 10% of mood disorders involve both poles of the mood continuum (Sanderson 2004). Mania, left untreated, may worsen to become a psychotic state People who suffer from manic depression have an extremely high rate of suicide, however the majority of depressions occur without episodes of mania (Malim and Birch 1996, Sanderson 2004).

Major depression:

This is manifested by a combination of symptoms that interferes with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. A major depressive episode may occur only once, but more commonly, several episodes may occur in a lifetime. Chronic major depression may require continued treatment indefinitely (Sanderson 2004).

Dysthymia:

This is a less severe type of depression and involves long lasting, chronic symptoms that do not seriously disable, but keep the individual from functioning well or from feeling good. Many people with dysthymia also experience major depressive episodes at some time in their lives and women are at greater risk of developing this condition than men (Malim and Birch 1996, Sanderson 2004).

The most disastrous consequence of depression is suicide. Moreover, within midwifery practise anxiety and depression in particular, are often subsumed within a diagnosis of postnatal depression (PND). This is somewhat of a misnomer as a significant number of women develop these symptoms during the antenatal period. Focussing on PND only, can have potentially serious consequences for women with severe mental illness during pregnancy, with the recurrence of psychiatric problems a significant cause of maternal death in the last three confidential enquiries (CEMD 2001, CEMACH 2004, CEMACH 2007).

2.6 Physiological reaction to stress

Seyle described the influence of stress on illness as a disease of adaptation and concluded that it is not stress that harms us but distress. Historically, scientists have linked stress and the immune system with illness, in particular with coronary heart disease. The physiological reaction to stress and anxiety is initiated by a complex sequence of innate responses to a perceived threat with the term stress used to describe any physical or psychological challenge that threatens or is perceived to have the potential to threaten (Malim and Birch 1996).

During exposure to a stressor the whole system of stress regulation is activated. Physiological changes occur from activation of two neuro-endocrine systems, the hypothalamic-pituitary-adrenal cortex system (HPA axis) and the sympathetic nervous system, the adrenal-medulla system (Mulder et al., 2002). The sympathetic nervous system acts directly on smooth muscles and internal organs invoking changes such as increased heart rate, dilated pupils, elevated blood pressure, increased respiratory rate and sweating (Malim and Birch 1996). Various hormones are released in large quantities into the bloodstream. The HPA axis releases corticotrophin-releasing hormone (CRH) which in turn acts on the pituitary gland triggering the release of adrenocorticotrophin hormone (ACTH). ACTH signals the adrenal glands to release hormonal compounds, epinephrine (adrenaline), increasing the blood pressure, heart rate and diverting blood to the muscles, norepinephrine (noradrenaline) and cortisol. Cortisol (glucocorticoid) releases glucose to power the muscles and the brain and the body adjusts to the situation through a 'fight or flight' response (Atkinson et al., 1990, Mulder et al., 2002).

The HPA axis communicates with several regions in the brain including the limbic system controlling motivation and mood, the amygdala which generates fear in response to danger, the hippocampus which plays an important part in memory formation as well as mood and motivation and interacts with other glandular systems among them those producing reproductive, growth and thyroid hormones. Once activated the stress response switches off the hormonal systems regulating growth, reproduction, metabolism and immunity. Normally, cortisol acts on the hypothalmus and exerts a feedback effect to shut down the stress response after the threat has passed, causing it to stop the production of CRH (Atkinson et al., 1990).

If the stressor is not removed adrenaline levels remain high and are instrumental in depressing the immune response with stress hormones (glucocorticoids) inhibiting lymphocytes/leucocyte proliferation and altering the balance of cytokine secretion. In the short term this response is helpful allowing a diversion of biochemical resources to deal with the threat however in the long term chronic stress with the depletion of lymphocytes leaves the body susceptible to illness (Malim and Birch 1996).

Psychoimmunology has emerged as the study of how the body's immune system is affected by psychological variables. The immune system as a surveillance mechanism protects the body from disease-causing micro-organisms and regulates susceptibility to disease and illness. A growing body of evidence suggests that stress affects the ability of the immune system to defend the body often having deleterious effects on health with conditions such as stomach ulceration, hypertension, tumours and psychopathology (De Catanzaro and MacIver 1992). Depression represents an altered immune state and changes in cytokine levels often accompany major depression and chronic inflammatory states can induce depressive symptoms (Schiepers et al., 2005). The system implicated in this association is the HPA axis with the most consistent endocrine dysfunction in patients with major depression being dysregulation of the HPA axis (Gennero et al., 1996, Dole et al., 2000).

The pathophysiology of psychosocial stress therefore, links stressful life events to an increased vulnerability for affective and anxiety disorders, with stressful life events often preceding the onset of depression and stress associated with the severity of the illness (Dunner et al., 1979, Brown et al., 1987, Hammen et al., 1992).

2.7 Immune response to infection and inflammation

In response to infection or inflammatory disorders such as rheumatoid arthritis, cells of the immune system produce interleukins, IL-1, IL-6 and tumour necrosing factor- alpha (TNF-α) causing inflammation. These substances trigger the release of CRH, with IL-6 promoting the release of ACTH and cortisol. Cortisol and other compounds respond by suppressing the release of IL-1, IL-6 and TNF-α, and switching off the inflammatory response. Ideally, stress

hormones damp down an immune response that has run its course. However, when the HPA axis continually runs at a high level, the damping down can lead to a decrease in the ability to release interleukins and fight infection (Atkinson et al., 1990).

In addition, the high cortisol levels resulting from prolonged stress can make the body more susceptible to disease by switching off disease fighting white blood cells. Conversely there is evidence that a depressed HPA axis resulting in too little corticosteroid can lead to a hyperactive immune system and an increased risk of developing autoimmune diseases such as lupus (Atkinson et al., 1990).

Any immune challenge that threatens homeostasis can be regarded as a stressor and certain cytokines, especially TNF-α, IL-1 and IL-6 may activate the stress system in vivo, by maternal stress acting through one or both of two physiological pathways, the neuroendocrine pathway and the immune/inflammatory pathway. Stimulation of the former may result in a premature activation of the maternal-placental-fetal endocrine systems thereby promoting parturition, with the latter pathway instigating an increase in the susceptibility to intrauterine and fetal infectious-inflammatory process promoting parturition through pro-inflammatory mechanisms. Placental CRH may also play a key role in orchestrating the effects of endocrine, inflammatory and immune processes in preterm birth (Wadha et al., 2001).

Important questions remain however, about the vulnerability to stress in some women, the nature of the stress and the timing with regard to pregnancy. The combination of stress and other factors such as infection may produce a bio-behavioural effect on the outcome of preterm birth. Neuroendocrine pathways via maternal and/or fetal HPA axes and regulated by inflammatory responses may result in the premature triggering of labour and a greater degree of activation of the placental-fetal endocrine systems, including CRH and oestrogens (Malim and Birch 1996). Immune mechanisms regulated by inflammatory responses are likely to affect the susceptibility to maternal infection such as bacterial vaginosis (BV), thereby promoting a pro-inflammatory response (Malim and Birch 1996). This has led to the suggestion that psychological morbidity is a cause of PTB with studies demonstrating an

increase in pro-inflammatory cytokines in stressed women compared to low stressed women (Coussons-Read et al., 2007).

2.7.1 Cytokines

The immune system has many different types of cells acting together to take care of infections and altered cells. Cytokines are small molecular weight peptides produced by cells in order to communicate and orchestrate this attack. Cytokines can have multiple functions depending on the cell that produces them and the target cell upon which they act (pleiotropism) with some more important than others in basic immunology and their functions are best studied within the context of an actual immune response (Goldsby et al., 2000).

All cells in the immune system are derived from pluripotent stem cells in the bone marrow by the process hematopoeisis. Under the influence of cytokines, the pluripotent stem cell may become a lymphoid stem cell or a myeloid stem cell. The lymphoid stem cell develops into B and T cells. Natural killer (NK) cells are lymphocytes that act in a similar manner to cytotoxic cells however these cells are not T cells. The lineage of the NK cell is not well understood. The myeloid stem cell develops into platelets, red blood cells or the granulocyte-monocyte line and monocytic cells include monocytes and macrophages. The granulocyte includes neutrophils, eosinophils, mast cells and basophils. Monocytes circulate in the blood and lymphatics but become macrophages when they enter the tissues (Goldsby et al., 2000).

The development of these cells from a stem cell involves cytokine growth factors and the development of a progenitor cell in each line. The progenitor cell is a committed cell, meaning that it is committed to that line of cell growth (for example an easinophil progenitor must become an easinophil, it can't become a neutrophil). In adults the hematopoietic cells grow and mature supported by the bone marrow stromal cells (Goldsby et al., 2000).

Originally, cytokines were named according to their function (like T cell growth factor, now called IL-2) but then the pleotropy of cytokines was identified making function specific names confusing. In order to avoid confusion, immunologists started naming some of the

cytokines as interleukins (IL) and numbering them as they were found. Interleukins is a name indicating that they are secreted by some leukocytes and act upon other leukocytes. The first interleukin identified therefore was IL-1 and the most recent IL18 and it is reasonable to believe that there are others still to be discovered (Goldsby et al., 2000). Elevated serum levels of numerous inflammatory cytokines have been found in intrauterine non-clinical infection associated preterm labour, when compared to non-labouring women, in particular Il-6 (Murtha et al., 1998), Il-2 (Alvarez-de-la-Rosa et al., 2000) and TNF-α (Gucer et al., 2001) suggesting a role for the inflammatory cytokines in preterm labour.

2.7.2 Leucocytes

Leucocytes and lymphocytes, cells of the immune system are central to the development, maintenance and resolution of an inflammatory response. Leucocytes are an important constituent of human endometrium and changes in endometrial leucocyte populations have been associated with recurrent miscarriage, differing population of leucocytes existing in the pre-implantation endometrium of women with recurrent miscarriage compared to those with successful pregnancy (Lachapelle et al., 1996, Quenby et al.,1999). Thus, the endometrial leucocyte population has been linked to adverse pregnancy outcomes. Similarly the peripheral leucocyte population has been associated with preterm labour (Gervasi et al., 2001, Sendag et al., 2002).

2.7.3 Cortisol

Cortisol is the most abundant circulating steroid and the major glucocorticoid secreted by the adrenal cortex. Physiologically effective in anti-inflammatory activity and blood pressure maintenance, cortisol is also involved in gluconeogenesis, calcium absorption and the secretion of gastric acid and pepsin (Coad 2005). Anomalous cortisol concentrations have been shown to exist in patients with acute infections, severe pain, diabetes mellitus or heart failure and in women either pregnant or on oestrogen therapy (Moawad et al., 2002).

Stress and anxiety are associated with elevated activity of both the HPA axis and the secretion of cortisol and the sympathetic-adrenomedullary system which results in the release of noradrenaline and adrenaline. There are strong correlations between maternal and fetal

levels of cortisol implying that the fetus may be exposed to increased levels of the stress hormone cortisol in utero (Gitau et al., 1998) with important implications. High levels of cortisol inhibit intra-uterine growth and may accelerate the onset of parturition indirectly and may alter the regulation of glucocorticoid receptors in the brain of the developing fetus with high levels of CRH found to predict shorter gestational length (Moawad et al., 2002). The HPA axis status, related to sub-clinical inflammation, psychological morbidity and pregnancy outcome can be measured by circulating levels of CRH and cortisol.

2.7.4 Corticotrophin Releasing Hormone

CRH is a 41-Amino acid peptide produced in the maternal and fetal hypothalamus and has been localised in the placenta and plays a pivotal role in the regulation of ACTH secretion. It is found extensively throughout the brain where it may act as a neurotransmitter and as central regulator of the stress response. Primarily produced by the syncytiotrophoblast in human placenta, it has also been detected in endometrial glandular epithelium, cytotrophoblast and deciduas. CRH levels are much higher in maternal than fetal circulation and much higher in the umbilical vein compared to the umbilical artery (Mulder et al., 2002). Placental CRH is biologically active and stimulates the pituitary-adrenal axes of both the mother and the fetus. High levels of CRH found in pregnant women stimulate an increase in CRH production by the placenta which rises exponentially as pregnancy advances. CRH has a positive feedback effect on the maternal hypothalamus and initiates a cascade of events which may lead to increased uterine activity and eventually delivery (McLean and Smith 2001).

Several researchers have investigated the role of CRH in normal and abnormal pregnancies and found high levels associated with PTL (McLean et al., 1998, McLean and Smith 2001, Leung et al., 2001, Wadhwa et al., 2004). Levels of CRH are rarely detectable in the non-pregnant state and in early gestation but present in increasing quantities in the second half of pregnancy (Lockwood et al., 2002), taking place in the placenta with peripheral circulation of the hormone (McLean and Smith 2001). CRH therefore plays a prominent role in the maturational preparation of the maternal-fetal-placental unit for labour and birth and PTL may be associated with premature activation of placental CRH secretion (Challis et al.,

2000). Elevated levels of CRH as early as 18-20 weeks have been found and are associated with a greater risk of PTD with significantly lower levels in women at term and may be associated with the pathogenesis of PTL (Hobel et al., 1999, Holzman et al., 2001). Maternal plasma levels determined at 28 weeks gestation as part of the Preterm Prediction Study were associated with an early spontaneous PTB under 35 weeks (Moawad et al., 2002).

2.7.5 Corticotrophin Releasing Hormone Binding Protein

Corticotrophin Releasing Hormone Binding Protein (CRH-BP) is a high affinity protein that binds to human CRH and neutralises its ACTH-releasing properties. The actions of CRH in the brain, pituitary and plasma are modulated by CRH-BP making it an important molecule to study as it is involved in regulating available CRH and is important in preterm labour. It is thought that CRH may act as a biological clock such that levels increase prior to delivery due to decreased levels of CRH-BP (Behan et al., 1996).

CRH-BP may be responsible for protecting the maternal pituitary from the high levels of CRH produced by the placenta. Studies of human CRH-BP have been hampered by the difficulty in isolating this protein in large quantities in human plasma. Any effects of CRH on parturition may be mediated through the CRH-BP protein, as the decrease in plasma levels seen towards term would allow increased levels of free CRH to act upon the myometrium and fetoplacental tissues. Moreover, its immediate recovery postpartum suggests that the fetoplacental unit is able to influence CRH-BP production (Perkins et al., 1993). Plasma levels elevated in PTL and reduced levels of CRH-BP in this condition would allow higher plasma levels of free CRH. The levels found in normal human non-pregnant plasma leads to the assumption that the liver is the major site of synthesis, although it is not yet known how production of CRH-BP is controlled (Behan et al., 1996). The decrease in plasma CRH-BP towards term and its immediate recovery postpartum suggests that the fetoplacental unit is able to influence CRH-BP production. Therefore it may be possible to determine the HPA axis status by measuring circulating levels of CRH-BP (Latendresse and Ruiz 2008).

2.7.6 Adrenocorticotropic hormone

Adrenocorticotropic hormone (ACTH) is a polypeptide hormone and is produced in the pituitary gland and serves to stimulate steroid production by the adrenal cortex. ACTH is controlled by the hypothalamic hormone corticotrophin releasing hormone (CRH) and by negative feedback from cortisol. The human fetus has a functioning HPA axis by mid-trimester. Placental CRH is released into the fetal circulation at much lower concentrations than maternal blood, but is capable of stimulating ACTH secretion from the fetal pituitary (McLean and Smith 2001).

2.7.7 Granulocyte Colony Stimulating Factor

Granulocyte-colony stimulating factor (G-CSF) is a haematopoietic growth factor that works by encouraging the bone marrow to produce more white blood cells and is a cytokine marker of inflammation which may have an important role in parturition. These peptides are a family of glycoprotein growth factors that regulate the survival, proliferation and differentiation of hematopoietic stem cells as well as the functional activities of mature cells. G-CSF increases in the cervix during labour and may stimulate proliferation of neutrophil subset (Peltier 2003). One well established factor of preterm labour is sub-clinical infection and evidence of systemic sub-clinical infection by measuring the cytokine G-CSF at 24 weeks has been shown to be elevated in women who subsequently have an early preterm delivery under 32 weeks gestation (Goldenberg et al., 2000, Goldenberg et al, 2005).

2.8 Immune regulation and response in pregnancy and labour

The immunological paradox of pregnancy was first recognised by Sir Peter Medawar in 1953. He describes the fetus as being "semiallogenic" to the mother, surviving in the face of a potentially hostile maternal immune system. The embryo is recognised as foreign to the mother immunologically therefore the immune system would treat the embryo as if it were a tissue graft and called the successful outcome of post-implantation pregnancy, the fetal allograft (Naz 2002). Implantation is the most dangerous time in immunological terms for pregnancy, when increased intimacy with the mother requires evasive mechanisms to lower antigenicity with the placental villous trophoblast the major tissue confronting the maternal immune system (Goldsby et al., 2000).

In the study of mice, the hormonal-cytokine network at the maternal-fetal interface has an important role in both blastocyst implantation and the maintenance of a successful pregnancy (Piccini et al., 2000). The role of cytokines during pregnancy is described as the decidua being populated by a variety of low levels of leucocytes, where during implantation, many leucocytes are natural killer (NK) cells which decrease in numbers as the pregnancy continues and are absent at term. However, approximately 30% of decidual cells at the site of implantation are macrophages with high levels remaining throughout pregnancy (Mor and Abrahams 2003).

One mechanism by which the fetus maintains its immunological privileges in the uterus is to tightly regulate the levels of cytokines at the maternal-fetal interface where excessive or aberrant production of pro-inflammatory cytokines would be harmful to pregnancy. The role of progesterone in the survival of the fetal allograft by exerting its immunomodulatory actions is unclear but may involve both direct and indirect actions on immune cells (Peltier 2003).

The innate immune system is not indifferent to the fetus and may have a role to play not only in host protection to infections, but also in the feto-maternal immune adjustment. An important aspect of this process is the establishment of an adequate microenvironment that will promote cell growth and will inhibit hazardous inflammatory immune reaction Pro-inflammatory cytokines such as IL-2, TNF-α, interferon-γ (IFN-γ), is suppressed in pregnancy because of the potential harming effects. The production of anti-inflammatory cytokines such as IL-4, IL-6, or IL-10 is enhanced (Mor and Abrahams 2003). Therefore cytokines contribute to the maintenance of an adequate balance at the placental bed. The maternal immune system can promote or inhibit growth and survival of the fetoplacental unit, but the precise mechanism involved, the key mediators, their modes of action and the extent of the influence of the immune system are far from clear.

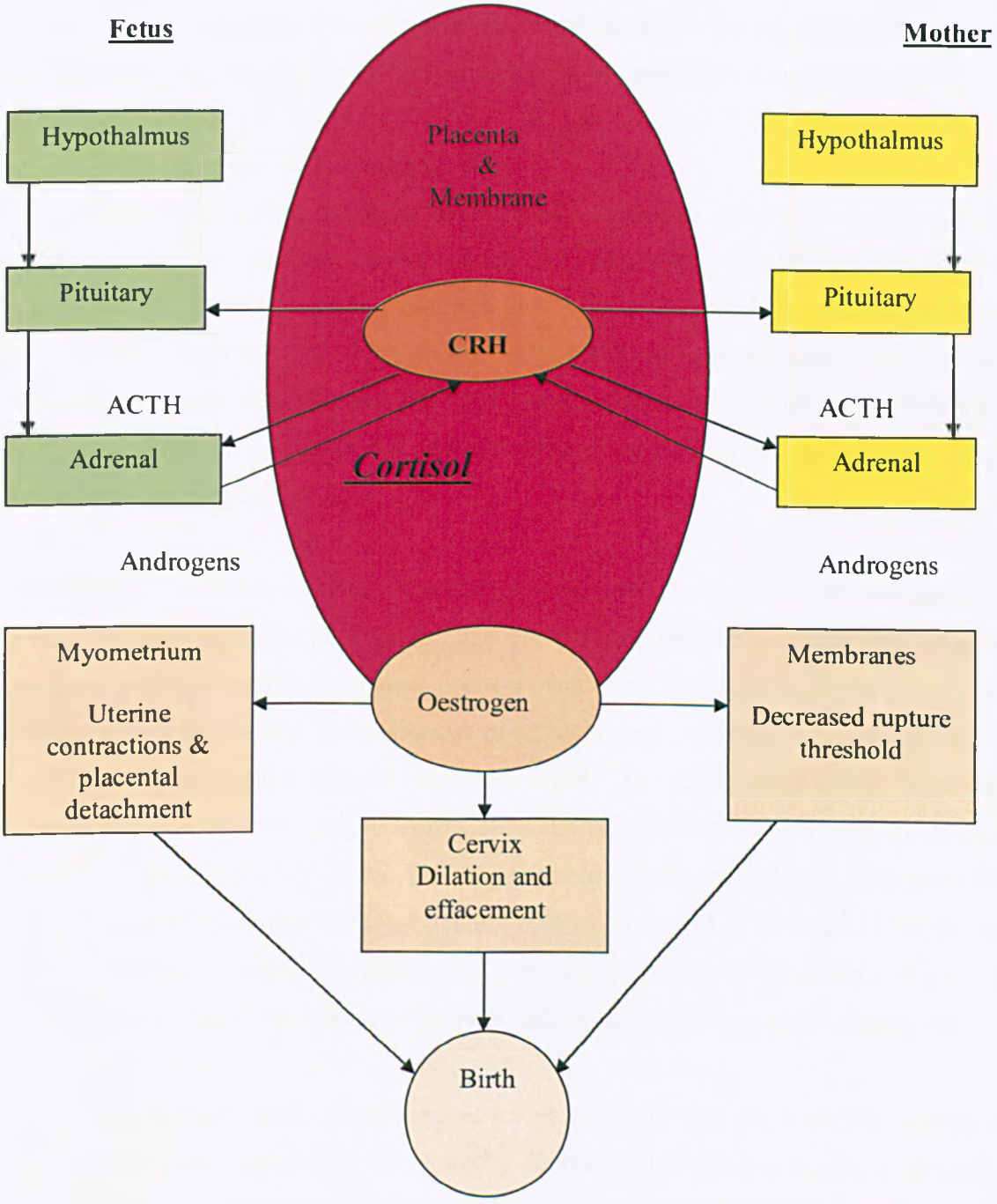
The common terminal pathway is the anatomic, biochemical, endocrinologic and clinical events that occur in the fetus and mother in both term and preterm labour (Romero et al.,

1997). The process of labour involves three physiologically interdependent processes, remodelling of the cervix to allow it to stretch open, weakening and rupture of membranes overlying the cervix and the initiation of rhythmic contractions of increasing strength and frequency to force the fetus and placenta out of the birth canal (Figure 1).

Figure 1 (2.8)

Neurohormonal Cascade Model for Parturition.

Adapted from Pike (2004)



Some of these processes seem to be mediated by pro-inflammatory cytokines, which suggests the immune privileges during pregnancy are revoked at the time of labour (Peltier 2003, Stjernholm et al., 2004).

The complexity of pregnancy is embedded in a matrix of social and psychological factors on one hand, and a series of structural, endocrinological and metabolic changes on the other.

2.9 Stress response and preterm birth

The study of interactions between neurological, endocrine, immune systems and the psychological state provides a framework for examining the relationship between behavioural and biological phenomena and their influences on health outcome (Ruiz and Pearson 1999, Majzoub et al., 1999). There is bidirectional communication of the immune and nervous system, through short and long communication loops, mediated by hormones, neurotransmitters and cytokines that bind to receptors on cells of the immune and nervous system (Ruiz and Pearson 1999).

The influence of stress and anxiety during pregnancy, by stimulating immunological disequilibrium in women with a history of recurrent idiopathic PTL is relatively unknown. Traumatic experiences from a previous preterm labour may influence the levels of stress and anxiety women experience in subsequent pregnancies and remains an important topic to investigate as pregnancy related psychomorbidity is poorly understood. Endocrine dysfunction in patients with major depression is known to be caused by dysregulation of the HPA axis, with a key study in the 1960's recognising that cortisol levels of patients with depression were higher than those of healthy controls (Michael & Gibbons 1963, Gibbons 1964). This seminal observation prompted a great deal of further research and it is generally accepted that sustained stimulation of the HPA axis is associated with major depression.

The resulting positive feedback mechanism may be amplified by the endocrine response to stress especially in women who are clinically depressed. Levels of cortisol are elevated in chronic anxiety and in subjects who experience stressful life events with the maternal HPA axis shown to cause sustained hypercortisolaemia which could explain the augmented

placental CRH production observed in those women who deliver preterm (Hobel et al., 1999).

Maternal emotional or psychosocial stress may therefore increase the risk of PTB through several interacting mechanisms. The neuroendocrine pathways via the maternal and/or fetal HPA axes may result in premature triggering of labour with immune mechanisms regulated by inflammatory responses affecting susceptibility to maternal infections and inflammatory processes through pro-inflammatory mechanisms (Green et al., 2005).

A central question in understanding parturition is whether the signals responsible for the activation of the common terminal pathway are similar in term and preterm labour.

Prostaglandins have been considered the key mediators for the onset of labour by inducing myometrial contractibility, changes in extracellular matrix metabolism associated with cervical ripening and through decidual membrane activation. Most evidence shows an increase in prostaglandin, produced by intrauterine tissue including amnion, chorion, decidua and myometrium and placenta, prior to the onset and during early labour. Many substances including, cytokines, growth factors and cortisol, increase prostaglandin biosynthesis however, the precise signals have still to be determined (Elder et al., 1997). The fundamental difference between term and PTL is that the former results from physiologic activation of the terminal pathway while the latter is the consequence of pathologic activation of this pathway, therefore preterm labour is a pathologic event.

Most physiological explanations agree that the stress response system resides in the HPA axis with the maternal stress hormone cortisol correlating with fetal cortisol levels mediating increased uterine artery tone, impairing blood flow through the placenta, with effects, which only occur in the fetus from 22 to 24 weeks gestation (Texiera et al., 1999).

Elevated maternal plasma CRH levels have been found to be higher as early as 16 weeks in women in PTL than in women who delivered at term (McLean et al., 1995). Therefore, there may be periods during pregnancy when the determinants of parturition are especially

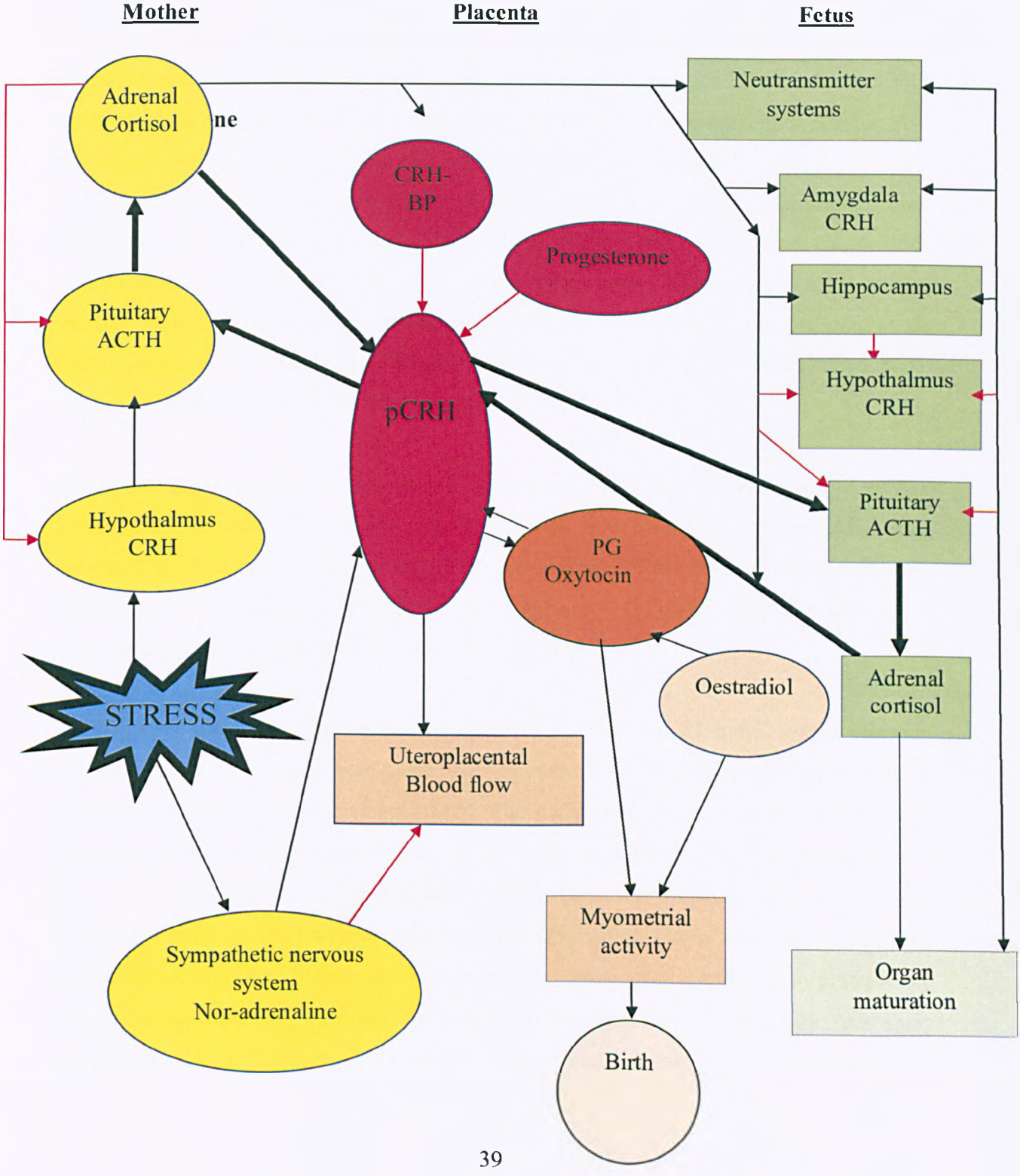
vulnerable to the effects of prenatal stress. This may be related to specific developmental events for example, the maturation of the fetal HPA axis. The premise of susceptible periods in pregnancy is supported in animal studies however, few human studies have incorporated multiple assessments of stress over the course of pregnancy and even fewer have tested hypotheses about time-specific effects of stress.

Transmission of maternal stress therefore, stimulates transplacental transport of maternal hormones culminating in a reduction in blood flow to the uterus and fetus and releasing placental CRH (pCRH) into the intrauterine environment leading to a premature activation resulting in uterine activity and eventual delivery. CRH-BP is absent in the fetus triggering stimulation to the fetal HPA axis, with fetal cortisol entering the placental circulation and promoting further production of pCRH which has been described as a feed-forward mechanism (Mulder et al., 2002). A premature rise in pCRH and a decrease in CRH-BP ultimately resulting in premature labour (Hobel et al., 1999). Moreover, changes in levels of specific maternal hormones may be early indicators of a raised stress level in the intrauterine environment.

Figure 2 shows the effects of maternal stress on uteroplacental blood flow and hormonal regulation in the mother, placenta and fetus. The activating influences are indicated by solid lines, inhibitory effects including negative feedback by red lines and the presence of feed-forward mechanisms at either side of the placenta is represented by thick lines.

Figure 2 (2.9)

Physiological Reaction to Stress and Regulation of the Maternal HPA Axis
Adapted from Mulder et al (2002)



2.9.1 Evidence from epidemiological studies

It is generally accepted that evidence from epidemiological studies identifies that smoking, low body mass index pre-pregnancy, young maternal age and socio-economic deprivation are associated with preterm delivery (Goldenberg et al., 2003, Green et al., 2005). Epidemiological studies have tended to concentrate on maternal stress and maternal infection (Terzidou and Bennett 2002, Wadhwa et al., 2001) nevertheless, not all women with high levels of stress or infection deliver preterm. However, there is an emerging consensus from the literature that psychosocial stress during pregnancy is associated with adverse outcomes such as: intrauterine growth restriction, low birth weight, miscarriage and preterm birth (Newton et al., 1979, Mutale et al., 1991, Cliver et al., 1992, O'Hare and Creed 1995, Texeira et al., 1999., 2002, Dole et al., 2003, Latendresse 2008), an increased risk of operative deliveries, epidural anaesthesia and admission to the neonatal unit (Chung et al., 2001), behavioural problems in children (O'Connor et al., 2002), and the development of schizophrenia in children in later life (Kashan et al., 2008b).

One of the largest epidemiological studies, a prospective population based study of women (n=5872) in Denmark indicated the risk of PTD was nearly doubled in distressed women compared to women with no distress (Hedegaard et al., 1996) with a subsequent study finding a 8.7% increase in the risk of PTB in women (n=2432) with stressful life events at approximately 20 weeks gestation (Nordentoft et al., 1996).

A recent large ecological study with very preterm births, between 22 and 32 weeks gestation (n=9490) found that women were more likely to come from very deprived areas as defined by the Index of Multiple Deprivation (IMD). The study discovered that socio-economically, the incidence was almost double when comparing the most deprived to least deprived areas in the Trent region of the UK (Smith et al., 2007). However, the study only looked at the relationship between the incidence of very PTB, deprivation scores and year of birth and acknowledged that other factors such as maternal age, previous pregnancy history, stress and environmental variables were not calculated in this approach. Nonetheless, the study highlighted an area of concern in terms of the impact socio-economic status remains to have on preterm and very preterm birth.

2.9.2 Evidence from animal studies

Historically, research on animals, mainly rodents, has had little doubt that exposure to stressful conditions during pregnancy has adverse effects on the offspring (Ivastan 1986). Animal studies suggest that psychological adversity can alter pregnancy outcome, in some species, exposure to noise (Joachin et al., 2001), unexpected handling or crowding the pregnant animal, is associated with lower birth weight, premature labour, abortion and smaller litter size (Ivastan 1986). However, research with rodents may not be an adequate model for the study of human fetal development and there remains uncertainty. Moreover, humans may have better protection than animals during pregnancy because of the longer gestation, with usually only a single fetus in utero. Studies in various species of monkeys have also shown that stressful stimuli can result in spontaneous abortion, low birth weight and placental insufficiency (Myers 1975, De Catanzaro 1992). Therefore, assuming that reaction to stress in pregnant primates are comparable with those in humans, it is plausible to hypothesise that stressful stimulation can have a similar situation in human pregnancy.

2.9.3 Immunological evidence

The establishment of a connection between pregnancy tissue and the lining of the womb is a crucial feature of early pregnancy. These communication pathways play an important role in ensuring the appropriate development of the placenta and baby. One mechanism which maintains the fetus during pregnancy is the tightly regulated levels of cytokines at the maternal-fetal-interface (Wadhwa et al., 2001, Peltier 2003, Kanellopoulos-Langevin 2003). The effects of stress are complex and comprise of immune suppression as well as immune activation.

Depending on the nature of the immune variable, some functions may be enhanced, whereas others are suppressed (Leung et al., 1999). Preliminary work in humans supports the concept that stress may affect pregnancy outcome. Research investigating spontaneous abortion has indicated that depression may be a risk factor for miscarriage, as stress and hormones may interact and induce changes in the cytokine production with high stress scores in women related to an increased number of some cytokines, mast cells and cells that stained positive for TNF-α in the decidua compared to women with lower stress scores (Arck et al., 2001).

This suggests that an imbalance in the maternal immune response caused by depression or stress may be abortogenic (Arck 2001).

2.10 Background to the current study

Exploring stress and preterm birth is based on the assumption that psychosocial stress increases problems in pregnancy. Many pregnant women and their families have benefited from major advances in the investigation of PTL and observational studies have been fundamental in informing healthcare practice. Despite this there remains uncertainty and the PTB rate remains constant. Recruiting pregnant women who have experienced traumatic events in pregnancy to participate in midwifery research creates a real challenge for midwives. Moreover, women experiencing premature labour and birth, despite the commitment from obstetricians and scientists, continue to rely on reactive management after diagnosis, rather than on prevention, highlighting the need for a change in emphasis towards earlier detection of those at risk and preventative measures.

At present little is understood about the levels of stress women endure when they have already experienced preterm labour and are pregnant again. A history of spontaneous preterm birth has been found to be the single most significant historical risk factor for a repeat event (Terizdou and Bennett 2002). Moreover, social and physical interventions have proved to be disappointing in preventing PTL with enhanced social support not shown to be effective in reducing the risk (Enkin et al., 2000).

The rationale for the SIP Study was to add valuable information to the midwifery knowledge base by exploring the relationship between maternal stress, maternal immune response and pregnancy outcome in this high risk group. The establishment of a specialist antenatal clinic for women with a history of idiopathic preterm labour offered a unique opportunity to conduct this study. Women attending the clinic were screened according to the clinic protocol. The screening involved high vaginal swab (HVS) as a baseline observation for infection and women were offered serial transvaginal ultrasound scans (TVU) at booking to measure cervical length and at 16, 20, 24 and 28 weeks gestation. Treatment followed the clinic protocol in brief, if shortening or funnelling of the cervix was detected vaginal

progesterone was initiated then follow up TVU arranged 2 weeks later. If the cervical shortening (<15mm) continued prior to 24 weeks gestation then cervical cerclage was also offered. If the cervical length was less than 5mm women were admitted to hospital for bed rest. On the basis of these results an individual pathway of care was planned. All women were to attend after the 20 week fetal anomaly scan and again at 28 weeks gestation making follow-up to the study possible. Moreover, the women approached welcomed the opportunity to be involved in the midwifery study.

A systematic review of the literature was conducted to identify gaps in knowledge and address conflicting evidence. The protocol is presented in Chapter 3 and formed the basis for the systematic literature review, which in turn informed the SIP Study.

Chapter 3

3. PROTOCOL FOR SYSTEMATIC LITERATURE REVIEW FOR THE SIP STUDY

3.1 Introduction

The aim of the systematic review was to explore literature associated with maternal stress, anxiety and depression during pregnancy, maternal immune response and preterm labour and birth. The review was important in order to identify available evidence and gain insight into relevant background information for the SIP Study. Premature labour and birth represents a public health concern for all those involved with a disproportionate impact on health services and substantial emotional and economic cost to families and communities. By approaching preterm birth in the context of a public health perspective and viewing it as a multidimensional construct with social, psychological and physical dimensions, we may be better able to understand it and improve women's chances of giving birth to a full term baby. Using the public health focus within midwifery, it may be possible to develop models for diagnostic and predictive tests which women will find acceptable with the ultimate aim of decreasing the incidence of preterm birth in the future.

3.2 Aims and Objectives

The aim of this protocol is to outline the process for a comprehensive literature search in a systematic way to answer the questions: Is stress, anxiety and depression associated with preterm birth? Is maternal immune dysfunction associated with preterm birth?

The objective was to enable the identification of studies that have explored the connection between maternal stress, preterm birth and maternal immune response.

3.3 Selection criteria

Inclusion criteria:

- Singleton pregnancy
- Gestational age calculated by ultrasound scanning.
- Maternal serum cytokine levels during pregnancy in relation to pregnancy outcome recorded as gestation at delivery.
- Maternal serum cytokine levels during pregnancy in relation to stress, anxiety or depression.
- Validated measurement of stress, anxiety or depression during pregnancy in relation to pregnancy outcome recorded as gestation at delivery.
- Validated measurement of stress, anxiety or depression during pregnancy in relation to immunological response during pregnancy
- Investigation of stress, anxiety or depression in relation to maternal serum cytokine levels and pregnancy outcome recorded as gestation at delivery.

Exclusion criteria:

- Investigations of cytokines in other maternal specimens for example; amniotic fluid, cervical mucus, placental tissue.
- Elective preterm delivery for maternal or fetal complications during pregnancy for example; intrauterine growth retardation, pre-eclampsia, diabetes, antepartum haemorrhage.
- Multiple pregnancies.
- Outcome not measured as gestational age at delivery.
- Non-validated measure of stress, anxiety or depression
- Gestational age not calculated by ultrasound scanning.

3.3.1 Type of studies

All eligible English and non-English studies were identified and included; cohort studies (retrospective and prospective), case-control and cross-sectional studies.

3.3.2 Type of participants

Studies of female adults, aged between 18 and 45 years, with a singleton pregnancy.

3.3.3 Type of outcomes

The main outcome measured being spontaneous preterm delivery (before 37 completed weeks) of a single baby.

3.4 Search strategy

The strategy was to search electronic databases with help from an independent information retrieval expert (LH). Searches were carried out in 2006, 2008 and 2010. Identifying papers involved a variety of other techniques carried out solely by the researcher (LW). Citation tracking (following up reference list in the bibliographies of papers and reports), hand searching midwifery journals which included; MIDIRS midwifery digest, the British Journal of Midwifery, Midwifery, Midwives (the RCM Journal) and Evidence Based Midwifery (RCM) and utilising web-sites for example the DOH.

The electronic databases and search dates included:

- Medline via OVID from 1966 to 2010, CINAHL, the cumulative Index to Nursing and Allied Health Literature via OVID from 1982 to 2010
- EMBASE via Dialog/Datastar from 1974 to 2010
- The Cochrane Library for 2006, 2008, 2010.

A reference list for each database was compiled of papers of interest. These lists were then searched for duplicate information and a definitive search list generated.

3.4.1 Search filter

The Observational Studies search filter used by SIGN has been developed by the Cochrane office Liverpool University, to retrieve studies most likely to meet SIGN's methodological criteria (http://www.sign.ac.uk/methodology/filters.html£obs)

3.4.2 MEDLINE via OVID (1996 to 2010)

1. exp Obstetric Labor, Premature/
2. ((preterm or premature) adj3 (labor or labour or birth or childbirth)).ti,ab.
3. 1 or 2
4. cytokines$.mp. or exp Cytokines/
5. 3 and 4
6. Epidemiologic studies/
7. exp case control studies/
8. Case control.t.w.
9. (cohort adj (study or studies)).t.w.
10. Cohort analy$.t.w.
11. (Follow up adj (study or studies)).t.w.
12. (observational adj (study or studies)).t.w.
13. Longitudinal.t.w.
14. Retrospective.t.w.
15. Cross sectional.t.w.
16. Cross-sectional studies/
17. or/6-16
18. 5 and 17
19 exp Stress/

20 exp Stress, psychological/

21 19 or 20

22 21 and 3 and 17

23 22 or 18

exp = 'explode' MeSH (Medical Subject Heading) – to pick up all other terms indexed under the main term in the MeSH tree

ti = title

ab = abstract

tw = text word

mp = title, subject heading word, abstract, instrumentation

$ = truncation symbol

3.4.3 CINAHL - Cumulative Index to Nursing and Allied Health Literature via OVID

(1982 to 2010)

1. exp Labor, Premature/
2. ((preterm or premature) adj3 (labor or labour or birth or childbirth)).ti,ab. (1314)
3. 1 or 2
4. cytokine$.m.p. or exp Cytokines/
5. 3 and 4
6. Prospective studies/
7. exp case control studies/
8. Correlational studies/
9. Nonconcurrent prospective studies/

10. Cross sectional studies/

11. (cohort adj (study or studies)).tw.

12. (observational adj (study or studies)).tw.

13. or/6-12

14. 13 and 5

15 exp Stress/

16 exp Stress, psychological/

17 15 or 16

18 17 and 3 and 13

19 1 4 or 18

exp = 'explode' MeSH (Medical Subject Heading) – to pick up all other terms indexed under the main term in the MeSH tree

ti = title

ab = abstract

tw = text word

mp = title, subject heading word, abstract, instrumentation

$ = truncation symbol

3.4.4 **EMBASE via Dialog/Datastar** (1974 to 2010)

1. PREMATURE-LABOR#DE.

2. ((PRETERM OR PREMATURE) WITH (LABOUR OR LABOR OR BIRTH OR CHILDBIRTH)).TI,AB.

3. CYTOKINE#.W..DE.

4. (CYTOKINE OR CYTOKINES).TI,AB.

5. 1 OR 2
6. 3 OR 4
7. 5 AND 6
8. CLINICAL-STUDY.DE.
9. CASE-CONTROL-STUDY.DE.
10. FAMILY-STUDY.DE.
11. LONGITUDINAL-STUDY.DE.
12. RETROSPECTIVE-STUDY.DE.
13. PROSPECTIVE-STUDY.DE.
14. RANDOMIZED-CONTROLLED-TRIAL.DE.
15. 13 NOT 14
16. COHORT-ANALYSIS.DE.
17. COHORT ADJ STUDY OR COHORT ADJ STUDIES
18. (CASE ADJ CONTROL ADJ STUDY). TI,AB.
19. (CASE ADJ CONTROL ADJ STUDIES
20. (FOLLOW ADJ UP ADJ (STUDY OR STUDIES)).TI,AB.
21. (OBSERVATIONAL ADJ (STUDY OR STUDIES)) .TI,AB.
22. (EPIDEMIOLOGIC$ ADJ (STUDIES OR STUDY)). TI,AB.
23. 8 OR 9 OR 10 OR 11 OR 12 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. 7 AND 23
25. STRESS#.W..DE
26. 25 AND 23 AND 5

27. 26 OR 24

WITH = in the same sentence

ADJ = next to

TI = title

AB = abstract

DE = EMTREE (EMBASE Subject Heading) term

= main EMTREE term is 'exploded' to pick up all terms below it in the tree

3.4.5 CENTRAL in the Cochrane Library (2006, 2008, 2010)

#1 MeSH descriptor Premature Birth explode all trees in MeSH product

#2 (preterm or premature) near (labor or labour or birth or childbirth) in All Fields in all Products

#3 MeSH descriptor Labor, Premature explode all trees in MeSH products

#4 MeSH descriptor Cytokines explode all trees in MeSH products

#5 cytokine* in All Fields in all products

#6 (=1 OR =2 OR =3)

#7 (=4 OR =5)

#8 (=6 AND =7)

#9 MeSH descriptor Stress explode all trees in MeSH products

#10 MeSH descriptor Stress, psychological explode all trees in MeSH products

#11 (#9 OR #10)

#12 (#11 AND #6)

#13 (#8 OR #12)

Near = within 6 words

* = truncation symbol

3.5 Methods of review

Papers were rejected on initial screening where the reviewer could not determine from the title and abstract whether the article involved pregnant women or that the outcome was preterm birth. When the title or abstract could not be rejected with certainty, the full text article was obtained for further evaluation. Full-text translations of all relevant English and non-English papers were undertaken. All abstracts, case reports, letters, editorials and reviews were excluded. Only published papers were reviewed and no authors were contacted.

3.5.1 *Critical appraisal of studies*

The inclusion of studies was assessed independently by two reviewers (LW and SQ) using a third reviewer where conflict arose (GL).

3.5.2 Data extraction

An Excel data extraction table was designed specifically for this review using headings for the identification of relevant information by two reviewers (LW and SQ). Studies were selected in a reproducible and objective fashion.

3.5.3 Dataset

Data included was recorded as; author; year; retrospective study; prospective study; singleton pregnancy; cytokines and gestation; cytokines and stress (validated tool); stress (validated tool) and gestation; stress (validated tool) and immune response; stress (validated tool) and anxiety and cytokines; number of women in study; meta-analysis (yes or no); meaning of the study; preterm labour; preterm birth; comments.

Data excluded was recorded as; author; year; reason for exclusion.

3.6 Results

Three electronic searches conducted in 2006, 2008 and 2010 yielded 1022 papers. Central identified 216 papers of which 1 paper was eligible. CINHAL identified 119 papers of which 6 papers were eligible. EMBASE identified 346 papers of which 26 papers were eligible.

MEDLINE identified 341 papers of which 12 papers were eligible. Therefore 45 papers from the electronic searches were assessed for this review. Hand-_searching yielded 33 papers. This included 1 abstract and 20 review articles leaving 12 papers of interest. In total 57 papers were assessed of these (18) + 5 = 23 were included and (30) + 4 = 34 excluded.

Chapter 4

4. LITERATURE REVIEW AND META-SYNTHESIS OF STUDIES

4.1 Introduction

This chapter presents an appraisal of the literature that informed the prospective observational study, beginning with a description of observational methodology and the principles of systematic reviews. The review focussed on observational studies, outlined in the dataset in Chapter 3 (3.5.3) as the focus for the SIP study was based on observational methodology and the principles of whether an observed relationship is likely to be causal. The chapter goes on to present an overview of the literature relating to maternal stress, anxiety and depression during pregnancy, maternal immune response and preterm labour and birth. During a preliminary search an alternative model was identified from a psychoneuroimmunological perspective which speculates about the role cytokines play in the mediation of depressive symptoms allowing an alternative model of causation to be explored. Both models are presented as a schematic representation of the mediation / moderation of stress in relation to cytokines and PTL, followed by a brief discussion of the difference between these terms and culminating in the use of mediation as the term most suitable for the model.

The chapter continues with a brief discussion about meta-analysis in relation to observational studies using the approach from Randomised Control Trials and goes on to discuss meta-synthesis, using the approach from qualitative literature. Meta-analysis of the papers was not possible within this review therefore meta-synthesis was explored as a means of pooling and analysing the evidence investigating the hypothesis that stress is associated with preterm birth. The chapter presents the Bradford-Hill (BH) criteria, which have been used widely within different disciplines as a tool for the assessment of biomedical causation and in epidemiological studies in particular to assess the causal nature of an observed association. Within this midwifery study, the criteria were used as framework to synthesise the included papers. Excluded papers and reasons for exclusion are presented separately and the chapter concludes with a discussion about the quality of included studies and the limitations of the

review. This review of studies was conducted using three extensive and comprehensive literature searches which included searching a range of electronic databases and hand-searching, reflecting the state of knowledge at the time of the searches as outlined in the search strategy in Chapter 3 (3.4).

4.2 Observational methodology and systematic reviews

Observational studies can be defined as aetiologic or effectiveness studies using data from existing databases, cross-sectional studies, case series, case control, designs with historical controls or cohort studies. Within the hierarchy of study design and in contrast to RCT's, observational studies are often viewed as having less validity, since the potential for biases known to afflict such studies could obscure, inflate or even reverse the real effects of treatment. That is the results may have arisen as a result of chance, bias, reverse causality, or confounding (Bowling and Ebrahim 2005). Observational designs lack the experimental element of random allocation to an intervention such as RCT's and rely on studies of association between changes or differences in a characteristic and the changes or differences in the outcome of interest. Observational methodology involves the investigator collecting data on factors (exposures) associated with the occurrence of the outcome or interest, without attempting to alter the exposure status.

Case-control and cohort studies are the two most commonly used designs within observational methodology, with the former, choosing study groups on the basis of their disease or outcome of interest and the latter by using comparison groups identified according to an exposure of interest (Stroup et al., 2000). Cross-sectional studies (prevalence studies) describe the health of populations, ecological studies describe observations on groups of people and case-series describes outcomes in a single group (Bowling and Ebrahim 2005). Observational studies tend to produce large numbers of seemingly plausible associations and are described as studies in which natural variation in interventions (or exposure) among study participants are investigated to explore the effect of the interventions (or exposure) on health outcome (Deeks et al., 2003).

Some authors broadly classify observational studies as either descriptive, presenting the occurrence and distribution of an outcome or analytic, which test hypotheses about disease causation. Analytic studies usually demand the use of controls (exposed versus unexposed or case versus control) whereas descriptive studies do not. Sometimes the distinction is not always clear with descriptive data used to generate and explore hypotheses and analytic studies containing descriptive data (Bowling and Ebrahim 2005).

Systematic reviews of evidence are designed to overcome the deficiencies of subjectivity, selectivity and timeliness. For many interventions the evidence base is relatively weak to inform practice and systematic meta-analysis may provide a useful summary estimate. The combination of results from different centres may also improve the generalizability of their findings and often inform research priorities highlighting the lack of available evidence in a particular area (Cullinan 2005).

The systematic review of studies is guided by the principle that the protocol should be written in advance, a complete literature search should be carried out and studies are selected in a reproducible and objective manner (Egger et al., 1998). The results of quality assessment can be used in a systematic review in several ways, including forming inclusion criteria for the review or primary analysis; informing a sensitivity analysis or meta-regression; weighting studies; or highlighting areas of methodological quality poorly addressed by the included studies and the impact of this on the review's conclusions (Deeks et al., 2003).

4.3 Dataset

An Excel data extraction table was designed specifically for this review using headings for the identification of relevant information by two reviewers (LW and SQ) as outlined in Chapter 3 (3.5.3). Studies were selected in a reproducible and objective fashion. In total 57 papers were assessed for the review of these 22 were included and 35 excluded.

4.4 Included studies

Included studies were conducted between 1979 and 2010, with a total of 9,966,962 women and from eight different countries (USA, UK, Jerusalem, Denmark, China, France, Sri Lanka, Canada).

Data extraction was conducted through the interpretation of the main findings in each paper. Table headings included bibliographic information, age, study type, population, year of study, antenatal or postnatal sample, hospital, type of sampling, risk group (high or low for PTL) and the tools used. Headings for the BH criteria included strength of association, consistency and biological gradient only and are described as yes or no or non-applicable (N/A). The remaining criteria are discussed within the body of the text together with a description of the papers which fitted into each criteria.

Reviewing the studies uncovered a range of quality, a lack of information needed to assess the study quality, a mixture of tools used and in some papers there was difficulty in identifying the statistical methods use. The results were reported in such a heterogeneous way that formal statistical meta-analysis was not possible. Hence a meta-synthesis was performed whereby the main findings were tabulated then analysed using the BH criteria. Included papers are presented in Table 1.

4.5 Excluded studies

Studies (n=35) were excluded for a variety of reasons and are presented with the reasons for exclusion in Table 2.

4.6 Models

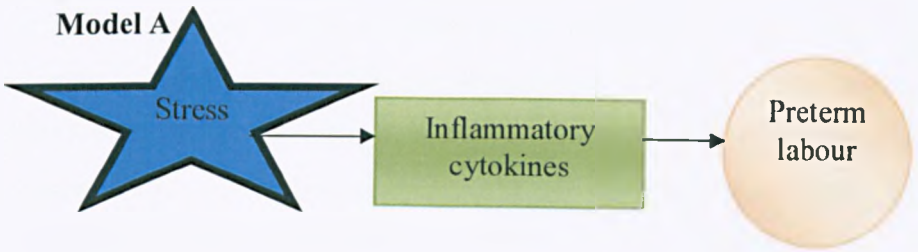
The literature search identified an alternative model from a psychoneuroimmunological perspective which questions the exact role of cytokines in the mediation / moderation of depressive symptoms. The question whether cytokines are causally involved in the aetiology of depression or represent immunological side effects of this disease remains unsolved (Schiepers et al., 2005) allowing an alternative model of causation to be explored. It remains unclear whether stress causes preterm birth or whether women who have high levels of pro-inflammatory cytokines are more stressed and therefore more prone to preterm birth. Two

models were generated in order to summarise the current literature. These two models enabled the generation of a specific testable hypotheses regarding the role of stress in disease mediation or moderation. In an attempt to clarify the situation a path diagram for each model was used depicting a causal chain. Path diagrams can be used as both descriptive and analytic procedures and show the stressor as the independent variable and the dependent variable is the outcome PTL.

The original hypothesis was:
Is psychological stress a mediator / moderator of the maternal immune system activation in preterm birth?

Figure 3 (4.6)

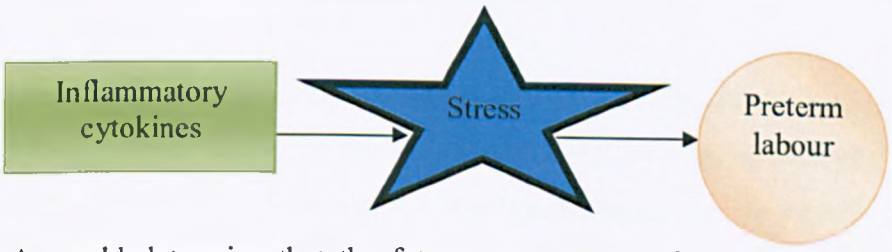
Model A



The alternative model could be:
Is the maternal immune system activation a mediator / moderator of psychological stress in preterm birth?

Figure 4 (4.6)

Model B



Model A would determine that the future management of women with a past history of preterm labour would include an assessment of stress in the antenatal period. Randomised

control trials (RCT) of methods to decrease stress such as psychotherapy may be used to assess the possibility of preventing preterm labour.

Model B would determine that future management should be aimed at identifying women who secrete high levels of pro-inflammatory cytokines and designing an RCT of novel pharmaceutical agents to reduce levels of pro-inflammatory cytokines before or during pregnancy.

If future research is based on the wrong model, not only will it show no benefit it may also have the potential to cause patients harm. For example giving anti-inflammatory agents to women whose major problem is stress could put women at risk of the side effects of the agents without treating the underlying disorder, or counselling women to decrease their anxiety and depression would be ineffective if the cause is high cytokine levels. Therapeutic interventions designed to modify psychological morbidity in those women at high risk of preterm labour may reduce the incidence of preterm labour as antidepressant administration is associated with a reduction in cytokine levels (Schiepers et al 2005). This may provide a novel, nonetheless controversial way to reduce recurrent preterm births in a very high risk population.

4.6.1 Moderator / Mediator

In general terms a moderator is a qualitative or quantitative variable that affects the direction and / or the strength of the relation between an independent (predictor) variable and a dependent (criterion) variable. Within this framework moderation implies that the causal relationship between two variables changes as a function of the moderator variable.

A variable may be said to function as a mediator to the extent that it accounts for the relation between the predictor and the criterion. Mediators explain how external physical events take on internal psychological significance, whereas moderators specify when certain effects will hold. Mediation is used when there is a strong relation between the predictor and the criterion variable. Mediators speak how or why such effects occur however, it is not uncommon for

these terms to be used interchangeably (Barron and Kenny 1986). Therefore within the original hypothesis, stress is a mediator of PTL.

4.7 Meta-analysis

Meta-analysis is a systematic approach to identify, appraise, synthesize and if appropriate combine results of relevant studies that have examined the same intervention through the same or similar dependent variables to be summarized statistically. This transforms the literature review from a purely subjective narrative into a more objective, "statistical" category to arrive at a conclusion about a body of research (Mulrow 1995, Stroup et al., 2000). In order to make research information more manageable, systematic reviews are required to synthesize the results and provide a basis for rational decision-making and it is undisputed that there is a value in combining the findings of Randomised Control Trials (RCT's) to establish best evidence for practise and guidelines.

Meta-analysis of RCT's is based on the assumption that each trial provides an unbiased estimate of the effect of an experimental treatment and the variables attributed to random variation. RCT's provide the best evidence of the efficacy of medical interventions however they are not immune to bias. Quality of trials is relevant to meta-analysis and flawed raw material will make flawed conclusions (Juni et al., 1999). The overall effect calculated should provide an essentially unbiased estimate of the treatment effect.

The Cochrane handbook (Higgins and Green 2006) is recognised as the authoritative guide on the techniques for systematic reviews and meta-analysis of RCT's by using standard criteria for the quality of studies which can be included. Originally meta-analysis was restricted to RCT's and is still preferred to meta-analysis of observational studies as these studies present particular challenges because of inherent biases and differences in study design. The numbers of published meta-analyses concerning observational studies has nevertheless increased substantially and may provide a tool to understand and quantify sources of variability in results across studies (Stroup et al 2000). The use of checklists in evaluating and scoring observational studies has reduced the biases in traditional review publications.

Quality scoring for meta-analysis in observational studies is controversial as they may lack demonstrated validity and results may not be associated with quality (Stroup et al., 2000). The MOOSE group (Stroup et al., 2000) have proposed a reporting checklist of items for authors, researchers and readers which builds on similar activities used for RCT's and is presented in Appendix 1. This was used as a basis for assessing the papers for the review.

4.7.1 Meta-analysis of observational studies

Meta-analysis of observational studies can be susceptible to bias inherent within observational research. The fallibility of meta-analysis may be introduced by the process of locating and selecting studies, including publication bias, language bias and citation bias. Moreover, low methodological quality of component studies is a potential source of systematic error, making critical appraisal difficult (Juni et al., 1999). Furthermore, meta-analysis can distance readers from the original data and leave them dependent on the care (or lack of care) taken by the meta-analysts. Plausible but spurious reasons and differences found between groups can easily be generated.

Systematic worthwhile reviews should employ strategies to avoid bias however Stroup et al argue that the statistical combination of studies is rarely appropriate in observational research because of this (Stroup et al., 2000). A clearer distinction is needed between systematic reviews and meta-analysis to prevent the former being discredited by poor versions of the latter (Smith and Egger 1999).

In observational studies there are fundamental differences as the studies yield estimates of association that may deviate from true underlying relationships beyond chance, due to bias and confounding factors (Egger et al., 1998). The reporting of meta-analysis of observational studies recommend the assessment of confounding, study quality and heterogeneity to be clearly reported in the methods section of reviews but moreover that thorough specification of quality assessment can contribute to understanding some of the variations in the observational studies themselves (Deeks et al., 2003).

The sources of bias and heterogeneity can be hypothesized prior to analysis and confirmed by the analysis. The application of formal analytic methods to observational studies has been controversial because of potential bias in the original studies makes the calculation of a single summary estimate of effect of exposure potentially misleading. The diversity of study designs and populations makes interpretation problematic when combining results.

The pressure for informed decisions within health care and the increase in research results has seen a corresponding increase in the need for results to be synthesized and analysed in order to answer urgent questions. In many research situations RCT's are not feasible and data from observational studies are necessary, however the key components of the design of a study may be much more important than the aggregate scores. Meta-analyses are themselves observational studies even when applied to RCT's and standards of reporting must be maintained to allow the proper evaluation of quality and completeness of any meta-analyses.

4.8 Meta-synthesis

Meta-synthesis is an interpretative integration of research findings which requires researchers to reintegrate all the results to realise a new interpretation of a phenomena. The aim of meta-synthesis within qualitative methodology is to create an innovative and integrative interpretation of research findings that is more substantive than those revealed by individual investigations (Meadows-Oliver 2007). This process enlarges the interpretive possibilities of data and involves the evaluation of the primary research paper with an emphasis on research design and data collection methods. By ensuring papers meet the review's inclusion criteria, by extracting and collecting data in a systematic way in order to categorise and synthesise.

Debates about meta-synthesis within qualitative literature are based on the philosophical position of the authors. However the importance of methodological rigour, the quality of the studies to be included and the analytical approach employed are recognised as in all other methodologies (Downe 2008).

Meta-synthesis enlarges the interpretive possibilities of data and differs from secondary analyses in that the former uses the findings of published research as data and the latter uses

raw data collected by original researchers to re-examine an issue under study. Within all research methodologies, synthesizing data of existing studies is necessary to enhance the generalizability of research results.

A meta-synthesis can represent a discrete and distinct approach to new inquiry based on critical re-interpretation of existing studies. It creates a process by which the nature of re-interpretation is explicit and meanings that extend well beyond those presented in existing studies are distilled (Reid et al., 2009).

4.8.1 Meta-synthesis of studies

There has been a great deal of observational research conducted that has examined the impact of stress and preterm birth, however within the literature search, there were no papers found which represented an analysis of those studies from a meta-perspective. After completing the literature review it was not possible to undertake a meta-analysis of the papers identified because of the lack of information needed to assess study quality, the mixture of tools used within studies and the difficulty in identifying which statistical methods were used in some papers. Moreover, results were reported in such a heterogeneous way that formal statistical meta-analysis was not possible, therefore the analytic strategy used was descriptive meta-synthesis (Downe 2008).

The aim of conducting a meta-synthesis of research results is to produce an integration of the findings from the studies, allowing a new interpretation of the results to be discovered. The new interpretation in turn enables the findings to have impact, by situating in a larger interpretive context and by presenting in an accessible and usable form (Sandelowski 1995).

The Bradford-Hill (BH) criteria have been used in different disciplines to review study results and there are many examples of the use of the criteria in an attempt to justify causal inferences. One example of their use is on the Website of the SV40 Cancer Foundation where there is a presentation of results of papers published in peer-reviewed medical literature to the nine BH criteria in respect to medulloblastoma and other brain cancers in order to demonstrate the casual efficacy of SV40 (Horwin 2010).

There are many more examples of applications of the BH criteria in academic journals covering many disciplines such; as determining whether asbestos causes mesothelioma (Lemen 2004); whether second generation antipsychotic drugs cause diabetes (Holt et al 2006); evaluating the effects of environmental carcinogens (Franco et al 2005); evaluating whether abuse experienced as a child or as an adolescent is causally related to urologic symptoms (Link et al 2007); reviewing the association of drug treatments and arrhythmias (Perrio et al 2007); the association between lung disease and walking in bracken (Wilson et al 1998); the role for genital ulcers as a risk factor for transmission of HIV (Dickerson et al 1996); a review of evidence supporting a causal link between dietary factors and heart disease Mente et al 2009); the relationship between the deployment-related issues and the evolution of the psychiatric condition post-traumatic stress disorder (McFarlane 2009) and the use of homeopathic treatment and the common cold (Davidson et al 2010).

This criteria is arguably the most commonly used method of interpreting scientific evidence in public health (Weed 2004).

Within this review, descriptive meta-synthesis was possible by using the recognised framework of the BH criteria which expressed the aim of the synthesis, to produce an integration of the findings from the studies, allowing a new interpretation of the results to be discovered. Each of the nine BH criteria: strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experimental evidence and analogy was applied to each paper and is presented in Table 1. The reviewers developed their own system for assessing the adequacy of the studies for meta-synthesis based on: the MOOSE guidelines as a guide for reviewing the quality of papers, the existing literature and the researcher's own experience regarding quality of observational studies. Each BH criteria was determined where possible by the statistical association presented within the results in each paper.

4.9 Bradford-Hill Criteria

Sir Austin Bradford-Hill a British medical statistician, and pioneer in epidemiology and randomised control trials, established nine widely used criteria in 1965, to determine the

strength of an association between a disease and its supposed causative agent. He asserted that the greater the Strength of Association the more likely it is causal. The estimate of the likelihood that the association is causal should be based on all nine criteria, with some criteria more useful than others. However, the weight of evidence that each single criterion contributes to the overall probability is not specified and is a matter of subjective interpretation. Hill did not intend the criteria to be used as a tick box, only as a guideline to the interpretation of results (Swaen et al 2009).

The meta-synthesis was conducted using the framework of Bradford-Hill (BH) to systematically review and synthesize observational literature identified on the subject of maternal stress and preterm birth.

These criteria have been used as a guideline to identify relationships within literature reviews and as a way of determining the causal link between a specific factor and a disease (Hofler 2005). Bradford-Hill's landmark paper outlined a systematic approach for using scientific judgement to infer causation from statistical associations observed in epidemiologic data (Phillips and Goodman 2004). Epidemiology deals with the characteristics of the human population and therefore is more an observational than experimental discipline and epidemiologists often have to infer causation without being able to bring objective proof.

Bradford-Hill criteria can be used for assessing whether an observed association involves a causal component or not. BH avoided defining explicitly what he meant by a causal effect and used the terms "viewpoints" and "features" to be considered when evaluating an association. His aim was to unravel the question: "what aspects of this association should we especially consider before deciding that the most likely interpretation of it is causation" and argued that none of the nine viewpoints could bring indisputable evidence for or against the cause and effect hypothesis (Hofler 2005).

The BH criteria outlines the minimal conditions needed to establish a causal relationship between two items and forms the basis of modern epidemiological research, which in turn

attempts to establish scientifically valid causal connections between potential disease agents and the many diseases that afflict humankind (Phillips and Goodman 2004).

Moreover, whilst the criteria were developed as a research tool in the medical sciences, they are equally applicable to sociology, anthropology and other social sciences, which attempt to establish a causal relationship among social phenomena (Phillips and Goodman 2004). It is widely acknowledge that the public health role within midwifery practise is influenced by the wider social context and therefore midwifery should also be included within this group who should identify and access this research tool. Indeed, the principles set by BH form the basis of evaluation used in all modern scientific research, by simply providing an additional valuable measure by which to evaluate the many theories and explanations proposed within the social sciences. Therefore the criteria seemed the most appropriate for use within the review for evaluating the evidence to determine whether stress is associated with preterm birth.

The cause of a disease is a condition, characteristic, event or a combination of factors which play an important role in producing the disease and logically, a cause must precede a disease and is sufficient when a disease cannot develop in its absence (Enock 2002). A sufficient cause is not usually a single factor, but often comprises of several components. Generally it is not necessary to identify all the components of a sufficient cause before effective prevention can take place and it can be hard to judge whether an association from an observational study is truly causal. The mnemonic ACCESS PTB: **A**nalogy, **C**onsistency, **C**oherence, **E**xperimental evidence, **S**trength of association, **S**pecificity, **P**lausibility of association, **T**emporal sequence of association, and **B**iological gradient (dose effect) can be useful as a guide for the use of Bradford-Hill criteria when reviewing papers (Enock 2002).

Finally, this review investigated literature describing maternal stress in pregnancy described as anxiety and / or depression as the causative agent and the outcome of preterm birth as the disease. The included papers were then synthesised using BH criteria to evaluate a possible cause and effect relationship within the studies reviewed. This conceptual model was deemed

to be the most appropriate framework to use for the meta-synthesis because of the overall aim, to examine the relationship between maternal stress and preterm birth.

Moreover, the review was conducted by assessing whether papers fitted the association theory of Bradford-Hill, by the researchers asking questions such as:

- Is the association with stress and PTB strong?
- Are there clearly defined groups of women identified within the papers?
- Were the cases and clinical outcomes measured in the same way within the groups?
- Was the assessment of outcomes objective?
- Is the association consistent from study to study?
- Is the temporal relationship appropriate?
- Is the temporal sequence of exposure and outcome in the same direction?
- Is there a dose response gradient?
- Does the association make biological and epidemiologic sense?
- Are the papers in the review in agreement with current understanding?
- Is the association analogous to a previously proven causal association?

Once the papers had been assessed by two reviewers (LW, SQ), they were grouped together based on the statistical evidence presented within the results section and then fitted to each criteria.

4.9.1 Analogy

This approach takes the form of thinking that if some conditions similar to "A" cause an outcome similar to "B" then this is evidence that "A" causes "B" (Van Reekum 2001). Bradford-Hill suggested that it would be sometimes acceptable to judge by analogy and gave the following example; "with the effects of thalidomide and rubella, we would be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy." Therefore for analogous exposures and outcomes an effect has already been shown (Hofler 2005).

Within the review all papers were found to meet the inclusion criteria for examining stress and PTB as supported in the literature. Therefore all papers met the criteria for analogy, because there is evidence to support that the physiological reaction to stress has been associated with physical illness and problems in pregnancy.

4.9.2 Consistency

Consistency among different studies can act as a substitute for replication. This criterion requires that similar results be obtained in many studies with different analytical strategies and is based on the principle that different approaches should yield similar results (Elder et al., 1997). Consistency is when a relationship is observed repeatedly in different populations, people, places, circumstances and time. For example if childhood leukaemia is associated with nuclear reprocessing plants, there should be excesses of the disease in more than one plant observed. Consistently finding an association within different study designs (retrospective and prospective) reduces the probability that an association can be due to a constant error in the same study design (Hofler 2005) and therefore strengthens the case.

Good consistency was found in two papers where the results were consistent within different populations in both black and white women (Berkowitz and Kasl 1983) and places, in both Hull and Manchester (Newton et al 1979) No consistency was found in seven 11 studies. Lobel et al (1992) found the risk of PTL in one group only, Perkins et al (1993) only in low risk women, Peacock et al (1995) in high risk groups and black women, Jesse et al (2002) found low self esteem and not stress was consistent, Dayan et al (2002) only women with low BMI and a past history of PTL, Copper et al (1996) and Misra et al (2001) only found in high risk groups. In the remainder of papers consistency was not found as women were described as one population.

Overall there was a consistent finding of a positive effect between stress and PTB within high-risk groups, however socially deprived women were found to be consistently high risk of PTL.

4.9.3 Coherence

This is similar to the biologic plausibility rationale criterion. Coherence is generally accepted when there is an absence of conflict with other knowledge and a causal conclusion should not fundamentally contradict present substantive knowledge. Bradford-Hill's usage of the term "generally known facts" indicates that the knowledge against which an association is evaluated has to be indisputable (Hofler 2005). The relevance of this criterion depends largely on the amount of knowledge that is known at this moment in time and as with biologic plausibility if the criterion is met it is supportive of an argument of causation and if not, it may be because there is not enough known yet or what is known needs to revisited (Van Reekum et al., 2001). An association therefore would underline a causal conclusion and help to identify the causal agent, for example lung cancer trends over time are what would be expected knowing about the changes in smoking behaviour within the population.

Coherence was met with all the papers in the review as there is evidence and a common acceptance that there is an increase in life stresses in general in the western world.

4.9.4 Experiment

Experimental evidence is the most compelling criterion. Bradford-Hill argued that a causal interpretation of an association from a non-experimental study was supported if a randomised prevention derived from the association confirmed the findings. For instance, after finding that certain events were related to the number of people smoking, one might forbid smoking to see whether the frequency of the events decrease consecutively (Hofler 2005).

Causation is more likely if evidence is based on randomised experiments, however it is not always ethical to conduct experiments for all research. To induce stress in humans for experimental reasons in an attempt to link the outcome of PTL would not be possible therefore a direct evidence of causality will be lacking. There is evidence of an association between PTL and stress and that this association is likely to be causal in origin. This cannot however be taken to indicate that stress is the cause of PTL in all cases.

There was only evidence from human studies analysed for this review however there is a strong body of animal and laboratory evidence as discussed in earlier chapters which supports that stress causes early parturition.

4.9.5 Strength of association

A strong association is more likely to have a causal component than a modest association for example Bradford-Hill found that the death rate from lung cancer was more common in people who smoke (over nine times) than in non-smokers, with the stronger the association between two phenomena, the higher the likelihood of there being a causal relationship (Hofler 2005). The strength of association is the function of the relative risk (RR) or odds ratio (OR) and a RR or OR of more than 2 is generally considered supportive of a strong association. Other methods for assessing the strength of association include correlation coefficient, the regression coefficient and the proportion of the variance accounted for by a variable or a subset of variables (Elder et al 1997). One way of assessing the strength of association is to question whether the removal of a factor decreases or prevents the presumed outcome and can be the most powerful criteria for showing causality.

The strength association was measured in various ways. The majority of papers (n=9) using OR or RR (n=6) standard regression co-efficient in one (Lobel et al 1992) and adjusted mean in another (Omer et al 1983). Other papers (n=9) were difficult to identify within the results section which method was used (Rich-Edwards et al 2005, Whitehead et al 2002, Peacock et al 1995, Omer (3) et al 1983) with the authors stating whether or not an association had been found.

A positive association was found in only five papers, two on the basis of the RR (Newton et al 1979, Dole et al 2003), two (Berkowitz et al 1983, Zhu et al 2010) with OR and one with standard regression co-efficient (Lobel et al 1992). A negative association was found in 15 papers (Omer (3) et al 1986, Perkins et al 1993, Henrickson et al 1994, Peacock et al 1995, Copper et al 1996, Misra et al 2001, Chung et al 2001, Jesse et al 2002, Rich-Edwards et al 2005, Ruiz et al 2001, Dayan et al 2002, Messer et al 2005), Harville et al 2009, Kramer et al

2009, Abeysema et al 2010. Whitehead et al (2002) used a threshold model for analysis therefore no OR nor RR were identified.

Five papers found an association in different groups within the same study. Peacock et al (1995) for the low social class women, smokers and those with trouble with their nerves but not in the low risk population of women; Dayan et al (2002) only in those with a low BMI or with a past history of PTL but not in the group described as low risk (with anxiety and depression); Jesse et al (2002) for depression but not for stress; Dole et al (2003) for pregnancy related anxiety but not for life events, Zhu et al (2010) for low income, younger women and low educational attainment.

Overall four (five) papers found a positive association which included a total of 3,337 (5137) women. Twelve (16) papers found a negative association and these included 15,461(18,174) women. Four papers found both negative and positive associations in the same studies. Is the strength of association strong? Within this review, the overall conclusion was that a weak association between stress and PTB had been found.

4.9.6 Specificity

This criterion describes the precision with which the occurrence of one phenomenon predicts the occurrence of another. The ideal is a one to one relationship, where a cause is both necessary and sufficient (Elder et al 1997). Specificity of association is complete when one manifestation follows from only one cause, giving strong evidence of cause and effect. However this criterion does not hold for example in infectious diseases, in which multiple pathogens may produce a number of outcomes (Van Reekum et al 2001). One factor influencing a particular population would be novel in the study of preterm birth however, this type of specificity is not met in preterm labour (PTL) because preterm delivery can and does occur without a known cause. Moreover, PTL is thought to be a multi-factorial disorder making it very unlikely that there is a single cause such as stress. Therefore the specificity within the relationship between stress and PTL is incomplete as PTL is described as a syndrome and stress may only be one of its possible causes.

4.9.7 Plausibility

Is the cause-effect plausible? Bradford-Hill proposed that the presence of a biological explanation supported the drawing of a causal conclusion. The observed association can be plausibly explained by substantive matter such as a biological explanations, meaning there is a greater likelihood of a causative relationship being present if it makes biological sense (Hofler 2005). A biologic rationale is necessary for the establishment of an argument for causation, for example, the association between genitourinary tract infections or multiple pregnancy with the risk of PTL could be used to demonstrate biological plausibility. However, BH did warn that what is considered plausible, changes with time for example, in the 19th century it was thought totally implausible that doctors not washing their hands could be responsible for the deaths of women on maternity wards.

The hypothesis that stress increases maternal immune response, which then acts as a mediator for PTL was not supported by the meta-synthesis. However, an untested but plausible hypothesis has been stated in the literature of stress causing high cortisol levels and triggering the onset of labour.

4.9.8 Temporality

"Which is the cart and which is the horse?" (Hofler 2005). Temporality (relationship in time) is where the factor must precede the outcome it is assumed to affect. For the relationship to be causal, the proposed causal effect must precede the effect (Elder et al 1997). As with all health-related research, the only way to be certain about temporal sequence is to conduct prospective studies. However the presence of the outcome of interest in some of the subjects prior to the onset of the causative agent does not necessarily invalidate the establishment of a temporal sequence (Van Reekum et al 2001). BH used the example of whether a particular diet triggered a certain disease or whether the disease led to subsequently altered dietary habits (Hofler 2005).

Within the papers reviewed, the temporal sequence of exposure to stress and outcome of PTL must be in the same direction, stress must precede the outcome of PTL. Although this

criterion might seem obvious at first the sequence of events is not easy to determine in clinical practice, but it is a question that should be asked.

All papers reviewed were included because they examined stress prior to the onset of PTL therefore the temporal association within the meta-synthesis was good.

4.9.9 Biological gradient

Bradford-Hill favoured linear relationships between exposure level and outcome, for instance, between the number of cigarettes smoked per day and the death rate from cancer (Hofler 2005). This criterion refers to the plausibility between the postulated cause and the effect as in biological plausibility (dose response). The likelihood of a causal relationship is increased if a dose response gradient can be demonstrated and if this can be demonstrated, the next question should be whether there is a dose-response gradient. For example, the level of stress women experience in pregnancy, i.e. the severity and the likelihood of PTL. If stress levels are higher or if women have more life events with PTL than women with low stress scores of fewer life events, this would exhibit a clear dose response. An important criterion supporting causality of association is the demonstration of a dose response relationship.

Five studies (Newton et al 1979, Berkowitz and Kasl 1983, Lobel et al 1992, Dole et al 2003, Zhu et al 2010) fitted the biological gradient (dose response) with studies finding that the more life events women experienced the more likely they were to have a PTB.

4.10 Quality of included studies

The overall quality of the studies was highly variable. An appraisal of the quality of all included studies was undertaken using a quality assessment tool specifically designed for the review. The strength of this review is its comprehensive coverage and assessment of the quality of the studies in order to conduct a meta-synthesis and meet Bradford-Hill criteria.

4.11 Limitations

Despite rigorous methods, the review was subject to a number of limitations. The search strategy was limited to the databases searched and the search terms identify a large number of

studies (n=640) mostly animal and laboratory papers. Appraisal of the abstracts did not always identify those papers to be non-human and the full texts were retrieved. It is possible that key papers may have been missed.

The review did not trace any unpublished studies and felt unable to contact some researchers to obtain missing data due to the age of the studies, therefore relied on the information reported in the articles. In some cases reporting was unclear regarding factors relating to study quality, provision of actual numbers and details of statistical analyses. In general the review has reported unclear issues as a negative association, rather than making assumptions. The strength of the review could be greatly improved if it were possible to contact all researchers and obtain summary or even individual person data on outcome exposure and potential confounders. This was not possible within the timeframe and was thought to be impractical and unnecessary within the context of the review.

4.12 Conclusion

This meta-synthesis illustrates the potential value of applying rigorous criteria to the establishment of arguments of causation in relation to stress and preterm birth. It is hoped that this review and meta-synthesis will facilitate and encourage the use of these or similar criterion within midwifery and in so doing allow midwives to be more certain in the strengths and the limits of their arguments of causation. Considering these criteria, and using research options increasingly available to midwives to address them, will potentially allow for improved research planning and methodology in studies of causation within the public health focus in midwifery.

The findings from the review emphasises the limited data available on the association between maternal stress and premature labour and birth. This review uncovered heterogeneity in the types of studies, psychological tools used and in the sampling methods. This in turn limited the choice of analysis and made the decision for meta-synthesis the only option to pool the data in order to explore associations.

Despite the major public health, economic and personal benefits associated with reducing preterm birth, reviewing the literature confirms that there is still little evaluation of the impact that stress and anxiety may have in determining whether a pregnancy continues to term. There is a scant amount of research that either focuses on pregnant women who have had a previous preterm birth as a distinct group, or gives clear unequivocal guidance in understanding the experiences of these women and the relationship of stress, anxiety or depression and the recurrence of PTB. This is a significant exclusion in the literature that the SIP Study hopes to address and it is against this background that the research question evolved.

The derived concepts using Bradford-Hill criteria presented here provides a theory of association between maternal stress and preterm birth from an observational perspective.

This systematic review and meta-synthesis of studies found that maternal stress is only associated with preterm labour in susceptible women. There is no clear definition in the literature about the level of susceptibility to stress which needs to be present before a woman is deemed to be at risk of preterm labour and birth.

Overall, the meta-synthesis of papers did not find a strong association within the papers and clearly therefore the Bradford-Hill criteria were not met.

Table 1 (4.1)

META-SYNTHESIS OF INCLUDED STUDIES (N=22)

Bibliographic information	Study type / evidence level / year	No. of women in study	Age	Stress / tools	Risk Group (PTB)	Strength of Association (PTB)	Consistency	Biological gradient (dose response)
Newton et al (1979) England	Random sample P/N NHS hosp in Hull & Manchester Year N/K	132 Term n=83 PTD n=30 VPTD n=19	14 – 38 Mean 25	Life Events A/N stress 3-4 days P/N	**Low** Mixed group	**Yes** RR=3 for life event in VPTL group	**Yes** Same in Hull & Manchester	**Yes** More life events - more likely to have PTL & VPTL
Berkowitz and Kasl (1983) USA	Random sample P/N Hospital Connecticut 1977	465 PTD n=166 Term n=299	N/K	Life events / Preg Desired/ Partner support. P/N Social readjust ment rating to measure A/N stress	**Low** Mixed group	**Yes** OR 2.12 with 5 or more life events in black & white women	**Yes** Both white and black women.	**Yes** More life events - more likely to have PTL
Omer et al (1) (1983) Jerusalem	Random sample P/N University Hospital Jerusalem 1983-84	113 PTL n=29 PTD n= 32 Term n=52 Jewish	PTD Mean age 28.9 CG Mean age 28.3	Life events / A/N stress. 6-9 months P/N	**Low** Mixed group	**No** Adjusted mean for PTL = 1.31 Adjusted mean for control = 1.41	**No** (only one population)	**No**
Omer et al (3) (1986) Jerusalem	Data from medical records P/N 4 hospitals Mainly Jewish Delivery outcomes 1973-74	5344 Dels	N/K	No stress Scores. Data from notes. Yon Kippur War - compare dels in Oct/Nov 1973 - Oct/Nov 1974	**Low** Mixed group	**No** Decreased number of PTB during the war compared to year after war	**No** (only one population)	**No**

Lobel et al (1992) USA	Consecutive sample A/N clinic University Hospital Los Angeles. 83 Latino 26 Afro/Am 16 Anglo/Am Low income Medicaid Means tested 1984-1987	130	18-42 Mean 28	Perceive stress scale. State anxiety. Life events. A/N & P/N x 1	**High** Low income Ethnic women	**Yes** Standardised regression coefficient =.23	**No** (only one population)	**Yes** More stress during preg more likely to have PTL
Perkins et al (1993) England	Consecutive sample White A/N DGH London Year N/K	1515	15-35	General health. Anx & dep scores.	**Low** Mixed group	**No** OR=0.99 for anx **No** OR=1.28 for dep	**No** Low risk women	**No**
Henrickson et al (1994) Denmark	Random Sample A/N Aarhus University Hospital Aug 1989– Sept 1991	3503 Women who work	<25 to >35	Self admin Question – A/N job strain	**Low** Mixed group of low stress & high stress jobs	**No** OR=1.3 in high strain jobs OR=1.4 in passive jobs	**No** (only one population)	**No**
Peacock et al (1995) England	Consecutive sample White A/N DGH London Aug 1982– Mar 1984	1513	15-35	General health questions Likert scale. Invent of life events. A/N	**Low** Mixed group	**No** In low risk group **Yes** In low social class, smokers, "trouble with nerves"	**No** Only in high risk groups, low social class, low education	**No**
Copper et al (1996) USA	Random sample A/N 10 medical centres, different geographical regions within the Maternal-Fetal Medicine Units Network Oct 1992-Jul 1994	2593	Mean 23	Psycho-social status scale	**Low** Mixed group 63% black 35% white 1% Hispan 1% Asian 1% other	**No** OR=1.16 with PTB	**No** Only in high risk group, black women	**No**

Misra et al (2001) USA	Women no A/N care Black Non-Hispanic Postnatal Urban University hospital Low income Feb 1995-June 1996	735	19-35	Prenatal Psycho-social Profile. Hassles Scale. Preg Beliefs Scale. Centre for Epidem Studies. Dep score on P/N ward	**High** Black low income women	**No** OR=1.92 Stress and PTD	**No** High risk women only	**No**
Ruiz (2001) USA	A/N 2 private practices central Texas Hispanic & Anglo-American Medicaid Year N/K	78	18-40	Perceive Stress Scale A/N	**Low** Mixed group	**No** RR=0.42 Reduction in stress correlated with length of gestation	**No** (only one population)	**No**
Chung et al (2001) China	Consecutive sample A/N University Regional Public Hospital Chinese Hong Kong Year N/K	959	17 – 40 Mean = 29	Beck Dep Invent A/N and 3 years P/N	**Low** Mixed group	**No** RR=0.23	**No** (only one population)	**No**
Whitehead et al (2002) USA	Random sample from P/N files 11 US states 1990-95	70,840	N/K	Preg risk monitor system P/N files	**Low** Mixed group	**No** Results from Threshold model only - shows increased risk of PTL with number of LE	**No** (only one population)	**No**

Jesse et a l (2002) USA	Convenience sample A/N 3 prenatal clinics Mainly rural Appalachian East Tennessee Year N/K	120	14 - 44	Bowman Gray Risk index. Kesner Index. Prenatal Psycho-social Profile. Daily Hassle Scale. Support Behav Invent. Self-Esteem Scale. Yale Task Force Geriatric assess. Abuse Assess	**High** Low income women	**No** RR=1.0 for stress **Yes** RR=3.8 for depression	**No** Stress not associated, symptoms of low self esteem were associated	**No**
Dayan et al (2002) France	Consecutive sample A/N University Hospital Caen French Oct 1997-Sept 1998	634	20 - 35	Spielberg State-Trait Anxiety Invent. Edin Dep Scale. A/N	**Low** Mixed group	**No** In low risk depressed or anxious **Yes** OR=6.9 If low BMI <19 **Yes** OR=4.8 *With H/O* PTL	**No** Only in women with low BMI & past history of PTL	**No**
Dole et al (2003) USA	Random sample A/N African-American North Carolina Mixed pop Nov 1996 - 00	1962	16 - 30	Life Exp Survey	**Low** Mixed group	**Yes** RR=2.1 with pregnancy related anxiety & PTB **No** RR=1.8 with life events & PTB	**No** (only one population)	**Yes** More stress during preg more likely to have PTL

Rich-Edwards et al (2005) USA	Matched cohort before & after 9/11 A/N Large medical practice Boston 1999 – 01	1790	Mean 32.5	Project Viva EDS A/N	**Low** Mixed group	**No** Lower risk of PTD	**No** (only one population)	**No**
Messer et al (2005) USA	Random sample A/N University Hospital North Carolina Nov 1996 – Feb 2001	1908	16-30	National Survey Family Growth Life Exp. Survey Ways of Coping. Centres for Epidem Study Dep Scale	**Low** Mixed group	**No** RR=1.7 In the highest quartile of life events & perceived stress	**No** (only one population)	**No**
Harville et al (2009) USA	Consecutive sample A/N from the Pregnancy, Infection & Nutrition Study (PIN) North Carolina 2001-04	1587	16-35	2 phone Interview Sarason Life Exp/Trait Anxiety Invent / Social Support/ John Henry Coping Scale	**Low** Mixed group	**No**	**No** (only one population)	**No**

Kramer et al (2009) Canada	Consecutive sample A/N from 4 Maternity Hosps Montreal 1999-04	251	20-35	Daily Hassles / Marital Strain/ Abuse assess/ Miller Intend Scale/ Arizona Social Support /Prenatal LE Scale/ Ros'berg Self Esteem/ Life Orienta'n Test/ Dep'n Scale	**Low** Mixed group	**No** OR=1.8 (pregnancy related anxiety & depression only)	**No** (only one population)	**No**
Abeysena et al (2010) Sri Lanka	Consecutive sample from 2 A/N clinics Sri Lanka May 2001-Apr 2002	855	26.4	GHQ/ LE Invent/	**Low** Mixed group	**No** **OR=1.8** (for life events only not stress)	**No** (only one population)	**No**
Zhu et al (2010) China	Consecutive sample from ANC at 2 hospitals Mar – Nov 200 China	1800	20-34	Life Event Scale/ Social Support Scale/ Coping Style Q	**Low** Mixed group	**Yes** OR= LE & stress **Yes** (Younger age-group RR 2.46) **Yes** (Lower education RR=2.76) **Yes** (Lower income RR=2.01)	**No** (only one population)	**Yes** More stress during preg more likely to have PTL

Table 2 (4.1)

EXCLUDED STUDIES (N=35)

Author / Country	Year	Reason for Exclusion
Norbeck JS and Tilden VP., USA	1983	Pregnancy complications only. Not PTL.
Omer H, Elizur Y., Barnea T., et al Israel	1986	Retrospective study comparing term & PTL women with psychopathological tendencies.
Freda MC., Anderson HF., Damus K., et al USA	1990	Lifestyle intervention study with women with a previous PTL
Green NL., USA	1991	Phd microfilm only. Not published. Stress scale used. Not validated questionnaire
Marzi M., Vigano A., Trabattoni D., et al Italy	1996	Small for gestational age babies only. Not PTD
Bergant AM., Reinstadler K., Monacayo HE., et al Austria	1997	Recurrent miscarriage only. No gestation at delivery recorded. Not PTD.
Brett KM., Stroatz DS., Savitz DA., USA	1997	High strain job compared to low strain job. No stress score measured.
Kaplan B., Shohat M., Royburt M., et al Israel	1997	Serum sampling taken in labour only. No stress score measured.
Mamelle N., Segueilla M., Munoz F., et al France	1998	Intervention study by talking to women already in PTL (translated from French)
McLean M., Smith R., UK	1998	Serum CRH & AFP only measured. No stress test.
Murtha AP., Greig PC., Jimmerson CE., et al ., USA	1998	Serum sampling only for IL-6. No stress test.
Alvarez-de-la-Rosa M., Rebollo FJ., Codoceo R., et al ., Spain	1999	Serum sampling for interleukins in labour only. No stress test.
Mackey MC., Coster-Schulz MA., Tiller CM., USA	1999	Qualitative Study. Women already in PTL. PTL experience.
Mackey MC., Williams CA., Tiller CM USA	2000	Retrospective study. Patients with history of PTL compared to control group. Daily hassles scale. Mood scale. No serum sampling.
Goldenberg RL., Iams JD., Mercer BM., et al., USA	2001	Repeat of other papers. Several maternal biological markers. No stress test.
Gucer F., Balkanli-Kaplan P., Yuksel M., et al ., Turkey	2001	Serum sampling for TNF-α only. Women already in PTL. No stress test.

Kramer MS., Goulet L., Seguin L., et al Canada	2001	Review and research proposal only.
Leung TN., Chung TKH., Madsen G., et al Hong Kong	2001	Serum sampling CRH only. No stress test.
Nowak M., Oszukowski P., Jaczewski B., et al., Poland	2001	Study related to infection & PTL only. (translated from Polish)
Petridou E., Salvanos H., Skalkidou A.,et al., Greece	2001	Retrospective study. Not validated stress questionnaire. Transient events only including coitus.
Thorsen P., Schendel DE., Deshpande AD., et al., Denmark	2001	Review and research proposal only.
Paternoster DM., Stella A., Gerace P., et al Italy	2002	Serum sampling only. No stress test.
Bahar AM., Ghalib HW., Moosa RA., et al Saudi Arabia	2003	Serum sampling only comparing women in PTL with term labour. No stress test.
Goldenberg RL., Iam JD., Mercer BM., et al., USA	2003	Multiple marker test for prediction of PTL. Retrospective & prospective. No stress test.
Rauchfub M., Gauger U., Germany	2003	Not validated stress questionnaire (translated from German)
Annells MF., Hart PH., Mullighan CG., et al ., Australia	2004	Serum sampling for genetic testing. No stress test.
Engels AM., Erichsen HC., Savitz DA., et al ., USA	2005	Serum sampling for genetic testing. No stress test.
Evans J., Heron J., Francomb H., et al UK	2005	Antenatal & postnatal depression measured. No stress test. Not PTL.
Sozmen S., Mungan T., Saygin D., et al Turkey	2005	Serum sampling in labour only. No stress test.
Renz H., Wilke C., Tekesin I., et al Germany	2006	Serum sampling in labour only. No stress test.
Curry AE., Vogel I., Skogstrand K et al USA	2008	Serum sampling only. No stress test
Gennaro S., Shults J., Garry DJ., USA	2008	Women already in PTL.
Vogel I., Goepfert AR., Thorsen P., et al USA	2007	Serum sampling only. Cervical measurements. No stress test
Grandi C., Gonzalez A., Naddeo S et al Argentina	2007	Stress test and coping strategies only. Not PTL
Whitcomb B., Schisterman E., Luo X et al USA	2008	Serum sampling only. No stress test

Chapter 5

5. RESEARCH METHODS FOR THE PROSPECTIVE OBSERVATIONAL STUDY

5.1 Introduction

This chapter will describe the methodology and tools used together with the rationale for their use. The chapter begins with a brief overview of qualitative and quantitative methodology and continues with a discussion supporting the value of mixed methods within research. The chapter goes on to present an outline of the procedures used for both the psychological tests and the laboratory work. A small cross-sectional study comparing HADS-A (anxiety) scores in low risk women without a history of a previous preterm birth as a comparison of anxiety levels with the high risk group in the SIP study is included. The SIP study and the focus of this thesis are based on the hypothesis:

"the maternal response to stress determines the risk of preterm delivery in women at high risk of preterm labour."

5.2 Aims and purpose of the study

To conduct a prospective observational study with a cohort of women aged 18 years to 45 years as a consecutive sample attending the Preterm Labour Antenatal Clinic (PTL). The preterm labour clinic is based in a tertiary referral centre with a mixed of population in both ethnic and socio-economic terms. Many of the women attending the clinic were referred from other healthcare providers outside of the geographical area. Within the study no attempt will be made to link economic deprivation or ethnicity to the statistical (SPSS) analysis as this information was collected through the routine booking history only and in so doing only minimal amount of information was collected. However this information will be examined and described as simple descriptive statistics of the routine baseline demographic information within the results discussion.

The purpose of the study was to:

- Measure maternal serum cytokine and hormone levels at two gestational periods in pregnancy.
- Measure maternal stress at two gestational periods in pregnancy using the Hospital Anxiety and Depression Scale (HADS) and the List of Threatening Experiences Questionnaire (LTE-Q).
- Explore women's responses to the LTE-Q as a qualitative study.
- Observe whether maternal immune state correlates with changes in psychological state.
- Observe whether changes in maternal immune or psychological state impact on clinical outcome.

5.3 Theoretical basis for methods used

The SIP study was conducted using both quantitative and qualitative methods. The ultimate aim was to develop a valid study with reliable and generalisable findings. Using both quantitative and qualitative approaches would achieve the strengths of both and generate a deeper insight and should be seen as an essential element within midwifery research. In order to meet the study aims, quantitative methodology will form the principle data collection with the additional, complimentary data from the qualitative study. In combining both quantitative and qualitative research an appreciation of the fundamental differences between the paradigms was necessary.

5.3.1 Quantitative

Quantitative research methods adopt a positivist ideology becoming predominant within health care research because of the need to predict the likely consequences of certain events. The basic belief system of positivism is rooted in realist ontology, the belief that there exists a reality out there, driven by immutable natural laws. The business of science is to discover the "true" nature of reality and how it "truly" works with the ultimate aim of science to predict and control natural phenomena (Guba 1990), by the use of experiments in tightly controlled conditions, with outcomes measured with high precision and findings carefully replicated (Bowling and Ebrahim 2005).

The epistemology of objectivism underpins the perspective of positivism by a commitment to objectivity, the view that characterises the researcher's primary role as that of onlooker, objectively observing events and looking for relations between them (Bowling 1997, Hicks 1998). The objectivist epistemology when applied to methodology places emphasis on testing hypothesis by deduction and providing concrete explanations. This approach requires quantification and involves the collection and collation of quantitative data (Dykes 2004).

The reliance of this scientific method is on data obtained through systematic empirical observation (Bowling 1997, Polit and Hungler 1997). Positivist approaches claim the label scientific for they assume things can be studied as hard facts and the relationship between these facts established as scientific laws (Smith 1998). This approach progresses from theory identified in a hypothesis to the empirical data collection and analysis, enabling the researcher to support or reject the initial hypothesis or theory.

5.3.2 Qualitative

Qualitative research accepts there is an array of different ways of making sense of the world and is concerned with discovering the meanings seen by those who are being researched and understanding their view of the world rather than that of the researchers (Jones 1995, Morgan 2004). Qualitative research such as the collection of narratives, interviews, focus groups and ethnographic work, provides rich insights into the experience of individuals, the meanings and interpretation of those experiences and the likely relationships between them. These methods uncover a different type of truth, but one that is no less important. Limitations stem from problems of replication and the time taken to acquire and interpret the data (Bowling and Ebrahim 2005).

Qualitative research usually operates from the premise that total detachment on the part of the researcher is unattainable. The researcher cannot be neutral or detached from the knowledge and gathering of evidence (Mays and Pope 2000, Morgan 2004).

Good qualitative research acknowledges that the research process cannot be value free and should demonstrate reflexivity by employing a self questioning approach, reflecting on their

role in the research process and the impact this may have, thus taking adequate steps to minimise bias (Morgan 2004). This methodology usually requires a high level of engagement and interaction from the researcher, where theories and concepts arise from the enquiry, with the generation of hypotheses often replacing the testing of hypotheses, explanation replacing measurement, and understanding replacing generalisability (Denzin and Lincoln 1994, Jones 1995).

5.3.3 Mixed methods

The combination of qualitative and quantitative designs can be defined as the use of both techniques in either parallel or sequential phases (Adamson 2005). Qualitative and quantitative approaches tend to be portrayed as opposing with the latter as natural science based, hypothetico-deductive and qualitative as interpretive, naturalistic or ethnographic (Robson 1993). Whilst quantitative and qualitative traditions differ, both have a common research purpose which is to achieve results that have significant implications.

Some researchers regard the two approaches as complimentary rather than competitive and suggest that the contradictions between approaches have been exaggerated, supporting the view that today's health care system requires new multi-paradigm approaches to deal with the diversity and complexity (Pope and Mays 1993, Hicks 1996, Lavender and Chapple 2003). It is only in the last decade that a wider acceptance of the clinical relevance of qualitative research has emerged which has manifest in the required knowledge of both quantitative and qualitative approaches on ethics committees, editorial panels and funding bodies (Kingdom 2004). Quantitative research sets out to test theory, qualitative research generates theory (Morgan 2004) moreover both techniques merely provide differing but non-competing representations, giving valid but different representations of the same phenomena (Adamson 2005).

5.4 Research design

Effective clinical practice should be underpinned by reliable evidence and clinicians should provide safe and effective care basing their practice on the best available evidence. Within healthcare there are various types of evidence available and assessments are made on this basis. Questions relating to aetiology or risk factors may be best addressed by observational studies: case-control and cohort studies. Those comparing two or more interventions are best dealt with by randomised control trials (Alderson et al 2004). In many situations RCT'S are not feasible and only data from observational studies are available. Stroup and colleagues define observational studies as aetiologic or effectiveness studies using data from existing databases, cross-sectional study, case-control design, cohort design or a design with historical controls (Stroup et al 2000). Therefore observational studies rely on studies of association between changes or differences in one characteristic and changes or differences in an outcome of interest. Observational designs have long been used in the evaluation of exposures that might cause disease or injury (Stroup et al 2000). Since the aim of the SIP Study was to explore the association between variables, a prospective observational design was deemed to be the most suitable.

5.4.1 Recruitment of research participants

All women referred to the PTL clinic were approached for recruitment.

Inclusion criteria for referral:

- Women with a history of at least one idiopathic preterm delivery between 24 –37 weeks gestation.
- Women were recruited after a routine baseline screen discussed in Chapter 2 (2.10) and evidence found of active infection.

Exclusion criteria:

- Women with a previous elective preterm delivery or delivery associated with abruption, intra-uterine growth restriction, thrombophilia, multiple pregnancy or fetal anomaly.
- Women diagnosed through the screening process and found to have an active infection requiring treatment.

5.4.2 Questionnaires

The assessment of stress needs an approach which accurately measures / characterizes stress during pregnancy using a multidimensional approach in both definition and tools. The approach should include assessments that objectively count significant events in a subject's life and the number and nature of stressors. In addition, because people can experience the same event very differently, it is important to evaluate the overall disposition and psychiatric symptoms, which moderate pregnant women's stress responses. In particular depression should be assessed as this significantly magnifies the perceived burden of a stressful event.

Two validated psychological tools were used to identify and measure psychological morbidity, the Hospital Anxiety and Depression Scale (HADS), which assesses state anxiety and general depression scores (Zigmond and Snaith 1983) and the List of Threatening Experiences Questionnaire (LTE-Q) which quantifies common life events that are likely to be threatening (Brugha and Cragg 1990. Both tools are validated for use in populations of pregnant women and are suitable to be used within a clinical situation giving a quantifiable score of psychological morbidity.

The HADS scale gives an accurate measure of state anxiety (A-State) and a separate measure of depression (dysthymia) with a classification of severity within the scoring system and is used in midwifery and other research to measure psychological morbidity.

LTE-Q is a self reported measure of life events experienced in the last 12 months and is recommended for use in psychiatric, psychological and social studies. LTE-Q gives quantitative data in terms of the number of live events experienced (yes / no answers) however it does not attempt to assess the degree of distress experienced as a distress score. LTE-Q has been used rarely within midwifery research however it is used widely in other disciplines investigating life stresses.

5.4.3 Study procedures for questionnaires

A unique code was created for each woman recruited which matched the questionnaires, booking histories and corresponding serum samples in the laboratory. HADS was coded and administered for self-completion at approximately 20 (between 18 and 22 weeks) and 28 weeks (between 26 and 30weeks) gestation. Scores for each woman were determined at the end of the clinic and those identified as high risk for depression (greater than 15) discussed with the consultant obstetrician and a plan of action made. The HADS questionnaire is not diagnostic, only a strong indicator, therefore with consent women were referred to their GP who has the expertise and knowledge of the local support services. All difficult cases were discussed with the Psychiatrist and advisor (DO) and the Consultant Obstetrician and supervisor (SQ). LTE-Q was coded and women interviewed with the answers to each question transcribed by the researcher (LW). Answers were typed in full at the end of the clinic when the interview was fresh in the researchers mind. LTE-Q was scored for number of life events.

5.4.3.1 Hospital Anxiety and Depression Scale (HADS)

HADS is a 14–item scale developed by Zigmond and Snaith (1983) and provides a brief state measure of both anxiety (seven items) and depression (seven items). It was designed for use in medical outpatient clinics to detect and assess the severity of anxiety and depression. The scale is self-administered and takes about 10 minutes to complete. Each item is scored from 0 to 3, with total scores ranging from 0 to 21 for both the anxiety and depression sub-scale. The four score ranges are classified as a measure of severity with normal (0-7), mild (8-10), moderate (11-14) and severe (15-21). Higher scores indicate greater anxiety or depression (Appendix 2). The choice of 4 responses to each item was adopted in order to stop the patient from opting for a middle grade. All items relating to both emotional and physical disorders for example dizziness and headaches were eliminated and the items selected were based solely on the psychic symptoms of neurosis and aimed to define carefully and distinguish between the concepts of anxiety and depression (Zigmond and Snaith 1983).

This scoring system was based on a study by Zigmond and Snaith (1983) which was conducted in a general medical outpatient department. Patients attending clinic were asked

to complete the questionnaire by the nurse before examination by the clinician. Patients were then interviewed by the researchers in a separate room and an assessment of anxiety and depression made without any knowledge of the scores on the self-assessment scale. Interviews were conducted jointly until confidence was reached about rating and interview technique. Data from the first 50 patients were calculated for internal consistency and the next 50 data tested in same way. Therefore 100 outpatients were scored and the scale developed was found to be a reliable instrument for detecting states of anxiety and depression. The study concluded that scores from 8 to 10 on each scale should indicate possible clinical disorder and from 11 to 21 to indicate probable clinical disorder, as these scores resulted in fewest false positives and false negatives when compared with psychiatric assessment (Zigmond and Snaith 1983).

HADS can be repeated at intervals and recorded on a chart using serial scores to gauge progress. Within the SIP study, the participants found it easy and acceptable for use in the busy antenatal clinic.

Moreover, HADS combines the measurement of both state anxiety and general depression in one tool. State anxiety is a response to environmental stressors and therefore this tool was found to be the most suitable for purposes of measuring anxiety in response to stressful life events. HADS also gives an index of mental state and a cut-off score for probable clinical levels allowing the researcher to offer referral for a more detailed mental assessment of women with a high depression score.

5.4.3.2 List of Threatening Experiences Questionnaire (LTE-Q).

LTE-Q was deemed to be the most suitable questionnaire to use for the SIP Study after consultation with the study psychiatrist (DO) and through the exploration of other interview tools. LTE-Q consists of a subset of 12 life event categories (Appendix 3) with considerable long-term contextual threat that has the reliability and validity of a brief life events questionnaire and is recommended for use in aetiological studies of adult psychiatric disorders and psychological dysfunction. It is also recommended in social studies, where other intervening variables such as social support, coping and cognitive variables are of

interest (Brugha and Cragg 1990). Historically, research into stressful life events tended towards the development of longer, more complex inventories and prior to the development of life event inventories, research was confined to the effects of major single events such as death of a spouse, losing a job or childbirth (Brugha and Cragg 1990).

LTE-Q was developed to overcome the problem of long inventories often with as many as 60 event categories and aimed to concentrate on the identification of severe events which have occurred in the year before the interview (Brugha et al., 1985, Brugha and Cragg 1990). This short questionnaire can be used to measure a substantial proportion of external stress and supports the proposition that a substantial proportion of measured adversity is accounted for by a relatively small group of the life events categories covered in one particular inventory (Brugha et al., 1985).

This tool can be used in combination within a semi-structured interview format as a 2-phase screening procedure where events described within the answers given to the questionnaire, can be coded during the interview for later contextual rating. Moreover, this tool was used to identify and separate the individual components of the life stress paradigm that may influence pregnancy outcome.

The occurrence of stressful life events (stressors) should be considered separately from symptoms of anxiety or depression (stress response). This delineation of the linked aspects of experience and response is considered critical for the identification and understanding of specific psychosocial and physiologic mechanisms through which, individual psychosocial factors may affect pregnancy outcomes as well as for the development of targeted interventions (McLean et al 2001).

Furthermore, LTE-Q allows an integration of data sources by measuring the yes / no answer as quantitative data but also gathering qualitative information within the 2-phase approach. By using the questionnaire within the semi-structured interview, the intention was to explore the possibility of gathering qualitative data for analysis.

5.4.4 Maternal serum sampling

Venous blood samples were taken at 20 weeks and again at 28 weeks gestation. The 5 millilitre sample was collected in two separate EDTA syringes and coded with the recruitment identification number and stored in ice until centrifuging at the end of clinic. By taking two samples this enabled separate samples to be defrosted at different times for assaying. Samples were centrifuged at 2000rpm for 10 minutes at 4°C in a refrigerated bench-top centrifuge (Sigma 415K), allowing the plasma and cells to separate. Each sample was divided into 250µl aliquots and stored in the Division of Reproductive and Perinatal Medicine, University of Liverpool laboratory freezer at -80°C until analysis. All sampling, coding, storing and database creation was carried out by the researcher (LW).

5.4.4.1 Study procedures for maternal serum sampling

Venous blood was sampled, centrifuged and assayed for the cytokines IL-6, TNF-α and G-CSF using enzyme linked immunoabsorbant assay (ELISA).

Each hormone identified for the study: Cortisol, Corticotrophin Releasing Hormone (CRH), Corticotrophin Releasing Hormone Binding Protein (CRH-BP) and Adrenocorticotropic hormone (ACTH) were assayed and are discussed briefly in Chapter 2 (2.4). The analysis was carried out by university staff. The researcher (LW) worked in the laboratory on a weekly basis after each clinic centrifuging, coding, freezing and storing serum samples. She spent a further two days at the conclusion of the study, carrying out basic ELISA assays with the final serum samples under the supervision of laboratory staff, which involves coating the plates with primary antibody and undertaking methanol extraction as described in 5.4.4.2.

5.4.4.2 Enzyme Linked Immunosorbant Assay

The enzyme linked immunosorbant assay (ELISA) is a well-established immunological technique used for the quantification of proteins (Appendix 9). ELISA combines the specificity of antibodies with the sensitivity of simple enzyme assays. ELISA works by means of a primary monoclonal capture antibody for the individual protein. This primary antibody adheres to the well of the ELISA plate as it incubates overnight at a set temperature. A blocking agent in the form of an unrelated protein is then used to block any uncoated plastic surface and prevent it from adsorbing the other reagents. Serial dilutions of the

recombinant or purified target protein are prepared, starting from a known concentration, to provide the reference standard curve. The samples containing unknown protein concentration are then prepared neat or to a known dilution. The standards and samples are added to individual wells in duplicate and incubated for a set time at a set temperature. The adsorbed capture antibody immobilises the protein of interest and binding takes place, a washing procedure removes other unbound antibodies (Wilson and Goulding 1986, Kemeny 1991).

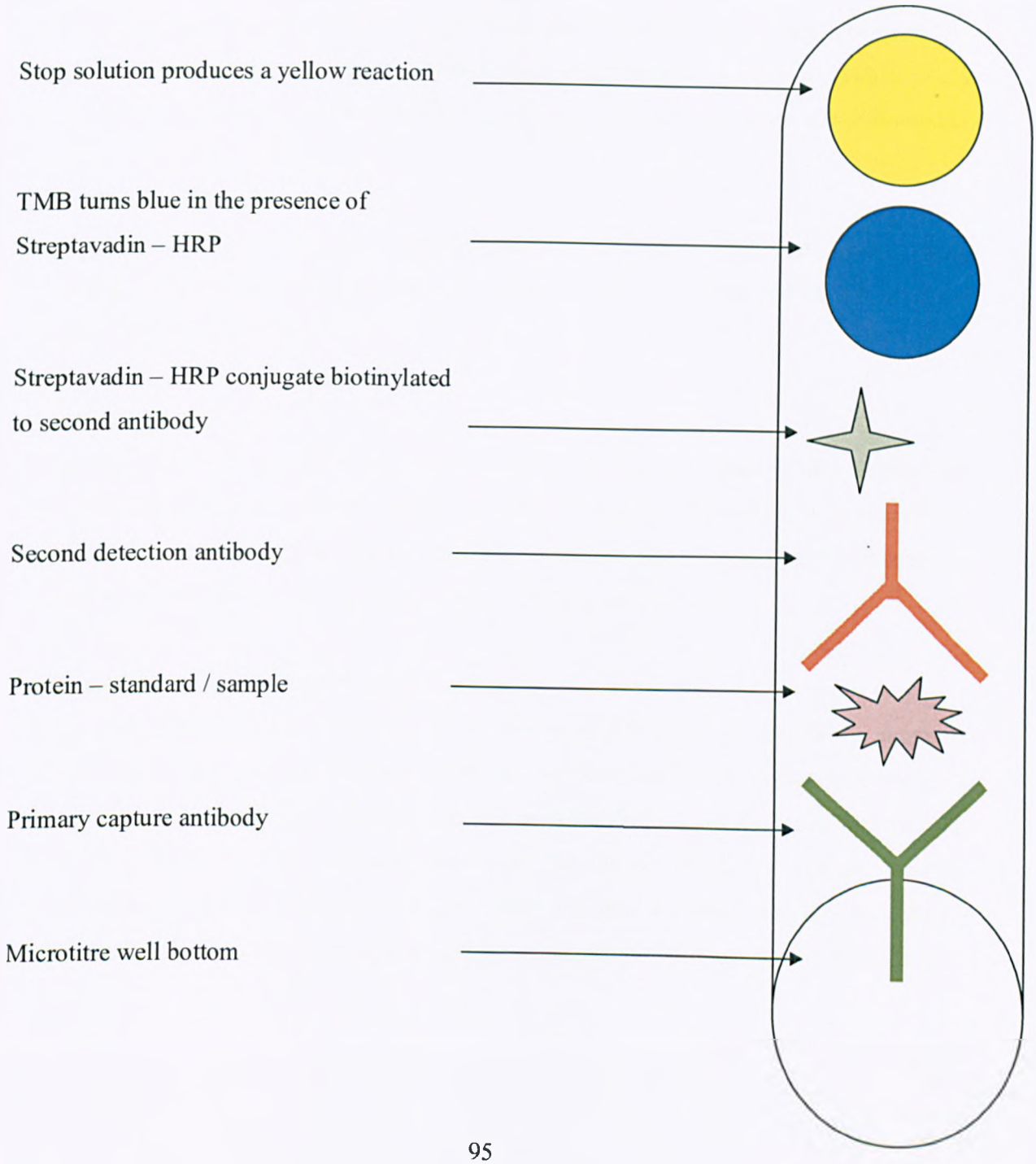
A second biotinylated detection antibody (usually polyclonal) with a linked enzyme in the form of horseradish peroxidase (HRP) is then added. Streptavadin conjugated to the HRP causes it to bind to the second antibody. Excess of this conjugate is washed away before the chromogenic substrate solution 3,3`, 5,5`-tetramethylbenzidine (TMB) is added and the plate is incubated in the dark at room temperature for a set period. HRP is specific to TMB and the interaction between these two agents produces a colour change to blue that is directly proportional to the amount of secondary antibody that has been bound (Wilson and Goulding 1986, Kemeny 1991).

The last step is the addition of 2N sulphuric acid (H_2SO_4), which stops the reaction and produces a further proportional colour change to yellow. The ELISA assay is built up in a stepwise fashion starting with the binding of the primary capture antibody to the microtitre well bottom until the stop solution terminates the procedure and produces a yellow reaction. The optical density of the yellow reaction is directly proportional to the concentration of protein in the sample (Figure 5). The colour change allows a colorimetric measurement to take place, as the ELISA plate is passed through a plate reader it determines the optical density of each well in the plate. By plotting the mean of the paired optical densities for the standards against the concentrations of the standards, the linear standard curve is produced. A natural logarithmic plot of both sets of variables ensures consistent linearization of the data (Wilson and Goulding 1986, Kemeny 1991). The mean optical density of the sample under analysis can then be plotted on the standard curve and the concentration can be read from the point of intersection

Figure 5 (5.4.4.2)

ELISA method

Adapted from Wilson and Goulding (1989)



5.5 Sample size

No published data was available from which to generate a sample size calculation for this study. After discussion with the university statistician (GL) and the study supervisor (SQ) a decision to recruit 200 women was made. This was based on a similar patient mix to the established Preterm Labour Clinic at Guy's Hospital, London. With a 25% incidence of recurrent preterm labour we estimate that 50 women out of 200 would have another preterm labour (delivery between 24 – 37 weeks gestation) and 150 women would not. Therefore, the sample size advised for statistical analysis using logistic regression analysis with 5 of the most predictive variables and a binomial outcome of preterm delivery or not was 200 women.

5.5.1 Ethical approval

Copies of the research proposal information sheet (Appendix 10) and consent form (Appendix 11) were submitted to Local Research Ethics Committee and ethical approval granted in 2004 (Appendix 12).

5.5.2 Consent

Information sheets were given to all women attending the Preterm Labour Clinic and the SIP Study discussed. At a subsequent visit and after the 20 weeks ultrasound scan, women were recruited. Written consent was obtained and signed in triplicate. One copy in the participants hospital notes, one copy on file in the university and one copy to women.

5.5.3 Confidentiality and anonymity

Privacy was guaranteed by conducting all interviews in private rooms within the antenatal clinic setting at the Liverpool Women's Hospital. At recruitment each woman was allocated a code allowing samples and questionnaires to be identified to the particular woman and matched to HADS, LTE-Q, maternal serum samples in the laboratory and the booking history. This ensures individuals can be identified and thus securing women's anonymity. The researcher (LW) was the only person to have access to the identification of the codes.

5.6 Data collection

Data was collected prospectively using a data collection sheet (Appendix 13) and spreadsheet using Excel 2000 (Microsoft), designed for the study. The antenatal and delivery details were collected retrospectively from the hospital computer system (Meditech).

5.6.1 Handling and storage of data

All serum samples were stored in Liverpool University laboratory according to HMI regulations to comply with the Human Tissue Act (2004). Serum sample data was kept on an Excel database on the university laboratory and researchers' computer at the Liverpool Women's Hospital on a secure drive with access only by a personal password. Disks and paper copies of results and booking histories were kept in a locked cupboard in a secure room at the hospital.

5.7 Data analysis

5.7.1 Analysis for the observational study

The computer software Statistical Package for the Social Sciences (SPSS) for Windows (version 14.0, Chicago IL) was used to analyse the data. Each variable was assessed as to whether it was a categorical or continuous variable and whether it was normally distributed or skewed. Then the data where transformed into the appropriate type and investigated as to whether it predicted preterm birth. The 5 variables best at predicting preterm birth were chosen. Where there were some variables of similar predictive ability and biological similarity these were tried sequentially in the logistic regression model until the model that best fitted the data was produced.

5.7.2 Feasibility of samples

Feasibility of samples was carried out with the first 50 completed samples. This was necessary as a preliminary exploration of samples to reassure the researcher that maternal serum sampling was of sufficient quality and quantity and could be measured using standard laboratory techniques (ELISA) and is discussed in Chapter 6.

5.7.3 Analysis for the qualitative study

Analysis of the transcripts began at the completion of each questionnaire. Answers to LTE-Q were written by the researcher and typed at the end of each interview. Data was given back to the participants at the 28 week visit to obtain validation (member checking). The researcher read the transcripts several times in order to gain an overall impression of the data. This stage of analysis relates to the major points of interest and shared characteristics within the answers. Patterns and themes were identified and grouped together. To minimise interpreter bias a sample of the answers were themed independently by another member of the research team (SQ). The analysis is discussed in Chapter 7 (7.8)

5.8 Cross-sectional Study

The objective of this small cross-sectional study was to assess anxiety levels using HAD-A scores from women without a history of preterm labour and compare these with the data from the prospective observational study. With the same local ethics committee approval for the SIP study, a cross-sectional study was conducted

5.8.1 Recruitment

A consecutive sample of women attending the ultrasound department for the routine 20 week anomaly scan at the Liverpool Women's Hospital were recruited. All patients attending were considered eligible provided they were able to communicate in English.

5.8.2 Control group

50 low risk women attending their 20 week anomaly scan with no history of a previous preterm labour

5.8.3 Inclusion criteria

Women with a singleton pregnancy at 20 week gestation.

5.8.4 Exclusion criteria

Women with a history of idiopathic preterm delivery between 24 –37 weeks gestation, with a history of major surgery or with a multiple pregnancy.

5.8.5 Preterm labour group

Women (n=200) recruited for the Stress, Immunity and Preterm birth study (SIP) study with a completed HADS questionnaire at 20 weeks gestation.

5.8.6 Consent

Women attending for ultrasound scan were identified by the researcher through the booking history in the notes before being approached to take part in the study. Information sheets were then given to women whilst waiting for scan. Opportunity was given to discuss the SIP study with the researcher and after the 20 weeks ultrasound scan, women were approached to consider participating in the study. Written consent was obtained and signed in triplicate for all participants. One copy in the participant's hospital notes, one copy on file in the university and one copy given to each woman recruited.

5.8.7 Study procedures for questionnaires

The HADS questionnaire was administered for self-completion at approximately 20 (between 18 and 22 weeks) after the scan to ensure consistency within the SIP study and handed to the researcher. The scores for each woman recruited was determined immediately and women identified as high risk for depression (score > 15) were discussed with the consultant obstetrician and a plan of action made.

5.8.8 Main outcome measures

Hospital anxiety and depression scores.

5.8.9 Data analysis

Anxiety and depression scores for the preterm labour group (PTL) and control group (CG) were analysed with the software GraphPad Prism, (version 5.02).

5.9 Conclusion

The SIP study has been conducted in two parts. Throughout the thesis the methods used are presented in the order in which the study was conducted. The analyses of the data obtained are detailed in the following chapters. Chapter 6 presents the findings of the prospective

observational study and feasibility study as a quantitative analysis with Chapter 9 presenting the findings from the semi-structured interviews as a qualitative analysis.

Chapter 6

6. RESULTS OF THE PROSPECTIVE OBSERVATIONAL STUDY

6.1 Introduction

This chapter is a presentation of the results of the SIP observational study and begins with a brief discussion about the feasibility of the first 50 samples and the plans made for analysis based on these findings and continues with a description of the analysis of maternal serum cytokines and hormones. Findings from the HADS questionnaire are presented for both 20 and 28 weeks gestation with anxiety scores from the small cross-sectional study presented as a comparison to those in the SIP study. A description of life events as a quantitative measure is also given at both 20 and 28 weeks gestation. The information disclosed within the answers to this questionnaire was also analysed thematically. Socio-economic, ethnic and demographic information collected within the booking history are discussed with outcome data and are presented as simple descriptive statistics. The chapter continues by setting out the results from the statistical analysis for the observational study using the computerised statistical package SPSS and concludes with an outline of the missing data and a discussion of the findings in relation to the objectives of the study.

6.2 Feasibility of samples

A feasibility exercise was carried out to assay the first 50 maternal serum samples in order to:

- test the ELISA kits
- assess collection tools for maternal outcomes
- test the quality of samples
- explore the analysis for maternal cytokines to determine which would best fit into the stress model.

The initial aim of the study had been to analyse maternal serum cytokines IL-6 and TNF-α as well as maternal hormonal response however, the feasibility exercise showed that analysis of theses cytokines may not be beneficial to the study as TNF-α was not detected in many women and there was no relationship found between IL-6 and gestational age at delivery.

The first set of G-CSF measurements were found to be higher in women who delivered before 35 weeks and there was a suggestion that changes in measures of psychological morbidity were associated with changes in markers of immune activation (IL-6 levels). However there was no direct evidence that these effects were related to outcome.

On the basis of this analysis we decided that cortisol would be a better hormone to analyse because of the evidence from the literature and also because of the study aim in trying to identify an association between maternal immune response and HPA axis activation. After much discussion it was decided that CRH, CRH-BP, G-CSF as well as cortisol and ACTH would be a better fit in a model to predict PTL as discussed in Chapter 2.

6.3 ELISA assays

Two hundred samples were analysed (100%) at 20 weeks gestation (C sample) and 151 (75.5%) at 28 weeks gestation (CC sample).

6.4 Hospital Anxiety and Depression Scale (HADS)

HADS scores were completed at 20 weeks for 200 women (100%) and at 28 weeks for 151 women (75.5%) with missing data for 49 women (32%) at the 28 week visit. The gestation of pregnancy at 20 weeks ranged from 18 – 23 weeks and at 28 weeks ranged from 26 – 34 weeks. The scoring system for HADS is discussed in chapter 5 (5.4.2.1). The range of severity is included within the tables, with a total score of 21 for each sub-group of anxiety and depression.

6.4.1 Anxiety (HADS-A) scores at 20 weeks

Simple descriptive statistics were conducted to determine the prevalence of anxiety and depression. HADS scores of greater than 11 for both anxiety and depression counted as pathological for the statistical model.

Table 3 (6.4.1)

HADS-A @ 20	Women (n=200)	Percentage	Outcome
0 - 7	74	37%	normal
8 - 10	52	26%	mild / possible clinical disorder.
11 – 14	52	26%	moderate / probable clinical disorder
15 -21	22	11%	severe anxiety.

The scores show that 37% of women (n=74) experienced normal anxiety, 26% (n=52) had a mild / possible clinical anxiety. 37% (n=74) had a probable clinical anxiety disorder with moderate / severe anxiety at 20 weeks.

6.4.2 Anxiety (HADS-A) scores at 28 weeks

Table 4 (6.4.2)

HADS-A @ 28	Women (n=151)	Percentage	Outcome
0 - 7	66	43%	normal
8 - 10	40	26%	mild / possible clinical disorder.
11 – 14	23	15%	moderate / probable clinical disorder
15 -21	22	14.5%	severe anxiety.

The scores show that 43% (n=66) of women experienced normal anxiety, 26% (n=40) had mild anxiety. 29.5% (n=45) with a probable clinical anxiety disorder with moderate / severe anxiety at 28 weeks. Therefore less women experienced higher levels of anxiety at 28 weeks, possibly related to the gestation of the last delivery and the influence of clinical care.

6.4.3 Depression (HADS-D) scores at 20 weeks

Table 5 (6.4.3)

HADS –D @ 20	Women (n=200)	Percentage	Outcome
0 - 7	148	74%	normal
8 - 10	29	14.5%	mild / possible clinical disorder.
11 – 14	19	9.5%	moderate / probable clinical disorder
15 -21	4	2%	severe depression.

The scores show that 74% (n=148) of women experienced no depression, 14.5% (n=29) had mild depression with 11.5% (n=23) with moderate / severe clinical depressive disorder at 20 weeks.

6.4.4 Depression (HADS-D) scores at 28 weeks

Table 6 (6.4.4)

HADS-D @ 28	Women (n=151)	Percentage	Outcome
0 - 7	106	70%	normal
8 - 10	29	19%	mild / possible clinical disorder.
11 – 14	12	8%	moderate / probable clinical disorder
15 -21	4	3%	severe depression.

The scores show that 70% (n=106) of women experienced no depression, 19% (n=29) had mild depression and 11% (n=16) with moderate / severe clinical depressive disorder at 28 weeks. A comparison between depression scores at both gestations shows that the scores remained similar throughout pregnancy.

6.5 Cross-sectional Study

The rationale for the cross-sectional study was to compare anxiety scores (HADS-A) in pregnant women with a history of preterm labour from the SIP study with a group of low risk women without a history of preterm labour. The selected sample, were women attending for the 20 week anomaly scan, the sampling frame was the population of other women attending the ultrasound department at this gestation and the study sample were the 50 women who agreed to take part in the study.

This small study aimed to compare anxiety levels in a convenience sample of low risk women (n=50) as a control group (CG) with the participants from the SIP study (n=200) in the preterm labour group (PTL). The purpose was to identify if women were less stressed during pregnancy if they had never experienced a preterm birth before. Anxiety and depression scores for the PTL group and CG were analysed with the software GraphPad Prism, (version 5.02) using the two-tailed Mann-Whitney test. The results concluded that

anxiety levels in women with a history of preterm labour are significantly higher ($\rho = 0.0006$) than in women without a history of preterm labour.

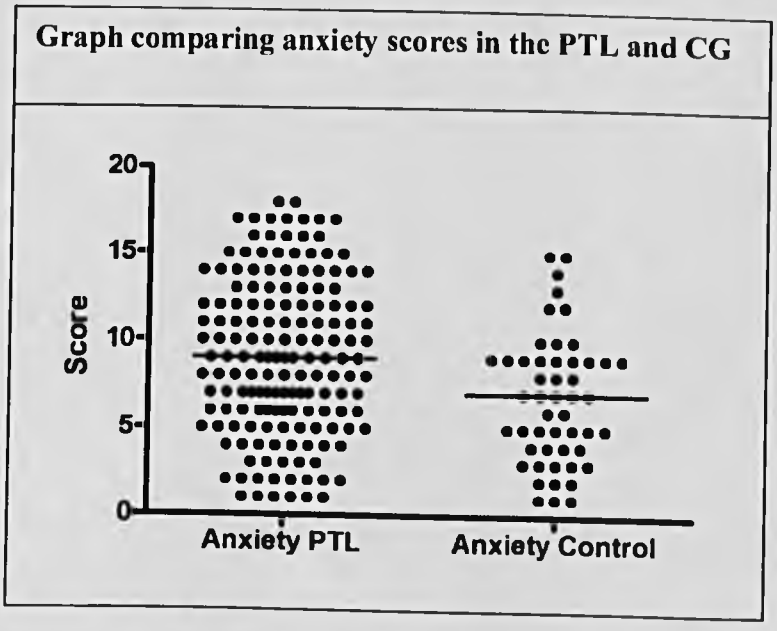
6.5.1 Results for the cross-sectional anxiety study

HADS scores for women (n=50) in the control group are presented in Table 7. The median average was used to compare women in the PTL group with women in the CG. Data shows that anxiety and depression are higher in the PTL group than the CG. HADS data is graphically illustrated separately in Figures 6 and 7.

Table 7 (6.5.1)

Median (and range) comparing scores at 20 weeks between the PTL and CG.				
	PTL		CG	
Anxiety	9	(1-18)	7	(1-15)
Depression	5	(0-17)	2.5	(0-12)

Figure 6 (6.5.1)



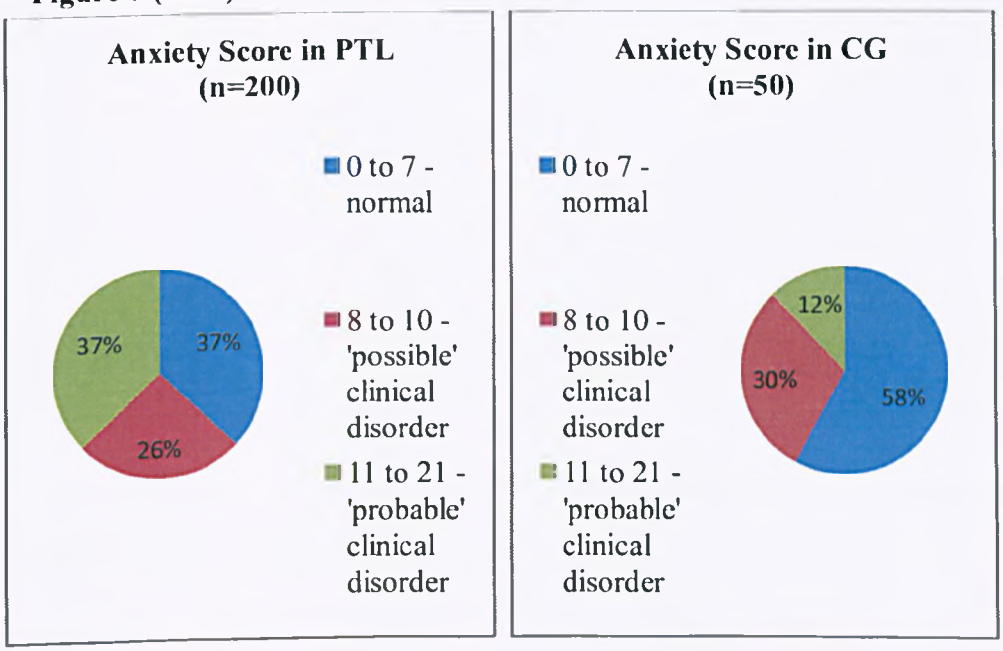
The ordinal data was skewed therefore a nonparametric statistical test was used to confirm the significance of the results. A two-tailed Mann-Whitney test was carried out using the GraphPad Prism 5 software. The results are shown in Table 8.

Table 8 (6.5.1)

Statistical Analysis Comparing Anxiety Scores in PTL and CG	
Mann Whitney test	
P value ρ<0.001	0.0006
Exact or approximate P value?	Gaussian Approximation
Are medians significantly different? (ρ < 0.05)	Yes
One- or two-tailed ρ value?	Two-tailed
Sum of ranks in PTL, Control	26668 , 4707
Mann-Whitney U	3432

The PTL group were compared with CG within the 3 severity categories. The results show that more women in the PTL group (37%), compared to the control group (12%) have a probable clinical disorder. Whereas women in the PTL group (37%) compared to the CG (58%) have an anxiety level considered to be normal.

Figure 7 (6.5.1)



Some limitations to the study should be acknowledged. This small study may have suffered from selection bias as the 50 control women were only selected on the four days suitable to the researcher and therefore depended entirely on which women were booked for the 20 week anatomy scan on those days. Potential bias may have been avoided by listing all the

women due to attend the 20 week scan on those days and randomly selecting 50. However the time scale for this small study made this impossible. There may also be a possibility of observer bias as family members and friends were present which may have resulted in participants experiencing less anxiety and scoring lower on the HADS scale.

6.6 Life events at 20 weeks

Two hundred women (100%) were interviewed about life events (LE) using LTE-Q at 20 weeks (Table 9) and 151 (75.5%) women at 28 weeks gestation (Table 10). For the purpose of the statistical model life events were grouped into two categories, </= 3 and =/> 4 as this made biological sense and gave enough women in each group for the model.

Table 9 (6.6)

Number of LE at 20 weeks	Number of women (n=200)	Range	Percentage
1	45		22.5%
2	31		15.5%
3	22		11%
4	14		7%
5	5		2.5%
6	0		0
7	0		0
8	3		1.5%
9	1		0.5%
10	0		0
11	0		0
12	0		0
Total	121	1 - 9	60.5%

The results show that 121 women (60.5%) reported significant life events ranging from one event to nine at 20 weeks gestation.

6.6.1 Life events at 28 weeks

Life events at 28 weeks were often the same stresses that had been mentioned at the 20 week visit which is important as a continuous source of stress throughout pregnancy, however there were no increases in life events at the 28 week visit.

Table 10 (6.6.1)

Number of LE at 28 weeks	Number of women (n=151)	Range	Percentage
1	26		17%
2	16		10.5%
3	6		4%
4	7		5%
5	2		1%
6,7,8,9,10,11,12	0		0
	57	1 - 5	38%

48 women (32%) had up to three LE, 9 women (6%) had four or five LE events with no women experiencing more than five.

6.7 Booking history data

Demographic data was examined using the routine booking information (Table 11) retrieved from the hospital computer records system (meditech).

Table 11 (6.7)

Booking history details	Number	Range	Mean	Percentage
Booking history completed	200			100%
Age	200	19–47	30	100%
BMI	109	16.1–40.4	25.94	54.5%
English language	196			98%
Non-English language	4			2%
Married	87			44%
Single	113			56%
White	178			89%
Black British	7			3.5%
Black African	2			1%
Asian	4			2%
Mixed race	2			1%
Other	7 (6 Welsh, 1 Vietnamese)			3.5%
Smokers (yes/no)	57			28.5%
Alcohol (yes/no)	13			6.5%
History of depression (yes/no)	22			11%
GP for depression (yes/no)	15			7.5%
Psychiatrist (yes/no)	3			1.5%
Anti-depressants used (yes/no)	6			3%
Cervical suture (yes/no)	14			7%
TAC (yes/no)	1			0.5%

The mean age of women in the study was 30 years. BMI was recorded for 109 women (54.5%). BMI had only been recorded at the hospital since 2007, therefore all women booked before that date would not have the BMI calculated as part of the booking history. BMI ranged from 16.1 to 40.4 with 25.94 as the mean BMI for this population.

A significant number of women (n=57) in the study smoked (28.5%) moreover, few women had recorded their intention to stop smoking within the booking information despite the risks associated with preterm labour.

Only 87(44%) of women in this study were married with the remaining 113 (56%) describing themselves as single or divorced. No information was gathered describing levels of support or stability within relationships.

The booking data revealed that 178 (89%) of women were white British, 7 (3.5%) black British and 13 (7.5%) women in the study described as other than British ethnicity. 196 (98%) were recorded as English being their first language with only 4 women (2%) who did not speak English.

Socio-economic data was gathered using postcodes converted to the Index of Multiple Deprivation Scale (IMD). The conversion to IMD scale was obtained from the CEMAC website (CEMAC 2009) and is based on a number of factors such as income, employment, crime and educational achievement with the higher the number corresponding with the deprivation in the area. On the basis of this information there is a weighted average score calculated for different geographical areas. The weighted average IMD score for Liverpool is 58.05 (Garcia et al 2008). Within the SIP study 25 women (12.5%) lived out of the area. 175 women (87.5%) lived within the Liverpool postcode with 57 of these women (28.5%) living in a postcode area above the average IMD score of Liverpool.

6.8 Outcome data

Outcome data was missing for four women and a further two women had a miscarriage therefore no birth weights were recorded for six women (Table 12).

Table 12 (6.8)

Delivery details	**Number**	**Range**	**Mean**	**Percentage**
Birth weight	194 misc (n=2) missing data (n= 4)	730g – 4492kg	3055kg	
Gestational age	196 (n=4 missing data)	19 - 41	37	
<37 weeks <24 24 – 32 33 - 36	65 (4) (15) (46)	19 -36 (5 – 23)		33% (2%) (8%) (23%)
>37 weeks	131	37 - 41		67%
Apgar				
1 min		0 - 10	Mode 8	
5 min		0 - 10	Mode 10	
Women with H/O depression				
< 37	7	20 - 36		3.5%
>37	14	37 - 41		7%

In total 33% of women delivered prematurely, with 3.5% of those with a medical diagnosis of depression. However the majority of women in the study (67%) delivered at more than 37 weeks gestation despite moderate to severe anxiety scores at 20 and 28 weeks affecting between 34 to 36% of women.

6.9 Plan for analysis

Three sets of analysis were performed on the data:

Analysis 1: The difference in variables between those delivering preterm (<37 weeks) and at term (>37 weeks).

Analysis 2: The investigation of whether HADS or LE scores correlated with any of the biological, serum markers of psycho-social stress. Maternal serum samples as biological markers were analysed systematically with each psychological score:

- CRH, CRH-BP, G-CSF, cortisol and ACTH were compared separately with anxiety at 20 and at 28 weeks.
- With depression at 20 and at 28 weeks.
- With life events (LE) at 20 and at 28 weeks.
- Then:
- High anxiety scores (above 11) at 20 and 28 weeks were compared with LE at 20 and 28 weeks.
- High depression scores (above 11) at 20 and 28 weeks were compared with LE at 20 and 28 weeks.

All were compared with outcome data (delivery before 37weeks) to determine whether there was a biological variable that correlated with stress; LE, HADS-A and HADS-D.

Analysis 3: A logistic regression model was constructed to predict PTL.

6.10 Statistical methods

General

The Excel database was checked and cleaned for errors before input into SPSS and analysis commenced. The central analysis of the study was based on a logistic regression model. The definition of prematurity by WHO was used (<37 weeks gestation), giving enough women in each graph to make the logistic regression possible, as 65 women delivered before 37 weeks and only 15 women delivered before 32 weeks. The referral rate to the clinic was predicted at 150 women per year. Therefore, by recruiting 200 women, 25 would be expected to deliver before 37 weeks (25%). As planned with the statistician at the start of the study, the sample size calculation suggested that a population of 200 women would be needed for a logistic regression model involving 5 variables. Thus the study was stopped when 200 women had been recruited. The data were analysed using the computer software the Statistical Package for the Social Sciences (SPSS) for Windows (version 14.0, Chicago IL). Initial descriptive statistics were conducted on demographic variables and to determine the prevalence of depression, anxiety and stress symptoms. All variables were identified prior to the analysis taking place on the basis of the published literature. Variables were transformed into the most appropriate for the analysis and each considered whether they were better described as categorical, continuous or logarithmic.

Descriptive statistics included means and standard deviations for continuous variables, and frequency distributions for categorical variables (Kirkwood 1990). Level of significance was determined as a ρ value of less than 0.05.

Continuous variables:

- Age
- Number of previous births > 37 weeks
- Number of previous births 24 – 37 weeks
- Number of previous births < 24 weeks
- Categorical variables as: (yes = 1 / no = 0)
- Smoker 1 / 0
- Cervical suture 1 / 0
- Alcohol 1 / 0
- Anxiety (>11) at 20 weeks 1 / 0

- Depression (>11) at 20 weeks 1 / 0
- Anxiety (>11) at 28 weeks 1 / 0
- Depression (>11) at 28 weeks 1 / 0
- LE =/> 4 at 20 weeks 1 / 0
- LE =/> 4 at 28 weeks 1 / 0

The variables Cortisol, ACTH, CRH-BP, CRH, G-CSF had a skewed distribution and thus were logarithmically transformed.

Categorical data was presented in charts with numerical data presented in histograms to look at the distribution and outliers.

Analysis 1

The following tests were used to determine differences in those who delivered preterm and term. The Mann Whitney U test was used to compare two groups with non parametric continuous data.

The Chi squared test was used to test for differences between two groups with categorical variables.

The t-test used to test for differences between two groups with continuous variables.

Analysis 2

Pearson bivariate correlation was used to explore any correlation between categorical variables.

Spearman's (rho) correlation coefficient was used to determine the correlations between the continuous data.

$P < 0.05$ was used as the limit of significance.

Analysis 3

Odds ratios (OR) were then calculated for each variable to assess its ability to predict preterm birth. Those variables with the greatest OR were chosen for the logistic regression model. Following this, independent variables which cannot be manipulated (such as age, demographic variables) were entered into the model first, followed by known predictors of

PTB from previous research (smoking, previous PTL, biological markers). Variables that made minimal significant difference to the model were then removed. This method allowed an explicit model to be tested to see how much variance in the dependent variable (preterm birth) is accounted for by certain independent variables when other variables are already in the model. As some of these were similar in nature and biological function, numerous logistic regression models were made until 5 variables were found which had the best ability to predict PTB.

6.11 Results

Analysis 1: Difference in variables between those delivering preterm and at term

The background variables for the sample on which measurements are reported are presented in Table 13.

Table 13 (6.11)

Variables	Preterm (1)	Not Preterm (2)	No	Diff in means/ pop	CI 95% Lower Upper	p.value
Age Mean	30.3 5.3	29.9 5.8	196	.47	-1.2 2.1	0.589 (t-test)
Non-smokers	32%	67%	196			0.1 Chi sq test (with Yates cont corr)
Alcohol	4.7%	6.8%	196			0.79 Chi sq test (with Yates cont corr)
Prev births > 37	Median = 0 Range 0-4	0 0-5	196			0.985 Mann Whit U test
24 – 37	Median = 1.0 Range = 0-5 Mean 1.2	1.0 0.9	196			0.82 Mann Whit U test
< 24	Median = 1.0 Range = 0-11 Mean 1.78	1.0 1.08	196			0.12 Mann Whit U test
Cx Suture	4.6%	2.6%				p=0.02 Chi sq test
Anx 20	Mean = 9.62 SD = 4.1	8.67 4.1		0.95	-2.20 0.30	0.85 (t-test)

Dep 20	Mean = 5.67 SD = 3.86	5.42 3.61		0.26	-1.36 0.85	0.78 (t-test)
LE 20	Median = 1 Range = 0-9	1 0-8				0.94 Mann Whit U test

Odds Ratio are presented in Table 14.

Table 14 (6.11)

Variables	N = 196	OR EXP (B)	CI 95% Lower	Upper	p.value
Age		1.02	0.96	1.07	0.58
Smokers		1.03	0.53	2.00	0.92
Alcohol		1.49	0.39	5.7	0.56
>37		0.99	0.68	1.5	0.98
24 -37		1.55	1.07	2.25	0.19
< 24		1.28	1.06	1.54	0.009
Cx Suture in place		4.1	1.3	12.97	0.014
HADS-A 20 weeks		1.06	0.98	0.14	0.13
HADS-D 20 weeks		1.02	0.94	1.11	0.65
LE 20 weeks >4		0.526	0.22	1.2	0.15
GCSF 20 weeks (log)		1.16	0.71	1.9	0.55
CRH 20 weeks (log)		1.86	0.56	9.7	0.46
ACTH 20 weeks (log)		1.61	0.29	8.96	0.59
CRH-BP		1.11	.56	2.1	0.75
CORTISOL		1.61	0.29	8.96	0.59

Table 15 (6.11)

20 weeks	Preterm	Term	p.value Mann-Whitney u-test
G-CSF	N= 63 Med=34.1	125 26.5	0.25
CRH	N=63 Med=252	125 2336	0.44
ACTH	N=60 Med=2.72	116 2.6	0.85
CRH-BP	N=35 Med=198	61 166	0.22

Analysis 2

Does HADS or LE scores correlate with any of the biological, serum markers of psycho-social stress?

There was no statistically significant correlation between either, the HADS anxiety or depression at 20 or 28 weeks and LE or any of the serum measurements of the HPA axis or G-CSF.

Similarly there was no statistically significant correlation between LE or any of the serum measurements of the HPA axis or G-CSF.

Analysis 3

Variables used in logistic regression model:

Many of the women were not available for sampling at 28 weeks. This meant there were too few results at 28 weeks for use in the logistic regression model. Therefore the 20 week gestation results were used; HADS-A 20 / HADS -D 20 / CRH / ACTH / CRH-BP / G-CSF, age / smoking / alcohol / previous babies above 37 weeks were not included in the model as they made no difference to the ability of the model to predict preterm birth.

The 5 variables were determined for the logistic regression model (Table 16) which would best predict PTL. The best variables had 72% prediction of the PTL in the study.

Table 16 (6.11)

Variable	Ex (B) OR	95% CI to CL		Significance
		Lower	Upper	
LE / 20	2.96	0.77	5.49	0.150
Birth 24 – 37	1.71	1.15	2.54	0.008
Birth < 24	1.30	1.06	1.59	0.01
Log of CRH at 20	1.57	0.26	9.37	0.62
Cervical suture	3.33	1.00	11.06	0.05

The logistic regression model was repeated with and without CRH levels at 20 weeks gestation and the overall ability of the model to predict preterm labour was improved with them in. CRH levels representing the placental and maternal unit had a small effect on improving the model to predict outcome (Table 16).

6.12 Missing data

There were 49 sets of missing data at 28 weeks; 12 women (6%) had delivered by 28 weeks gestation and 37 women (18.5%) were not interviewed at 28 weeks for a variety of reasons; where they had either returned to their referring hospital, delivered whilst on holiday or were not seen because the researcher had not been in clinic that day. There were 4 women with delivery data missing at the conclusion of the study. When there was no birth information identified on the hospital database, women were contacted twice by letter and a delivery summary form was enclosed for completion. If women did not return the form, the original referring hospital and the GP were contacted for missing information. This was successful in all but 4 cases.

6.13 Discussion

The results presented here suggest that there is little support for the hypothesis that there is an association between stress and premature birth in this group of susceptible women. The SIP study and the focus of this thesis were based on the hypothesis:
"the maternal response to stress determines the risk of preterm delivery in women at high risk of preterm labour."

The contributing factors associated with PTB as identified in the literature have been divided into three groups: sociobiological variables, past obstetric history and complication of the current pregnancy in order to discuss the results pertinent to the SIP study.

Sociobiological variables:

Age, smoking, life events, anxiety and depression were found not to be predictive of PTL in this study. The mean age within the sample was 30 years, which would not suggest a high risk group as identified in the literature (Mattison et al., 2001, Dayan et al., 2002, Green et

al., 2005). The risks of smoking and PTL are well recognised (Hall et al., 1997, Goldenberg et al., 2008). In this group of women there was a high proportion who smoked (28.5%). However there was no statistical difference in smoking rates in those with recurrent preterm and non-recurrent preterm labour. Furthermore smoking did not predict preterm labour either as an individual model or in the logistic regression analysis. Hence whilst smoking is a contributory factor to preterm labour in the general population it did not predict recurrent preterm labour in this study. There were no women in this sample with problems of drug misuse and self reported alcohol consumption was higher within the group who delivered at term (6.8%) than the preterm group (4.7%).

The BMI ranged from 16.1 to 40.4 with 25.94 as the mean for this population therefore no correlation was found with other studies identifying low BMI with PTB (Dayan et al., 2002).

44% of women (n=87) in this study were married with 56% describing themselves as single or divorced. Levels of support or stability within relationships was not included, however thematic analysis within the qualitative study identified a number of women with ongoing problematic relationships and is discussed in chapter 9.

89% (n=178) of women were white British, 3.5% (n=7) black British and 7.5% (n=13) of women described as "other" ethnicity. 98% (n=196) were recorded as English being their first language with only 2% (n=4) who did not speak English. No correlation could be found with PTB and associations with race and ethnicity (Hall et al., 1997, Goldenberg et al., 2003) as the population with the SIP Study were predominantly a white British group.

Socio-economic data was based on the weighted average IMD score for Liverpool which is 58.05 (Garcia et al 2008). Within the SIP study 28.5% women (n=57) of lived within a postcode above the average IMD score of Liverpool. This link between socio-economic status (SES) and pregnancy outcomes correlates with other studies (Mattison et al., 2001, Steer and Flint 2004, Green et al., 2005). Different aspects of SES such as education, unemployment or annual income, may impact on how well women cope with stress and may be the main underlying cause of pregnancy problems. However within the SIP Study despite

the majority of women in the study living in area above the average IMD score for Liverpool no correlation was found with preterm labour rates.

The results show that the levels of anxiety and depression detected with HADS had no association with PTL supporting others in the literature review (Peacock et al., 1995, Perkin et al., 1993, O'Donnell et al 2009). However many studies have compared low stressed women with women reporting high levels of stress in their lives (Misra et al., 2001 Lobel et al., 1992 Berkowitz et al., 1983. Henrickson et al., 1994 Jesse et al., 2003) and have found a positive association. The Cross-sectional study did find that women in the SIP study were more stressed than in the low risk control sample (ρ. value 0.0006). No outcome data was collected from the low risk (control) group therefore, an association with gestation at birth could not be made. The number of life events, were not associated with PTL in conflict with other studies (Copper et al., 1996, Dole et al., 2003).

There were changes in levels of anxiety throughout pregnancy at the two time periods of 20 and 28 weeks with 37% of women have moderate to severe anxiety at 20 weeks and 30% at 28 weeks. All women were told that there baby had a 98% survival rate after 28 weeks with the intention that reaching this gestation would alleviate anxiety.

The study failed to detect a biological response to stress as there was no correlation found between the HPA axis and the questionnaire detected measures of stress. No correlation was found in maternal serum samples for CRH, CRH-BP, G-CSF, cortisol and ACTH as others have reported (McLean et al., 1998, McLean and Smith 2001, Leung et al., 2001, Wadhwa et al., 2001) therefore they were not associated with PTB in this study. This lack of correlation supports the theory that there may be a 'damping down' of the biological reaction to stress in pregnancy as with the placental CRH production overriding the effects of maternal stress.

Past obstetric history:

The results presented here show that those women with a history of previous preterm birth between 24 and 36 weeks gestation are more likely to deliver preterm again (ρ.value 0.008) corroborating with the evidence that a previous preterm birth is a major contributory factor in

a repeat event (Keirse et al., 1978, Terizou and Bennett 2002, Goldenberg et al., 2003, Lykke et al., 2009).

Complication of the current pregnancy:

Women in the SIP study were not a homogenous group and the study found that it may not be stress and anxiety that matters but other biological factors. All women were managed within a strict clinical protocol in the preterm labour antenatal clinic. All women had transvaginal ultrasounds of the cervix at 16, 20, 24 and 28 weeks gestation or more frequently if shortening was detected. A cervical suture was inserted if the cervical length was < 15mm before 24 weeks. 7% of women had this cervical shortening and a cervical suture inserted. Of the women who delivered preterm 4.6% had a suture and those who delivered at term 2.6% had a suture. Furthermore, the use of ultrasound scan indicated that cervical shortening predicted preterm delivery. The most plausible explanation is that cervical shortening is an accurate predictor of preterm labour that was not prevented by cerclage in some cases. Hence cervical shortening was more important than any other factor in predicting preterm birth in the women attending the clinic.

The women in the SIP study were screened and treated if necessary for infection negating the link with infection and PTL which have been found in other studies (Chamberlain 1995, Campbell and Lees 2000, Mattison et al., 2001, Wadhwa et al., 2001, Peltier 2003, Steer and Flint 2004, Green et al., 2005). This may have had an impact on the lack of maternal immunological / inflammatory response found in the serum samples needed to support the HPA axis activation theory.

The SIP study results could be explained in part by the attendance at the clinic which may have influenced women's responses to stress especially if most of the stress experienced was related to their previous preterm birth experience. In addition, it is conceivable that women who were genuinely grateful to be part of the study, also felt that they were being treated as "special" which in turn may have resulted in those women being able to cope with stress better.

Other studies have found no association between stress and preterm birth however one recent study found no association between cortisol and anxiety in maternal samples taken at 17 weeks gestation (O'Donnell et al 2009). In this study all samples were taken in the morning questioning the diurnal variation in cortisol in pregnancy. This paper argues that the link between antenatal stress and the maternal HPA axis functioning may be weak and that with maternal cortisol increasing to term under the drive of placental CRH and the maternal adrenal cortex, this may have a reduced capacity to respond to psychological stress or maternal emotional state.

It is not known at what gestational age the maternal HPA axis starts to lose its responsiveness, or how much individual variability there is in this respect. One factor that may confound the links between maternal antenatal emotional state and cortisol is a dampening down of the HPA axis responsiveness later in pregnancy moreover the emotional state in pregnancy may alter the function of the placenta in other ways, independent of cortisol.

Chapter 7

7 RESEARCH METHODS FOR THE QUALITATIVE STUDY

7.1 Introduction

The purpose of this chapter is to outline the research methodology for the SIP Qualitative study and present an overview of this part of the thesis whilst providing the rationale for the use of qualitative analysis. The chapter continues with a discussion of the philosophical theory underpinning qualitative methodology and continues with a description of the methods used for data collection, a critique of the interview tool (LTE-Q) and an examination of 'think-aloud techniques', culminating in the conduct of the interviews and the participants involved.

7.2 Aims and purpose of the study

The aim of the study was to add valuable information to the knowledge base about women who have experienced a preterm birth from the perspective of the answers given to a Life Events questionnaire (Appendix 3). The main observational study gathered information using the List of Threatening Experiences Questionnaire (LTE-Q) and this was used in the quantitative analysis. However, the purpose of the qualitative study was to analyse the responses from LTE-Q as a complimentary technique within the semi-structured interviews, allowing a 2-phase approach to LTE-Q as discussed in chapter 5 (Brugha 1990). This also allowed an examination of 'think-aloud' methods to be explored in particular when using such a structured questionnaire within a qualitative study. Think-aloud technique has applications in psychological and educational research on cognitive processes and for the knowledge acquisition in the context of building knowledge-based computer systems (Van Someren et al 1994). In many cases the 'think-aloud' method is a unique source of information on cognitive processes. The exploration of this method within the format of LTE-Q allowed the researcher to understand women's responses to the questions as a preliminary qualitative investigation, which in turn generated information new to the SIP Study and enhanced the existing data. This information also aimed to generate data not identified by the observational method alone and therefore increase the understanding of the preterm birth experience.

Within the observational study a meta-synthesis of the literature review was conducted using Bradford-Hill's criteria (Chapter 4) as a systematic approach to review the literature and explore association and causation (Phillips and Goodman 2004, Elder et al., 1997). The use of causation in research is widely recognised within quantitative analysis and causal arguments are usually framed in terms of the effects of variables on each other. There is a distinction however, between the methods used in quantitative and qualitative research and can be described as a technical matter, with choice dependent on the specific question the researcher wishes to answer (Barbour 1996).

Quantitative methods are most appropriate for addressing questions of prevalence, causality, prediction, comparison and for measuring outcomes (Barbour 1996). Moreover, qualitative methods are used for addressing questions of process such as decision making, whereas perceptions, understandings and experience are not widely used in causal arguments (Mason 1996, Barbour 1996). However, developmental, mechanical and comparative arguments all imply something about why and how social phenomena or processes occur or operate, and in this sense qualitative research does deal with questions of causality (Mason 1996). Qualitative research wishes to speak and think of causation in a different way and may be particularly good at understanding causality because of its attention to detail, complexity and contextuality and because it does not expect to find a cause and effect in any straightforward fashion (Mason 1996). Qualitative research does provide insights into the process of data construction and it helps to identify relevant variables for study (Kingdon 2004).

The primary aim was to explore the stories women tell within their answers to a life events questionnaire (LTE-Q). The secondary aim was to explore causation by finding out whether women related stressful life events to their previous preterm birth experience. Therefore, the qualitative study aims to highlight the importance of contextual information given within the answers to LTE-Q which in turn enables the researcher to reflect the wider experiences of women and add valuable information to the study as a whole.

7.3 Qualitative methodology

Qualitative research is "exciting and important because it enables us to understand what matters to women and why" (Morgan 2004), through the development of concepts that help us understand social phenomena in natural rather than experimental settings with an emphasis on the meanings, experiences and views of the participants (Pope and May 1993, Pope and Campbell 2001). Qualitative research is distinctive from quantitative research in that it aims to answer questions such as "what, why and how" (Pope and May 1993, Kuper et al., 2008) taking an interpretive naturalistic approach to its subject matter. Qualitative researchers study things in their natural settings, attempting to make sense of or interpret phenomena in terms of the meanings that people bring to them, and as with quantitative methods, relies on data obtained through systematic empirical observation (Denzin and Lincoln 1994).

There are very different epistemological underpinnings to quantitative and qualitative methodology. These differences hinge on the distinction between positivist and the interpretivist / constructionist traditions, between the process of enumerative induction and analytic induction, between goals of prediction and intelligibility (Barbour 1996). Moreover, each paradigm covers a spectrum of approaches each with its own distinctive set of assumptions.

Constructionism emerged as a critique of objectivist epistemology, focussing particularly on reality as it is perceived and experienced by ordinary members of society in their everyday lives and that humans exist within an external world and that they are inextricably linked with that world (Dykes 2004). The constructionist epistemology is concerned with understanding from others perspectives and therefore, qualitative methodologies constitute an obvious way of eliciting this data (Dykes 2004, Kuper et al., 2008).

The appropriateness of the constructivist position is based in part on the researcher's philosophical stance and the nature of the data required. She (LW) suggests that it is her own values, beliefs and perspectives that have influenced the very basis of this study and the identification of the responses given through the use of the questionnaire. Because of this she

(LW) would claim that the research could not be value free. This concurs with Guba's view that enquiry cannot be value free. If "reality" can be seen only through a theory window many constructions are possible (Guba 1990). The conception of the researcher's role therefore changes significantly from a detached spectator to an involved participant, aiming to understand fellow human beings (Cuff 1990). Researcher reflexivity is actively acknowledging the role of the researcher in the research process (Morgan 2004, Mays and Pope 2000). It is with this in mind that constructionism provides a set of useful philosophical concepts to study the views of women.

There is value in mixing qualitative and quantitative research. Quantitative methods excel at summarising large amounts of data and reaching generalisations based on statistical projections. Qualitative research excels at "telling the story" from the participant's viewpoint, providing rich descriptive detail that sets quantitative results in their human context. Therefore, an interpretive approach was used to explore women's perceptions relating to stressful life events using LTE-Q as a framework within the semi-structured interview. Moreover the use of the LTE-Q tool enabled the exploration of these findings through the answers given.

7.4 Methods of data collection

Baseline data collected from the hospital computer records system (meditech), included age, previous pregnancies, mode of delivery, a history of mental illness, additional significant health problems, smoking and medication. Psychological morbidity was measured at 20 and 28 weeks gestation using, the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983) and LTE-Q (Brugha and Cragg1990).

Women were approached for one to one semi-structured interviews using the LTE-Q as a framework to explore common life events. Responses were written alongside each question and were scripted by the researcher. Member checking at 28 weeks formed part of the audit trail. Women read the transcripts from the previous interview checking, adding or deleting information and confirming the interpretation of answers, ensuring they resonated with their own perspective (Walsh and Baker 2004). Such an approach is controversial as a genuine test

of validity, however useful for the study as the researcher was writing the answers verbatim rather than transcribing from a recording. Field notes were used as a tool to research ideas about causation, general impressions, feelings, observations and also thoughts about concepts and links in information given within the LTE-Q (Walsh and Baker 2004).

7.4.1 List of Threatening Experiences Questionnaire (LTE-Q)

Researchers have long been interested in understanding how individuals and environments affect each other and one focus has been on life events. The measure of life events used in the SIP study was taken from the List of Threatening Experiences (LTE) developed by Brugha and colleagues (Brugha et al., 1985). The reliability and validity of the questionnaire version of the LTE (LTE-Q) was assessed by Brugha and Cragg (1990), in a study of 50 psychiatric patients and informants (Brugha and Cragg 1990). This study found a high test, re-test reliability and good agreement with informant information (Reid et al 2009). LTE-Q is a subset of 12 life event categories with considerable long-term contextual threat that has the reliability and validity of a brief life events questionnaire and can be used to measure a substantial proportion of external stress. The analysis presented by Brugha and colleagues, supports the proposition that a substantial proportion of measured adversity is accounted for by a relatively small group of the life events categories and can be covered in one inventory (Brugha et al., 1985).

This short inventory can be used where cost or other practical considerations preclude the use of more sophisticated methods which require extensive interviewing time and detailed training of users. It can also be used as a 2-phase approach within a semi-structured interview format by analysing the answers separately (Brugha and Cragg 1990).

7.4.1.1 Origins of Life Events research

In 1818 Heinroth first formally suggested the hypothesis that emotional conflicts related to external events can precipitate mental illness, in his designation of the term "psychosomatic." Later in the early part of the 20th century, Adolf Meyer popularised the "life chart" methodology. This approach emphasised the importance of dynamic interplay among biological, psychological and social factors such that important life events within a person's

biography became the foci of attention for studying health and disease (Atkinson et al., 1990, Chatterjee and Arora 2005). However there was no formal scale or schedule for assessing life events at that time.

Until the 1960's studies on the relationship between life stress and the development of physical and mental disease have relied mainly on investigating the health consequences of single events such as bereavement, divorce or retirement (Katschnig 1988). The publication of the Schedule of Recent Experience (SRE), a 42–item self-rating list of life changes with predetermined adjustment scores by Rahe and Holmes (1967) signalled the advent of a new methodological approach to establishing links between life stresses and illness (Kashnig 1988, Chatterjee and Arora 2005). However, in the 1970's recognition of a new generation of researchers began to challenge previous methods in particular, the development of life events interviews and life events scales (Brown and Harris 1988).

A number of tools for measuring life events emerged over time. Amongst them the Social Readjustment Rating Scale (SRRS) taken from the Schedule of Recent Experiences by Homes and Rahe (1967); the Schedule of Life Events developed by Pakel and colleagues (1975) and the Bedford College Life Events and Difficulties Schedule (LEDS) developed by Brown and Harris (1978). The LEDS scale is still the most widely used interview method and was the precursor to the Life Threatening Experiences Questionnaire (Chatterjee and Arora 2005, Brugha et al., 1985, Kashnig 1988, Holmes and Rahe 1967).

Life events can occur in a variety of domains such as family, health and work, at different times in life, in particular marriage, retirement and during pregnancy. They are also affected by history as in war or in times of illness or divorce. The relationship between stress and illness varies with pre-existing vulnerability factors such as social support systems, skills, attitudes, beliefs, and personality characteristics, rendering some people relatively immune to stress induced illness and other relatively susceptible (Burns 1988, Atkinson et al., 1990).

Today it is unanimously accepted within health care that exposure to daily life stressors, have an important causal relationship on health and well being, nevertheless, controversy remains

over the use of tools to measure life stressors. Two contrasting methods of measuring life events have developed over time, the checklist (inventory) and the personal interview (panel). The Schedule of Recent Experience (SRE) is used to illustrate the checklist approach and Life Events and Difficulties Scale (LEDS) the panel technique (Brugha et al., 1985, Katschnig 1988, Brown and Harris 1988). Despite their popularity however, checklists have been criticised on their reliability and validity as a measure of stressor exposure. Whereas the personal interview through the use of qualitative probes, specifying precisely the characteristics of life events is thought to be able to produce the actual risk of illness and the timings of life events in relationship to the outcomes (Chatterjee and Arora 2005).

The SIP study used a mixed methods approach by using the yes / no answers to LTE-Q as a quantitative analysis and the extended responses given within the answers were analysed thematically, allowing the women's framework of meaning to those questions to be explored. Therefore the use of LTE-Q was two-fold and was deemed to be the best tool to use within the semi-structured interview and within the confines of a busy antenatal clinic.

7.4.2 Hospital Anxiety and Depression Scale (HADS)

HADS is a 14-item scale (Appendix 2) providing a brief state measurement of anxiety (7 items) and depression (7 items). It is self-administered, takes about 10 minutes to complete and determines how participants have been feeling in the past week. Each item scored from 0 to 3, the total scores range from 0 to 21 for both anxiety and depression sub-scale. Score ranges can be classified as a measure of severity with normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) with higher scores indicating greater anxiety or depression (Zigmond and Snaith 1983).

7.5 Critique of the Research Tool

The interview is a flexible and adaptable way of findings things out, and is described as a kind of conversation, a conversation with a purpose (Robson 2002, Walsh and Baker 2004). It is initiated by the interviewer for the specific purpose of obtaining research-relevant information, focussing on content specified by research objectives of systematic description, prediction or explanation (Cohen and Mannion 1989). Much qualitative work is interview

based and there is a consensus that there are three main types of interviews: structured, semi-structured and unstructured interviews (Britten 1995, Walsh and Baker 2004).

Structured interviews consist of administering questionnaires. Interviewers are trained to ask questions, mostly fixed choice, in a standardised manner. This approach has similarities to the quantitative survey and is predominantly utilised in this way (Walsh and Baker 2004, Carter and Henderson 2005). Structured interviews do not exclude the possibility of the use of unstructured questions but these are at the prerogative of the interviewer, not the interviewee.

Unstructured or in-depth interviews give the interviewee control of where they want to take the topic of enquiry and may only cover one or two issues. This frees research participants to talk about the topic without feeling constricted by the questions set by the interviewer (Pope and Campbell 2001). However despite the open-endedness of this style the researcher continues to influence the focus by prompting questions through the dynamic of emerging themes in the data (Walsh and Baker 2004). Therefore, this requires active listening and constant reflection to draw the interviewee out by formulating new questions in response to what is being said.

Semi-structured interviews are based on a mix of open and closed questions centred around a topic. The strength of this format allows the interviewer and the interviewee some flexibility to diverge from the outline and add to or develop questions (Carter and Henderson 2005). Unstructured and semi-structured interviews both require sensitivity and flexibility from the interviewer, and the careful use of follow-up questions or 'probes' to draw out the topic and gather detailed information. This format also has the ability to uncover unanticipated ideas of the research question not previously considered (Pope and Campbell 2001) providing an opportunity to follow up interesting responses and observe non-verbal cues, which help to understand the verbal response. This has the ability to change or in some cases reverse its meaning giving the potential for rich and illuminating material. A limitation with this method however, is that people may find talking about their experiences and being interviewed a difficult process (Robson 2002).

The standardised health status questionnaire is used widely to obtain subjective assessments of health, however there is little research investigating the meaning of the data they produce. Statistical tests will highlight some problems with the structure and wording of a questionnaire, but they cannot shed any light on the way in which respondents interpret questions or their intended meaning when they select a response (Mallinson 2002). Questionnaires therefore, have a problem of meaning and failure to consider subjective interpretation within the evaluation of response. Mallinson (2002) argues that psychological and sociological evidence show that the processes involved in interpretation of questions and the formulation of answers are complex and even slightly amended response options will mean that different people will give different answers.

Standardised questions are used to avoid potential sources of bias that arise when questions are reworded but this does not automatically standardise meaning. The meanings that respondents intend to convey with their reply can only be explored through in-depth probing, resembling a natural conversation where people intuitively probe to establish intended meaning. Therefore the issue of meaning is absolutely central to understanding subjective views and the limitations in using a questionnaire for qualitative data collection can only be overcome if used within a semi-structured interview format (Mallinson 2002, Carter and Henderson 2005).

Multi-method approaches are increasingly advocated in health service research and the use of standardised self-completion questionnaires within in-depth interviews in qualitative research has been termed "questerviews" (Adamson et al., 2004). The conventional focus of the separation of quantitative and qualitative approaches has been predominant with much scepticism that integration is possible. Moreover, qualitative methods are still seen as supportive, in assisting in the derivation of variables or helping to provide explanations for unexpected results. Rarely are the two approaches seen as being integrated equally (Adamson et al., 2004, Kingdon 2004). More recently there has been a move to explore the meanings and interpretations of standard survey questions, using qualitative methods (Mallinson 2002). Adamson et al., (2004) suggest that the incorporation of standardised questions in qualitative

interview topic guides using the technique of "questerviews" is a tangible and pragmatic way of doing this by validating survey data and enhancing quantitative data.

The semi-structured interview was considered to be the most appropriate strategy when considering the overall objectives of the SIP Study. The use of a predetermined framework within LTE-Q enabled the same topics to be covered with each woman, whilst still allowing women to have flexibility in their answers and identify areas perhaps neglected by the interviewer. It confirmed the pre-specified topics (life events) to be discussed and explored, as well as new areas or ideas being uncovered. By encouraging some freedom within the interview schedule women were able to explore and discuss their experiences, enabling the interviewer to check that they had understood the respondents meaning, instead of relying on their own assumptions (Britten 1995).

Preparation for interviewing can be time consuming. Arrangements to use private rooms or visit women at home and confirming arrangements, rescheduling appointments if necessary all require planning and time. The transcribing of questionnaire answers, although less time consuming than in-depth interview tapes can still be a lengthy process. The actual interview session can vary in length with the women themselves dictating the length of the individual interview.

7.5.1 The use of questionnaires in qualitative research

Questionnaires in qualitative research and within semi-structured interviews are based on open ended questions that define the area to be explored. Good questions in qualitative interviews should be open ended, neutral, sensitive, and clear to the interviewee, based on behaviour or experience, on opinion or value, on feeling, on knowledge, and on sensory experience and those asking about demographic or background details (Pope and Campbell 2001).

Most qualitative researchers will have a list of core questions to be covered, unlike quantitative interviews which are based on highly structured questionnaires the order in which questions are asked will vary. As will the questions designed to probe the

interviewee's meanings. Wordings should not be standardised as the interviewer will try to use the person's own vocabulary to frame further questions as she becomes more familiar with the topic being discussed. In general large qualitative studies do not often interview more than 50 or 60 people, although there are exceptions (Holland et al 1990).

Interview probes are generally described as three types:

- Detail-orientated probes using questions such as; when did this happen in your life? How are you going to deal with the situation?
- Elaboration probes are based on questions such as; can you give me an example of what you are talking about? I'd like to hear you talk more about that?
- Clarification probes tend to ask for an expansion to the answers given by stating; I'm not sure I understand what you mean, can you talk a little bit about that? (Kuper et al 2008).
- Qualitative studies address different questions than those addressed by quantitative research and qualitative interviews try to be interactive and sensitive to the language and concepts used by the interviewee by keeping the agenda flexible. They aim to go below the surface of the topic being discussed, explore what people are saying in as much detail as possible and uncover new ideas that were not anticipated at the onset of the research. The use of questionnaires within qualitative research is controversial and most qualitative researchers would not recognise questionnaires as an appropriate toolbecause they commonly require the subject to respond to a stimulus, and thus they are not acting naturally. Nevertheless they have their uses, especially as a means of collecting information from a wider sample than can be reached by personal interview. The use of interview probes within a structured questionnaire format is similar to the 'think-aloud technique', a method borrowed from cognitive psychology to investigate thought processes whilst performing tasks (Hurd 2007).

7.5.1.1 Think-Aloud Technique

Think-aloud technique is used widely in protocol analysis. It concerns verbal and written protocols that result from instructions to think aloud during a task. Ericsson and Simon (1980) proposed that participants can give concurrent verbal expression to their thoughts (think aloud) while completing tasks without changing objectively measurable performance

(accuracy). These involve the respondent reporting aloud about what they are doing, 'think aloud technique' (Fox et al 2010).

This method can be used by psychologists and other social scientists who want to know more about cognitive processes (Van Someren et al 1994). Participants are instructed to verbalise overtly all the thoughts they would normally keep to themselves. However, it is not the participants' task to explain or verify the cognitive strategies behind what they are doing, neither to report their elementary sensations as in the classical method of introspection. Verbal report is a research tool of cognitive science for studying the cognitive content of thinking, such as the relation between verbal and non-verbal codes, serial vs. parallel thoughts, and how to maximise the accuracy and minimize the reaction of thinking aloud upon the content of thinking. The unquestioned assumption is that thinking aloud mirrors internal cognitive processes of symbolic activity that are the basis of thinking (Richardson 1996).

The use of this research method supports the theory that since thoughts are concurrent rather than retrospective, they are considered to be more authentic and less structured than the results obtained from the use of questionnaires alone. A major advantage is their human quality, in that they give the data, 'a unique soul', deepening our understanding of human cognitive processing (Marcella et al 1999).

However, one problem with data from this technique is that respondents often raise tantalising points, but don't unpack them. Therefore, common prompts are used to ask the respondents for general thoughts on the subject being investigated. The need to develop conversational rapport and to put the respondent at ease is essential. In the execution of a comfortable interaction between the researcher and the interviewee, it is recognised that impromptu discussions tend to take place, with respondents taking the opportunity to voice opinions on unrelated issues (Hurd 2007).

It is important whilst using this method that an open conversation develops, rather than an interrogation. The researcher undertaking data collection using this methodology must be

approachable, flexible and able to adjust his/her communications style to the individual respondent. This methodology successfully gathers a variety of interlinked forms of highly informative data, via a single data collection tool, in order to achieve simultaneously both a rich source of revealing information and qualitative reflections (Marcella et al 1999).

7.5.2 LTE-Q

LTE-Q format is based on the use of closed questions allowing a quantitative measure of life events to be analysed. However, it can be used as a 2-phase method of data collection within a semi-structured interview where the data is scored using a panel of experts when used for psychological assessment purposes. However, for the purposes of this study, an approach similar to the 'think-aloud technique' was used and responses were analysed thematically using framework analysis. The qualitative study was designed during the course of data collection early in the project when the researcher (LW) recognised that the responses to LTE-Q were being interpreted by the women themselves and women were answering about their previous preterm birth experience to which ever question they felt appropriate. This in turn naturally stimulated the use of interview probes by the researcher and culminated in the uncovering of feelings and experiences from the women not covered by the interview tool alone. These responses in return needed to be explored in more depth using qualitative methodology. Therefore the epistemological stance of knowledge and the objective approach of enquiry was used to establish whether stressful life events in relation to a previous premature birth were an important factor for this group of women.

Moreover, good research qualitative and quantitative is designed as well as improvised. One of the merits of qualitative research is its particular openness to serendipitous invention. However one of its failures has been an unwillingness or inability on the part of its practitioners to specify how that openness to 'what situations make available' can be both systematic and creative (Silbey 2003).

Qualitative research is celebrated for its flexibility, the temporal coincidence of collection and analysis and should be able to adjust to the forms of data, modes and cites of collection in response to the ongoing processes of analysis and interpretation. Moreover, all research

develops, throughout stages of design, collection and analysis. Almost all research both quantitative and qualitative, produces much that was unanticipated and therefore had to be responded to with adjustments along the way

The LTE-Q tool collected data through the use of the structured format, however it also enabled the use of interview probes to clarify and open out the discussion uncovered within the answers.

This supports the argument that the mode of analysis rather than the type of data more appropriately describes work as qualitative as long as the researcher provides an account of how the conclusions were reached, the form of data collected, how the data will be put into a form appropriate of manipulation and analysis, how the data will be analysed and synthesized.

It is easy to fall into the trap of using questionnaires like a form of laboratory equipment and to forget that like most social research tools they are open to interpretation. The issue of meaning is absolutely central to understanding subjective views and without the assessment of women's understanding of the questions through qualitative analysis it is difficult to establish their validity.

7.6 Sampling and setting

Women were recruited as a purposive sample attending the Preterm Labour Antenatal Clinic at the Liverpool Women's Hospital. Purposive sampling is appropriate when using a Phenomenological approach due to the importance of selecting individuals who have knowledge of the phenomena concerned (Clifford 1997).

7.7 Ethical approval

Ethical approval was received in 2004 from the local ethics committee.

7.7.1 Consent

Information sheets were given to all women attending the clinic during the first appointment and written consent was obtained and signed in triplicate for all participants, details in Chapter 5.

7.7.2 Confidentiality and anonymity

Confidentiality cannot be totally offered in qualitative research because reporting the findings will entail using quotations from interviews. All that can be offered is anonymity, so that identities are protected through the use of pseudonyms or codes (Manning 2004). All interviews were conducted in private rooms within the antenatal clinic setting ensuring privacy. At recruitment each woman was allocated a code allowing questionnaires to be identified to particular women, matched to the HADS score, maternal serum samples in the laboratory and the information from the booking history. This enabled individuals to be identified by the researcher and thus securing women's anonymity. The researcher (LW) was the only person to have access to the identification of the codes.

7.7.3 Handling and storage of data

Data from the semi-structured interviews and HADS were kept on the researchers (LW) computer at the Liverpool Women's Hospital on a secure drive with access only by a personal password. Disks and paper copies were kept in a locked cupboard in a secure room at the hospital.

7.8 Data analysis

Analysis of the transcripts began at the end of the clinic after the semi-structured interviews and completion of the questionnaires, allowing the process to be iterative, dynamic, cyclical and reflexive (Carter 2004). Answers to LTE-Q were written in long hand by the researcher at the time of the interview at 20 weeks and 28 weeks and typed at the end of each interview into a more readable format. Where possible the data from the first interview, was given back to the participants at the 28 week visit to obtain validation or "member checking" (Carter 2004) a technique in which the researcher's account is compared with those of the participants to establish a level of agreement. This approach is considered controversial by

some writers, as a genuine test of validity (Mays and Pope 2000). However, it was considered useful for this study as the answers were written and not recorded verbatim.

7.1.8 Interpretive approach

Qualitative data analysis does not attempt to present reality, it is interpretative, allowing different researchers to perceive and interpret data in different ways (Carter 2004). The research process is an iterative one, moving from collection of data to analysis and back until the description is comprehensive.

Analysis of qualitative data should be cyclical and reflective, as an ongoing process through all stages of the research. The researcher reads the transcripts several times in order to gain an overall impression of the data, allowing this repetitive process to reveal previously unnoticed words. This process of breaking up or down of the data permits the researcher to see it in a new way (Sandelowski 1995). This stage of analysis related to the major points of interest and shared characteristics. Patterns and themes are then identified and grouped together. Repeatedly returning to reconsider and be reflexive, involves self scrutiny by considering the researchers influence on the data. Therefore, all research is interpretive and is guided by a set of beliefs and feelings about the world and how this should be understood and studied.

7.1.9 Framework analysis

Framework analysis was developed by the National Centre for Social Research as a content analysis method which involves summarising and classifying data within a thematic framework. Framework analysis is a qualitative method that is aptly suited for applied policy research and is better adapted to research that has specific questions, a limited time-frame, a pre-designed sample and a priori issues (Srivastava et al 2009).

Although similar to grounded theory, the key difference between this and 'grounded theory' approaches is that the integrity of individual respondents accounts is preserved throughout the analysis, rather than the deliberate attempt to 'fracture' the data in order to open up new avenues for analysis (Mason 1996). Reflecting this focus on maintaining the integrity of

respondent's narratives, in the analysis, data is sifted, charted and sorted in accordance with key issues and themes using five steps: familiarization, identifying a thematic framework, indexing, charting, and mapping and interpretation. This involves listening to tapes and re-reading field-notes or transcripts until the researcher is closely familiar with their entirety. Following on, the next step is a thematic analysis to develop a coding scheme, where themes in the data become the labels for codes (Srivastava et al 2009.

In framework analysis the process of applying codes to the whole data set in a systematic way is described as indexing. Like grounded theory, the analysis part of framework analysis entails comparison, both within and between cases. This is facilitated by charting, which involves rearranging the data according to this thematic content, either by case or by theme. These charts contain only summaries of data and examples in the charts are referenced back to the original transcript (Mason 1996, Srivastava et al 2009).

Framework analysis is flexible during the analysis process in that it allows the user to either collect all the data and then analyze it or do data analysis during the collection process. A narrative approach was used for the SIP study which aimed to tell women's stories through the answers to LTE-Q and how the experience of a preterm birth had impacted on their every-day lives, therefore framework analysis was deemed to be the most suitable approach for this purpose.

What moves framework analysis beyond a sophisticated thematic analysis is the final stage of looking at relationships between the codes, known as mapping and interpretation, where diagrams and tables can be used to physically explore the relationships between the concepts and typologies developed from them, and associations between the concepts (Srivastava et al 2009.

Framework analysis provides an appropriate approach where the research questions are predetermined. Thus in the context of the SIP study this enabled an exploration of what women were answering to the structured format of the LTE-Q questionnaire. Moreover, it identified how these answers compared to the definitions that were prompted and how the

use of terms varied across the sample. This in turn helped to arrange the data by creating themes, by looking across the interviews allowing the criteria to be identified in terms of how women judged their previous pregnancy experience. Therefore the use of LTE-Q guided the thematic framework.

Devising and refining a thematic framework is not an automatic or mechanical process, but involves both logical and intuitive thinking. It involves making judgements about meaning, about relevance and importance of issues, and about implicit connections between ideas. Strategies are used to increase the credibility of the findings and the believability and authenticity of the analysis by using quotes from the interview transcripts as examples of particular definitions. This allows the interpretation built from the data to be explicit and through maintaining enough detail to judge the content of women's accounts.

To minimise interpreter bias and assess the plausibility and trustworthiness of the researchers (LW) interpretation of the data, a sample of the answers were themed independently by another member of the research team (SQ).

7.9 Discussion

The SIP Qualitative Study used framework analysis approach to analyse the responses to LTE-Q. This study will go some way to understand the complex perspectives of women with a previous preterm birth. Through the process of actively listening to women and seeking to understand their personal story, we should be more able to match our midwifery interventions and care to individual circumstances. This is fundamental to the professional health care ethic. Moreover, from a public health perspective, this study should generate interest given the lack of published literature pertaining to pregnant women's experiences of a previous preterm birth, life events and stress. This new information will lead to future midwifery investigations of women's experience of a preterm birth using a more explorative in-depth qualitative methodology.

Chapter 8

8. PROTOCOL AND SYSTEMATIC LITERATURE REVIEW FOR THE SIP QUALITATIVE STUDY.

8.1 Introduction

The aim of the systematic review was to explore qualitative literature to gain insight into relevant information uncovered in the qualitative study. A qualitative approach deals with how people understand their experiences and is generally used more within the discipline of midwifery. As maternal stress and anxiety play an important role in the psychological wellbeing of all pregnant women, this review was important in identifying information that has explored women's views in relation to a previous history of preterm birth or pregnancy loss.

The review focussed on qualitative information in order to understand the area of investigation and to determine whether this corresponds with the findings of the qualitative study which in turn focussed on the experiences of pregnant women with a history of recurrent spontaneous premature labour in relation to a life events questionnaire used within a semi-structured interview format. Nevertheless, due to the scant amount of data uncovered the search also included papers describing recurrent pregnancy loss (PL).

An overview of the literature is presented from the author's perspective, in order to explore the issues that she perceives as salient to the study. There is a wealth of literature published of women's views about labour and birth; few studies however have explored women's views in relation to preterm labour/birth and life events. In order to identify systematically and present a representative body of literature, a search was conducted limited to qualitative studies in English only. The review presents the literature eliciting information to support the study.

The search was undertaken on two occasions, once by the researcher alone (LW) and secondly with the support from an information retrieval expert (LH). Several difficulties

with the first electronic search were encountered and an unmanageable number of potentially relevant papers were identified when using the term miscarriage, pregnancy loss and preterm birth. Extra support therefore was needed for the second search and with the combination of literature searching expertise and the researchers own subject knowledge a more targeted and precise retrieval of literature was undertaken. Some of the difficulties in the first search also related to the varied and imprecise use of the term "qualitative" which was emphasised by the wide range of study designs and collection methods cited in the publications.

How qualitative research questions are formulated has implications for the literature review. Some researchers believe that a thorough literature search should be conducted at the beginning of the research process, as is often the case in quantitative studies (Cresswell 1994, Miles and Huberman 1994). These authors argue that researchers must describe their project in terms that are familiar to key groups (peers, funding bodies) and that reading the existing literature can save time and help strengthen the study design. However, others believe the existing literature should be reviewed only after the research is underway so researchers have an opportunity to gain some understanding of the phenomena of interest from the research participant's perspective (Crabtree and Miller 1999). Reviewing the literature earlier may impede the researcher from truly listening, observing and remaining open to new concepts and ideas. Within the SIP qualitative study the review was conducted after data collection to investigate whether there was evidence supporting themes and categories identified within the study through the use of the interview tool.

8.2 Aims and Objectives

The aim of the protocol was to outline the process for a search of literature in a systematic way. The objective was to enable the identification of papers that have explored women's views in relation to the experience of preterm labour/birth or pregnancy loss in a subsequent pregnancy.

8.3 Selection criteria

Inclusion criteria:

- Women's experience of preterm labour/birth
- Women's experience of pregnancy loss
- Women's experience of a subsequent pregnancy after preterm labour/birth
- Women's experience of a subsequent pregnancy after pregnancy loss
- Exclusion criteria:
- Papers not published in English.
- Papers using non-qualitative methodology.

8.3.1 Type of studies

Eligible qualitative papers were reviewed and included data collected through the use of questionnaires, structured interviews, semi-structured interviews, focus groups and in-depth interviews.

8.3.2 Type of participants

Women with a history of preterm labour/birth or pregnancy loss and their experience in a subsequent pregnancy.

8.4 Search strategy

Two electronic databases were searched with the help from an independent information retrieval expert (LH) for papers describing stress, anxiety and depression during pregnancy, preterm labour/birth, pregnancy loss, women's experiences, women's views and qualitative methodology. Identifying papers involved a variety of other techniques carried out solely by the researcher (LW). Citation tracking (following up reference list in the bibliographies of papers and reports), hand searching midwifery journals which included; MIDIRS midwifery digest, the British Journal of Midwifery, Midwifery, Midwives (the RCM Journal) and Evidence Based Midwifery (RCM) and utilising web-sites for example the DOH.

8.4.1 CINAHL - Cumulative Index to Nursing and Allied Health Literature via OVID (1982 – 2009)

1. CINAHL; LABOR, PREMATURE/; 1449 results
2. CINAHL; (preterm OR premature).ti,ab; 10449 results
3. CINAHL; (labor OR labour).ti,ab; 9637 results
4. CINAHL; (pregnancy AND loss).ti,ab; 786 results
5. CINAHL; 2 AND 3; 968 results
6. CINAHL; 1 OR 4 OR 5; 2641 results
7. CINAHL; "subsequent pregnancy".ti,ab; 166 results
8. CINAHL; "next pregnancy.ti,ab; 26 results
9. CINAHL; 7 OR 8; 188 results
10. CINAHL; 6 AND 9; 39 results

8.4.2 PsycINFO

((next pregnancy) or (subsequent pregnancy) or (new pregnancy)) and ((preterm birth) or (premature birth) or (pregnancy loss))

8.5 Methods of the review

Papers were rejected on initial screen if the reviewer (LW) could determine from the title and abstract that the article did not describe stress, anxiety and depression during pregnancy, previous preterm birth, previous pregnancy loss, women's experiences, women's views and qualitative methodology. When the title or abstract could not be rejected with certainty, the full text article was obtained for further evaluation. Only published papers were reviewed and no authors were contacted.

8.5.1 Critical appraisal of studies

The inclusion of studies was assessed independently by two reviewers (LW and SQ). An data extraction table was designed specifically for this review using headings for the identification of relevant information by two reviewers (LW and SQ). Studies were selected in a reproducible and objective fashion. Data included was recorded as; author, year, country; sample size, description; methodology; tools, analysis; findings; comments.

8.6 Literature search results

The electronic search yielded 131 papers, CINAHL identified 39 of which 7 were eligible, PsycINFO identified 92 of which 5 were eligible. Hand searching identified through journals and reference lists yielded 10 papers of which 1 was eligible. In total 141 papers and abstracts were assessed for the literature review of these, 13 papers were included (Table 17) and 128 excluded.

Table 17 (8.6)

INCLUDED STUDIES RELATING TO WOMEN'S VIEWS OF PREGNANCY LOSS AND PRETERM BIRTH

Author/Year/ Country	Sample size/ description	Methodology	Tools / Analysis	Findings
Cote-Arsenault D Mahlangu N (1999) USA	72 women one or two perinatal losses	Descriptive study Self-administered questionnaires	Thematic analysis	Past pregnancy Current pregnancy Self Anxiety Safe passage Ways of coping Binding-in Grief and loss Points in time Ways of coping
Cote-Arsenault D Dombeck MTB (2001) USA	72 women one or two perinatal losses	Descriptive study Self-administered questionnaires	Spielberg State-Trait anxiety Inventory. Pregnancy anxiety scale (PAS)	Assignment of fetal person-hood Pregnancy anxiety State anxiety Guarded emotions Anxiety about pregnancy Marking off progress
Cote-Arsenault D Morrison-Beedy D (2001) USA	21 women 3 focus groups Snowball sampling	Phenomenology Interpretive cross-sectional study	Colaizzi's procedural steps Thematic analysis	Dealing with uncertainty Wondering if baby is healthy Waiting to lose baby Holding back emotion Loss happened and can happen again Changing self
Cote-Arsenault D Bidlack D (2001) USA	73 women PL Support Groups	Survey Self-admin questionnaires Open responses	Content analysis (Weber 1990) Thematic analysis	Losing another baby Health of baby Emotional stability of self Impact of another loss on future Lack of support Fear of bad news Own impact on baby Worries never end

Smith Armstrong D (2002) USA	103 couples 3 groups	Cross-sectional survey Structured and telephone interviews	Depression Scale (CES-D) Pregnancy outcome quest (POQ) Prenatal attachment inventory (PAI)	Pregnancy specific anxiety in subsequent pregnancies Depression Pre-natal attachment
Tsartsara E Johnson MP (2006) Greece	17 pregnant women	Interpretative Phenomenological Analysis Semi-structured interviews	Thematic analysis	Confusion Emptiness Guilt Fear of falling pregnant again Denial
Modiba L (2008) South Africa	10 mothers	Phenomenological interviews 4 phases	Thematic analysis	Lack of control Uncertainty Fears about the baby
Mackey MC Coster-Shultz MA (1992) USA	10 women	Naturalistic Purposive sampling Semi-structured interviews	Thematic analysis	Feeling unbalanced Sensing unbalance Responding emotionally
Coster-Shulz MA Mackey MC (1998) USA	10 women in PTL and P/N	In-depth interviews	Thematic analysis	Aware something was wrong Feeling unbalanced Making sense of experience Addressing other life stessors Emerging from the PTB experience with added growth
MacKinnon K (2006) Canada	8 women Home Care Program	Institutional Ethnography In-depth interviews	Thematic analysis	Fear of going home Feeling alone Responsibility of keeping the baby in
Barlow JH Hainsworth JM Thornton S (2007) UK	8 women in hospital	Exploratory descriptive study Semi-structured interviews	Thematic analysis	Uncertainty The search for meaning Communication Attribution of causality Coping with pregnancy and admission Ambivalence Prior experience Re-evaluation of life-style
Danerek M Dykes AK (2007) Sweden	17 mothers 6 fathers	Grounded theory In-depth interviews	Thematic analysis	Inter-adapting Interaction Re-organising Caring
Moyzakitis W (2004) UK	6P/N women with distressing births	Semi-structured interviews Feminist approach	Thematic analysis	Role of caregiver Impact on self image Impact on relationships Severity of experience

8.7 Importance of exploring women's views of preterm birth and pregnancy loss.

Exploring women's views of PTB and PL is based on the assumption that psychosocial stress increases problems in pregnancy such as, premature labour, intrauterine growth restriction, low birth weight, miscarriage and congenital malformations. This has been a focus for many disciplines over the years (Mutale et al., 1991, Cliver et al., 1992, Hedegaard et al., 1996, O'Hare and Creed 1995, Arck et al., 2001). The association however remains controversial. Nonetheless, findings from the SIP Qualitative study reinforced the assumption that some women view their previous experience as vindication for stressful events in their lives. This highlights the importance of gathering contextual information to reflect the wider needs of this group of women when they access midwifery care.

Reviewing the published literature confirmed a paucity of qualitative midwifery research that relates solely to pregnant women's experiences of PTB. At present little is understood about the levels of stress women endure when they have experienced a PTB and are pregnant again.

An appraisal of the literature uncovered a range of approaches investigating women's experiences using qualitative methodology. Studies that explored the relationships of pregnancy loss in a subsequent pregnancy are examined first followed by the experience of premature labour and finally the emotional depiction of loss as 'disenfranchised grief.'

8.7.1 The impact of perinatal loss on a subsequent pregnancy.

Six studies examined the relationship of perinatal loss on a subsequent pregnancy. The first exploring pregnancy after perinatal losses at various gestations quantified the perception of person-hood to the lost fetus (Cote-Arsenault and Dombeck 2001) and found that the more importance women assign to what they have lost in a previous pregnancy influences the amount of anxiety they experience in a subsequent pregnancy. As pregnancy progresses emotional attachment to the fetus is linked to the attribution of person-hood. This highlights the internal battle with anxiety many pregnant women have in wanting to protect themselves emotionally throughout a subsequent pregnancy, by deliberately not assigning 'person-hood' to their unborn baby, just in case the pregnancy does not continue. This analogy illuminates

the co-existence of both negative and positive feelings felt by women with this shared history and offers important insights into women's perspectives of a subsequent pregnancy.

Women (n=72) who had lost babies during pregnancy, were found to acknowledge that a successful outcome was not guaranteed. This second study described guarded emotions, anxiety about pregnancy and in marking off progress in terms of safety and development of the baby. There was a sense of self having been affected by the past experience with attributed feelings of shock, denial and anger. The authors describe a more distant emotional attachment being used as a protective mechanism by women with the aim of surpassing significant points in time or milestones. Coping through changed behaviour to ensure the safe passage for themselves and the baby seemed to be influenced by the amount of anxiety measured in pregnancy. However, the overriding fear was of a recurrence of pregnancy loss that manifested in a guarded attachment to the new pregnancy (Cote-Arsenault and Mahlangu 1999).

A later study by the same author, Cote-Arsenault and Morrison-Beedy (2001) explored pregnancy loss and long-term effects. Losses ranged from 34 years ago to the previous year. A snowball sampling methodology was used with three focus groups. Women (n=21) portrayed loss as a life-altering event, not feeling emotionally safe despite the type of losses, the gestation or the time frame involved. Themes included: dealing with uncertainty, wondering if the baby is healthy, waiting to lose the baby, holding back emotion, acknowledging that loss happened and it can happen again and changing self. The feeling of a loss of control and a sense of accomplishment when surpassing the time of a previous loss were found, together with emotions of high anxiety and looking at pregnancy as a process to get through. For some, the previous experience was an assault on their core identity and self-confidence, losing belief in them-selves and thus affecting their relationships. The study indicated many common experiences with women, in particular dealing with uncertainty, highlighting the need for midwives to acknowledge that pregnancy and birth experiences, often many years ago continue to have long term effects on some women in a subsequent pregnancy.

A survey again by the same primary author (Cote-Arsenault and Bidlack 2001) with a convenience sample of women from a pregnancy loss support group (n=73) involved pregnant and non-pregnant women. Eight categories of concerns were identified, including losing another baby, emotional stability of self, impact on another loss on the future and worries that never end. The main findings were scepticism about pregnancy after a previous loss. This study emphasises that clinicians should be cognisant of the constellation of concerns and emotions experienced by women and therefore should provide the supportive care throughout a subsequent pregnancy. However, the study was limited due to the composition of the sample, which included a minority of women (n=17) currently pregnant with the majority not pregnant (n=56). Nevertheless, the authors found that women frequently used words like, anxious, scared and nervous, with the pregnant group fearing losing another baby, worried about the overall health of their baby and that their feelings were having a negative impact on the baby. They experienced a constant fear of being given bad news, expressed as 'will my body fail me again.'

One paper compared three groups of couples and examined levels of depressive symptoms, pregnancy specific anxiety and prenatal attachment in a subsequent pregnancy after pregnancy loss (Smith Armstrong 2002). Groups divided into couples with a history of pregnancy loss (n=40), pregnant for first time (n=33) and previous successful pregnancies (n=30). Structured questionnaires and telephone interviews measured depression and anxiety in both fathers and mothers and concluded that depressive symptoms affected parent infant attachment. Unsurprisingly, higher rates of depression were found in parents with a history of loss than in first time parents. An obvious limitation of the study, acknowledged by the author in terms of using volunteers who may not be a representative sample of expectant parents at large. Moreover, this study may reflect only the experiences of those most affected by their loss or those parents most interested in sharing their stories with researchers. Nevertheless, highlighting emotional distress after pregnancy loss in a subsequent pregnancy is important, supporting the need to reduce psychological distress in the future through interventions to reduce anxiety. This is an important focus for the midwifery profession to explore, by offering families extra support in partnership with other services throughout a subsequent pregnancy.

The literature review identified the most dominant emotion reported was anxiousness which is congruent with the choice of anxiety as the most common variable used in a wide variety of research exploring views of women after pregnancy loss. Identifying and supporting this vulnerable group of women by acknowledging their previous experience may help them articulate their emotions during pregnancy and perhaps reduce anxiety.

Tsartsara and Johnson (2006) interviewed women (n=17) with a variety of past obstetric histories including miscarriage using Interpretive Phenomenological Analysis (IPA). Two dominant themes emerged, the 'uncertainty of pregnancy' and the 'dual nature of pregnancy' identifying the apprehensions and anxieties experienced regarding the outcome of a subsequent pregnancy. The paper portrayed a pre-occupation of fear and uncovered the meaning women attached to their ongoing pregnancies. This was reflected through a questioning of the ability to fulfil their feminine identity, their capacity to reproduce and the social role of motherhood. Anxiety expressed by women irrespective of the type of loss gives insight that each pregnancy is experienced as leading to a unique baby, a unique chance to achieve motherhood and is a unique indicator of personal success for a woman's feminine identity.

Finally, Modiba (2008) explored experiences of mothers (n=10) with pregnancy loss in order to develop a care programme to support women better. The study found a mixture of psychological and physical symptoms. Women expressed feelings of confusion of losing one's mind and emptiness conveyed as 'no fulfilment.' Sadness of losing the baby with emotional pain and anger targeted towards themselves, nurses and doctors. Feeling of guilt as if they may have caused the death, fear of becoming pregnant was an overarching symptom, as well as feelings of denial at losing the baby. For some, this was expressed as failure to fulfil expectations, frustration, loneliness and lost hope of becoming pregnant again.

8.7.2 The preterm labour experience

The preterm labour and birth experience is notably absent from midwifery/qualitative literature with five studies found. Treatment for PTL is often antepartum bed rest at home or

in hospital, with admission to hospital increasing the likelihood of stress and anxiety for women.

The first paper by Mackey and Coster-Shultz (1992) described how women cope with the stress of PTL and bed-rest at home and identified situational stressors including lack of control, uncertainty and fears about the baby. Moreover, the authors argue that most of the research locates the responsibility for coping solely with women and families and does not investigate how women's experiences are socially organised. Women with a previous PTL experience became more conscious of their body signals as a profound sense of personal responsibility for preventing it happening again, of being careful, in terms of almost suspending their lives. Women felt that they were alone with this responsibility at home and engaged in self-regulating activities.

A later paper by the same authors (Coster-Shulz and Mackey 1998) used a naturalistic design to recruit a purposive sample of women. Semi-structured interviews were conducted and views expressed about interpreting and managing pregnancy, feeling unbalanced as if there was something wrong, physical and emotional changes, fear for the safety of the baby and their ability to manage a pregnancy. Women with a previous PTB felt anxious it would happen again and described being scared as if life was on hold and that the world they knew had come to a standstill. Moreover, women in this study reported multiple stresses in their lives, suggesting that stress was a serious problem for them and may be related to PTL as other studies have found (Hedegaard et al., 1992, Mutale et al., 1991, Mackey & Coster-Shultz 1992).

One paper describes how women's experience is socially organised through the use of Institutional Ethnography a feminist methodology, looking for patterns of how something is organised to recur (MacKinnon 2006) and identified invisible forms of work and explored social organisations of experience. The study focussed on three primary questions; how do pregnant women experience living with preterm labour, how do women describe the work they do everyday caring for themselves, their unborn babies and their families, and how do societal discourses, institutional structures and nursing processes shape women's

experiences? Women (n=8) with experience of PTL were asked about the work they do and the complexities of their lives. An overriding sense of fear was expressed, as fear of going home and being alone with the added responsibility of 'keeping the baby in.' The experience of PTL and the sense of personal responsibility for preventing a PTB practised as being careful. Women, all part of a Prenatal Home Care Programme were home living alongside the threat of PTL, were more conscious of their body signals and described a sense of suspending their lives until the threat of prematurity was over.

Barlow and colleagues (2007) conducted an exploratory descriptive study of the views of women (n=8) admitted to hospital in PTL through semi-structured interviews. Issues exploring the understanding of their condition, their expectations concerning delivery and their views about hospital admission resulted in a key aspect of women's experiences was concerned with their search for meaning to help make sense of their sudden and unexpected hospital admission. Women continued to feel anxious despite assurances that all was well and they acknowledged that they had considerable stress in their lives, which they perceived as precipitating or aggravating their condition.

The final paper interviewed mothers and fathers separately in a hospital setting in Sweden (Danerek and Dykes 2007). Mothers (n=17) and fathers (n=6) explored the experience of threat of early delivery and eventual PTB. Using grounded theory, a core category of inter-adapting emerged and found that during the hospital stay, the most stressful issues were parent's concern for the baby and separation from family. Parents managed the situation by mutually adapting to each other, family members, significant others and caregivers. However, implications for practice were specific to this hospital setting and may not be generalisable. Nevertheless, the suggestion that feelings of separation can be reduced and family bonds strengthened through integration is important for all clinicians looking after women with problematic pregnancies where separation from families is likely to occur.

8.7.3 Disenfranchised grief

Pregnancy can embody dreams as it represents the potential for fulfilling hopes of a natural process with the baby as an opportunity to alter the course of a lifetime. For many women the

trauma of pregnancy loss or a baby born prematurely can cause a variety of reactions including grief. For some, this experience may not manifest until sometime later. Disenfranchised grief, a term quoted by Read and colleagues (2003) to described grief that resurfaces during a subsequent pregnancy accurately depicts what women are experiencing, with the psychological effects often altering women's locus of control and ability to deal with the next pregnancy

The final paper explored women's experiences of traumatic or distressing births from a feminist perspective using semi-structured interviews (Moyzakitis 2004). A self-selected group recruited through public advertising identified themselves as having a traumatic or distressing experience of birth. Four major themes emerged from the data: role of the caregiver, impact on self-image, impact on relationships and the severity of the experience. Several sub-categories emerged as loss of self, grief and not being the same person as before. Women found difficulty in preserving the integrity of self and the impact the birth experience had on relationship with the baby and partner. Although some women may not be describing a pregnancy loss or a previous preterm birth, they described the birth as it occurred to them, in language that resonates with women in the SIP study.

8.8 Conclusion

The review presented here focussed exclusively on research identified through the literature search and does not represent fully those views of women who have experienced a previous PTB. Nevertheless, the review goes some way to understand the anxieties of women during a subsequent pregnancy. Moreover, the review has uncovered the scant amount of qualitative midwifery research focussing on this group of women and uncovered a tendency to group together with losses ranging from early miscarriage to neonatal death.

The rationale for the qualitative study was, to add valuable information to the limited midwifery knowledge base about stress, anxiety and life events within pregnancy for this group of women. There is a significant exclusion in the midwifery literature that this study aimed to address. Critiquing the literature for pregnancy loss as well as preterm birth

identified similarities between the difficulties women face and helped to develop a conceptual framework for the SIP Qualitative study (Morgan 2004).

Chapter 9

9 FINDINGS FROM THE SIP QUALITATIVE STUDY.

9.1 Introduction

The purpose of this chapter is to present findings from the semi-structured interviews conducted with the List of Threatening Experiences questionnaire (LTE-Q). The chapter begins with background information and continues by outlining the conduct of the interviews. An overview of the characteristics of women interviewed in relation to the three main themes identified is provided. Themes are described as Damaged Self, Damaged Child and Damaged Relationships. A brief outline of the Hospital Anxiety (HADS-A) and Depression scores (HADS-D) and number of Life Events (LE) in relation to the themes is also presented. All transcripts were subjected to framework analysis. The chapter continues by discussing categories within themes and corresponding quotes to support these from the literature review. Concluding with the limitations of the study, the plans for future research and the implications the qualitative study has for midwifery care for this group of women.

9.2 Background information

Semi-structured interviews conducted in the antenatal clinic at the Liverpool Women's Hospital and lasted between 10 and 45 minutes. Responses to the questions were hand written. Interviews (n=200) were carried out between 18 and 22 weeks gestation which fell within the time-frame for the 20 week visit and between 26 and 30 weeks for the 28 week visit (n=151). LTE-Q questions were left open to interpretation and where possible member checking of the answers were undertaken at 28 weeks, forming part of the audit trail.

LTE-Q contains 12 questions and interviews were structured within this format, however as with any conversation, there were diversions at times, and it became evident during the interviews that one issue would trigger another. Despite the structured format of the interview tool it did allow the researcher to ask for clarification by using interview probes in response to the answers. Some women responded to the questions in whichever way they interpreted them and were not bound by the actual question itself.

Disenfranchised grief, a term quoted by Read and colleagues (2003) describes grief that resurfaces during a subsequent pregnancy. This became evident throughout the interview process, the psychological effects of a past experience altering women's locus of control and ability to deal with the next pregnancy. Throughout the interviews, previous experience and underlying grief was evident in the way women answered regardless of the question asked and unrelated to the interview schedule. This uncovered new data and made the study possible.

Women acknowledged that they had never been asked about stressful life events during pregnancy before furthermore, LTE-Q was not investigating life events in relation to a previous preterm birth, but for many women this gave them the opportunity to ground their answers in their previous birth experience. Women linked stressful life events to their previous experience and good data was generated because of this. Some women described this as a painful process, as it was the first time they had returned to the hospital since the last preterm birth or pregnancy loss.

Fifty-two women (26%) were identified from the main study participants (n=200) purely from the responses they gave to the questionnaire. The qualitative data will be presented from the 20-week interview only. Member checking did take place when women were interviewed again at 28 weeks. However some women had delivered by 28 weeks (n=12), others had moved back to the original referring hospital and others were not seen as the researcher was unable to be in clinic that day (n=37). Moreover the semi-structured interviews at 28 weeks revealed no real changes in the data collected and very little new information emerged.

The researcher (LW) conducted 150 interviews with the remaining 50, undertaken by another member of the research team (SQ) as part of the prospective observational SIP study. All women attending the clinic were very keen to take part with only two declining, over a period of three years because of needle phobia. Both of these women still wanted to be recruited even though they were unable to give a blood sample, feeling strongly that their experience last time was related to stressful life events.

9.3 Coding of quotations

Codes were used throughout to protect the identity of the women involved.

9.4 Characteristics of the women interviewed (n=52)

52 women from the 200 women recruited to the study were identified through the responses they gave to specific question within the questionnaire. Three themes emerged; Damaged Self (DS), Damaged Child (DC) and Damaged Relationships (DR). Each theme corresponded with a question. Damaged Self with question one, Damaged Child with question two and Damaged Relationship with question five.

Characteristics of the women interviewed are presented as demographic details including; gravidity, parity, age, past medical history, past obstetric history and outcome for the current pregnancy. These were linked to the categories and themes for each woman and are outlined in Table 18 for Damaged Self (DS), Table 19 for Damaged Child (DC) and Table 20 for Damaged Relationship (DR).

In the DS group (n=23) ages ranged from 21 to 41 years, in the DC group ages ranged from 24 to 36 years (n=5) and the DR group, ages ranged from 20 to 53 years (n=24).

HADS anxiety and depression scores and number of Life Events are presented within each table as a measure of stress for each woman within the three themes.

Table 18 (9.4)

DAMAGED SELF: CHARACTERISTICS OF WOMEN (n=23) FROM LTE-Q1

CODE	AGE	G	P	Past Pregnancy History	Medical / obstetric History	Pregnancy outcome	LE	HADS-A	HADS-D
C6	40	7	2	PL @ 9,9,10 & 24 2 x LB at 38 IOL for hypertension Non-smoker	Essential hypertension	IOL @ 37 for hypertension complicated by DIC, amniotic fluid embolism, hysterectomy Baby A&W	8	8	5
C9	21	5	0	PL @ 6,10,18 PTB @ 26 SB Non-smoker	None	PTL 24 Baby died.	7	12	4
C14	36	4	2	1 LB @ 40 PTB @ 33 A&W PL @ 23+ Non-smoker	None	SVD @ 38 Baby A&W	4	14	13
C18	24	2	0	1 LB @ 23+ baby died Non-smoker	None	IOL @ 39 Baby A&W	2	12	5
C22	36	9	1	PL @ 9,10,16, 18,21,22 PTB @ 35 baby A&W Non-smoker	None	PL @ 20	4	15	7
C25	27	2	0	PL @ 23+ Non-smoker	None	IOL @ 38 maternal request Baby A&W	1	11	11
C28	31	2	0	PL @ 23+ Baby died Non-smoker	None	Elective C/S @ 40 maternal request Baby A&W	3	14	8
C33	25	3	1	PTB @ 32 Baby A&W PL @ 19 Smokes	None	PTB @ 33 Baby A&W	2	10	5
C39	38	4	2	LB @ 39 Baby A&W LB @ 38 Baby A&W PTB @ 24 Baby died Non-smoker	None	IOL @ 38 Baby A&W	2	5	2

C45	25	8	2	PL @ 5,5,7 PTB @ 30 Baby A&W PL @ 18 LB @ 38 Baby A&W PL @ 7 Smokes	None	SVD 38 Baby A&W	2	13	8
C57	24	3	1	LB @ 39 PTB @ 32 Baby A&W Smokes	None	PTB @ 36 Baby A&W	3	11	6
C65	38	3	1	IOL SB @ 28 PL @ 22 Non-smoker	None	SVD @ 38 Baby A&W	2	13	7
C80	41	4	0	PL @ 16, 14, 20 Non-smoker	Cervical loop excision	SVD @ 25 LB	1	16	14
C87	31	4	0	PTB @ 24 Baby died PTB @ 24 Baby died Non- smoker	None	IOL @ 38 Baby A&W	4	15	12
C90	27	3	0	PL @ 17, 20 Non-smoker	None	SVD @ 39 Baby A&W	1	10	3
C137	29	5	3	PL @ 9 PTB @ 36 Baby A&W IOL @ 36 Baby A&W PTB @ 25 Baby died Non-smoker	Grand mal epilepsy PIH	PTB @ 34 Baby A&W	1	4	1
C140	30	3	1	PL x5 <12 & 23+ baby died Non-smoker	None	Delivered elsewhere No details	5	8	5
C155	38	5	3	LB @ 39 Baby A&W LB @ 40 Baby A&W PL @ 8 PTB @ 24 Baby survived Non-smoker	None	IOL PROM @ 35 SVD Baby A&W	2	12	9
C161	27	3	1	PTB @ 24 Baby died Smokes	None	SVD @ 37 Baby A&W	1	14	5
C170	33	2	1	PL @ 6 & 23+ Smokes	None	SVD @ 39 Baby A&W	2	14	7

C177	25	4	2	PL @ 6 PTB @ 24 Baby survived PTB @ 25 Baby died Smokes	APS	IOL @ 38 Baby A&W	2	14	4
C180	34	3	1	PTL stopped &delivered @ 40 Baby A&W PL @ 22+ (baby born alive, died) Non-smoker	None	PL @ 19	3	15	6
C198	23	2	0	PL @ 23+ Non-smoker	Appendicitis & Septicaemia	IOL @ 39 Baby A&W	3	8	5

Table 19 (9.4)

DAMAGED CHILD: CHARACTERISTICS OF WOMEN (n=5) FROM LTE-Q2.

CODE	AGE	G	P	Past Pregnancy History	Past Medical / obstetric History	Pregnancy outcome	LE	HADS-A	HADS-D
C13	24	3	1	PTB @ 23+ Baby survived PL @ 8,9 Non-smoker	None	IOL @ 39 maternal request Baby A&W	3	11	11
C34	38	4	1	PL @ 14 PTB @ 29 Baby A&W PL @ 5 Non-smoker	None	IOL @ 38 Baby A&W	1	14	6
C41	36	4	1	PTB (twins) @ 25 1 baby survived Smokes	None	IOL @ 35 previous obstetric history Baby A&W	5	6	5
C110	24	2	1	PTB @ 25 baby survived Smokes	None	LB @ 39 Baby A&W	2	13	5
C126	27	4	3	PTB @ 25 Baby died PTB @ 28 Baby A&W PTB @ 30 Baby A&W Non-smoker	Cervical suture	PTB emergency C/S @ 32 Baby A&W	1	10	2

Table 20 (9.4)

DAMAGED RELATIONSHIP: CHARACTERISTICS OF WOMEN (n=24) FROM LTE-Q5.

CODE	AGE	G	P	Past Pregnancy History	Past Medical / obstetric History	Pregnancy outcome	LE	HADS-A	HADS-D
C5	23	3	2	PTB @ 27 baby A&W PTB @ 36 baby A&W Non-smoker	None	SVD @ 39 Baby A&W	3	8	6
C7	53	10	3	PTB @ 28&26 PL x 6 @12 LB @ 38wks Non-smoker		IOL @ 38 LB	4	4	8
C9	21	5	0	PL @ 6,10,18 PTB @ 26 baby died Non-smoker	None	PTB @ 24 Baby died.	7	12	4
C13	24	3	1	PTB @ 23+ baby survived PL @ 8,9 Non-smoker	None	IOL @ 39 maternal request Baby A&W	3	11	11
C17	23	3	1	PL @ 16 PTB @ 34 Baby A&W Smokes	None	SVD @ 37 Baby A&W	2	15	9
C19	32	2	1	PTB @ 29 Baby A&W Smokes	None	IOL @ 39 maternal request Baby A&W	2	5	11
C27	31	3	2	PTB @ 33 Baby A&W 2 x term births Babies A&W Non-smoker	None	PTB @ 36 Baby A&W	1	7	0
C30	34	6	2	PL @ 8,15,18 IOL @ 36 PROM Baby A&W SVD @ 42 Baby A&W Non-smoker	None	Delivered elsewhere No details	1	16	8

C49	20	3	2	PTB @ 34 baby A&W IOL for IUD @ 26 Smokes	None	Elective C/S @ 38 Baby A&W	2	15	6
C51	40	3	0	PTB @ 24 SB PL @ 9 Non-smoker	Depressed on treatment	PTB @ 36 Baby A&W	4	16	11
C57	24	3	1	LB @ 39 PTB @ 32 Baby A&W Smokes	Psychiatrist, alcohol problem	PTB @ 36 Baby A&W	3	11	6
C61	22	6	1	PTB @ 23+ Baby died PTB @ 24 SB PL @ 7,9 PTB @ 36 baby A&W Smokes	None	SVD @ 37 Baby A&W	1	8	5
C75	36	4	1	PTB @ 23+ baby died PL @ 18 IOL @ 41 Baby A&W Non-smoker	None	Elective C/S @ 39 (breech) Baby A&W	2	16	6
C88	20	2	1	PTB @ 24 Baby A&W Non-smoker	Grand Mal epilepsy	PTB @ 36 Baby A&W	2	12	7
C108	25	2	1	PTB @ 27 Baby A&W Smokes	None	IOL @ 40 ROM Baby A&W	2	10	8
C110	24	2	1	PTB @ 25 Baby survived Smokes	None	SVD @ 39 Baby A&W	3	13	5
C127	28	5	4	IOL @ 40 Baby A&W PTB @ 27 Baby A&W PTB @ 28 Baby died PTL C/S @ 26 Baby A&W Non-smoker	None	PTB @ 28 Baby A&W	2	9	4
C130	27	2	0	PL @ 23+ Non-smoker	None	IOL @ 38 Baby A&W	3	11	11
C151	26	4	3	Elective C/S @ 39 (breech) Baby A&W PTB @ 32, 36 Babies A&W Smokes	Depression medication	Emergency C/S @ 39 (breech) Baby A&W	3	12	8

C166	24	6	5	PTB @ 36,32,35 Babies A&W PL @ 12 PTB @ 31 (twins) babies A&W Smokes	None	PTB @ 32 Baby A&W	4	11	7
C170	33	2	1	PL @ 6 & 23+ Smokes	None	SVD @ 39 Baby A&W	2	14	7
C175	21	7	0	PL @ 22+ PL x 5 < 12 Smokes	None	IOL @ 36 SB	3	14	6
C177	25	4	2	PL @ 6 PTB @ 24 Baby survived PTB @ 25 Baby died Smokes	APS	IOL @ 38 Baby A&W	2	14	4
C191	31	5	1	PL @ 6 LB @ 42 Baby A&W PL @ 5, 22+ Non-smoker	None	Elective C/S @ 38 Baby A&W	2	12	6

9.4.1 Damaged Self: Question 1

Q1: Have you suffered a serious illness, injury or assault in the last year?

11.5% of women (n=23) from the SIP study (n=200) answered Q1 by relating to this question by describing how they felt about their previous preterm birth or pregnancy loss. Women described this as an illness, injury or assault to themselves because of their experience of a previous preterm birth or pregnancy loss.

9.4.2 Damaged Child: Question 2

Q2: Has a serious illness, injury or assault happened to a close relative in the last year?

9% of women (n=5) wanted to explain that they considered their children had suffered an injury as a direct consequence of being born premature. Women answered this question in order to explain how they felt about this.

9.4.3 Damaged Relationship: Questions 5

Q5: Have you had a separation due to marital difficulties in the last year?

46% of women (n=24) answered this question by expressing views about their damaged relationships in reference to their previous birth or pregnancy loss others described unstable relationships in general. Seven women (13%) answered this question and talked directly about the strain of a preterm birth on their relationships and how this has remained an important source of stress during this pregnancy.

9.5 HAD scores within themes

HAD scores for anxiety (HADS-A) (Appendix 14) and depression (HADS-D) (Appendix 15) were linked to codes and themes at 20 weeks only (n=52) as the 28 week scores (n=38) revealed no significant changes in the data collected. HADS-A scores (Appendix 16) at 28 weeks and HADS-D (Appendix 17) are also presented. This allowed a greater understanding of the anxiety and stress some women were experiencing throughout this pregnancy. This in turn enabled a greater understanding of the responses, presented as in quotes from the answers to LTE-Q.

9.6 Life Events within themes

Number of Life Events experienced, were linked to each theme, at 20 (Appendix 18) and 28 weeks (Appendix 19):

The DS group had twenty-three women, five women had one life event (21%), eight had two (34%) and two had three (9%). Three women had four (13%), one woman had five (4%) and two had eight (9%) at 20 weeks.

The DC group consisted of five women. Two had one life event (40%), one had three (20%), one had four (20%) and one had five (20%) life events at 20 weeks.

DR with twenty-four women, three had one (10%) ten women had two (34%) and seven had three (24%). Three had four (10%) and one had seven (3%) life events at 20 weeks.

9.7 Framework Analysis

Semi-structured interviews were subjected to framework analysis interpreting the data given as answers to LTE-Q, allowing the participants 'framework of meaning' to be explored. The data were managed manually, without the aid of a software package. The aim of interpretive approach is to identify common themes across the participants that form a pattern of understanding. Answers locate the researcher towards the interpretive position, by among other things searching the data for and organising them around relevant interpretive categories or themes, by developing transparent and systematic mechanisms for arriving at the interpretations and for drawing on lay interpretations (Robson 2002).

To meet this objective, it was crucial to search for the commonality as well as diversity of participants' experiences. Individual answers were considered in relation to the overall interview, and each was assessed for the meaning of the phenomena (Carter 2004). This is a cyclical process where the researcher moves back and forth between the whole text and segments of the text to gain some understanding of the phenomena being explored. In the first instance the researcher (LW) carried out thematic analysis. This involved reading and re-

reading the data in a search for emerging themes, which ascertained marked differences in the interpretation of three questions by women.

To minimise interpreter bias and assess the plausibility and trustworthiness of the researcher's (LW) interpretation of the data, the sample interviews and data from each of the three questions of interest were themed independently by the study supervisor (SQ). Collaborative reflective discussions (Van Manen 2002) then took place to generate insight and understanding. Themes were examined, articulated and re-interpreted. Given the involvement of the researcher in the research process, it was considered important to provide sufficient amounts of data (answers to the three interview questions) to allow identification of the foundations upon which the findings of the study have been grounded. This process of transparency allows critical scrutiny of the researcher's interpretation of the data and further evaluation of the robustness of the findings through the use of verbatim quotes and allows authenticity from the interviews to be verified (Robson 2002).

Transcripts were selected and are presented in Appendices 20, 21, 22 and 23, as an example of the variation in the answers given by women when using the LTE-Q as a framework within a semi-structured interview.

9.8 Themes and Categories

Women acknowledged that they had never been asked about stressful life events during pregnancy before, furthermore, the LTE-Q was not investigating life events in relation to a previous preterm birth, but for many women this gave them the opportunity to ground their answers in their previous birth experience. Several categories emerged and combined into three main themes, providing the framework for discussing findings within the context of the available literature. Themes emerged from the way the women interpreted the questions and are described in relation to the word 'damage' (Table 21). The definition being loss or harm resulting from injury to persons, property or reputation and can be described in relation to destruction, devastation, harm, hurt or suffering (Onions 1993).

Table 21 (9.8)

Themes	Categories
1. Damaged Self	(i) pregnancy as an illness, injury or assault (ii) physiological imaging (iii) inability to heal
2. Damaged Child	(i) pre-occupied with suffering child (ii) existing day to day
3. Damaged Relationships	(i) relationship overshadowed by loss (ii) resignation of relationship (iii) instability of relationship

A temporal relationship, supporting the perception of an association between stressful life events and a previous preterm birth (PTB) or pregnancy loss (PL) from the women's perspective was found. The two events were linked together by women, without actually being asked the question, highlighting that the previous experience was an important aspect of women's focus.

LTE-Q concentrates on events in the last year. Women disregarded this time-frame and answered regardless of the criteria. Cote-Arsenault and Morrison-Beedy (2001) found that PL ranging from 34 years ago to the previous year was consistently portrayed by women as life-altering, despite the gestation of pregnancy or the time-frame involved.

9.9 Damaged Self

Q 1: Have you suffered a serious injury, illness or assault in the last year?

11.5% of women (n=23) from the study (n=200) answered Q1 by relating to it as an illness, injury or assault to themselves because of their previous experience. Women responded to the word 'suffering' within the question by stating that the death of their baby caused suffering to them and that they are still suffering throughout this pregnancy. Viewing a previous preterm birth as an illness has not been identified within the literature however pregnancy as a process to get through and emotions of high anxiety were a shared experience. Pregnancy as an assault on core identity (Cote-Arsenault and Morrison-Beedy

2001) and feeling unbalanced as if there was something wrong with physical and emotional changes has been described in other studies (Coster-Shulz and Mackey 1998).

9.9.1 Pregnancy as an illness

Women regarded the previous PTB as an illness because it elicited a similar emotional response, linking the concept of stress to the answer. Women responded by employing a cognitive strategy, which uncovered a think-aloud process being used in order to answer the question in the way they felt most appropriate for them in the form of introspection. Stress associated with past experiences may have triggered answers to Q1 with stress in mind. Hospitalisation may have played a part in this interpretation with a previously normal pregnancy suddenly becoming a traumatic experience.

For one woman the pregnancy was linked to a real illness, surgical intervention and premature birth resulting in the baby dying. She simply answered:

C198: "Yes, can I talk about my last pregnancy? I was ill with appendicitis, septicaemia, loss of a child."
HADS-A=11(moderate) HADS-D=4 (normal)

Others describe the pregnancy in terms of illness:

C22: "Feels like being ill... it's not like being pregnant... it's worse than that. I felt like I was ill not just pregnant. I see this pregnancy as an illness because of what happened last time... been in hospital since16 weeks and four days. I was very stressed last pregnancy... sick all the time... sick at the thought of going through this all again. Up until last Thursday, then I thought, here we go again. But since Thursday I think I've coped very well."
HADS-A=15 (severe) HADS-D =7 (normal)

For some women the view of pregnancy had changed to be one of constant worry, not enjoyable, others describe their inability to heal or to be a whole person again and that

pregnancy was a trial to get through. This view of pregnancy as an illness or injury was echoed by the description of the death of a baby as an injury to one woman:

C87: "Yes... I would classify the death of my baby as an injury to me. I don't know why but I feel it's like an injury because it's so painful and still raw... I feel so anxious especially leading up to my appointments here but I feel better afterwards. I'm still very emotional and I'm terrified to be told something is wrong. It is an actual physical feeling of pain."
HADS-A=15 (severe) HADS-D=12 (moderate)

These women answered with the context of illness and injury in mind and related their previous experience within these terms, explaining that the attendance at the hospital triggered those feelings again. Fear and anxiety seemed to be the most commonly shared emotion experienced by women and they described the actual physical feelings of pain which in turn changed the pregnancy experience from a normal physical occurrence to an abnormal experience.

For a minority of women (n=4), their answers were delivered in statements to the questions without any explanation. They were already very emotional in response to the question. These women's need to disclose was relevant to women despite the question not asking about the last pregnancy:

C155: "Yes, I had a baby at 24 weeks. The baby has lots of problems... never ending. The baby was in hospital up until 6 weeks ago."
HADS-A=13 (moderate) HADS-D=8 (mild)

C 161: "Yes, my daughter died at 3 weeks and 4 days old."
HADS-A=14 (moderate) HADS-D=5 (normal)

C170: "Yes, my unborn child at 23 weeks."
HADS-A=14 (moderate) HADS-D=7 (normal)

C177: "Yes, my son was very ill after being born prematurely as 25 weeks... he died"
HADS-A=14 (moderate) HADS-D=4 (normal)

Women shared an overwhelming need to tell about the death or their baby regardless of the aim of study, the questionnaire, or the questions asked. The current pregnancy for most women was clearly over-shadowed by their previous loss. Women were constantly reliving the past pregnancy in terms of the outcome of premature labour and loss of a baby. Their current pregnancy was also very important but their reality was somewhat obscured by their past experience. Their aim was to externalise the thoughts going through their heads, triggered by the questionnaire but not in response to the actual question.

All women identified within this category were suffering moderate to severe anxiety, with one woman suffering from moderate depression.

9.9.2 Physiological Imaging

Women with a preterm birth experience are perhaps more conscious of body signals than other women. This is accompanied with a sense of personal responsibility for preventing it happening again and being careful, in terms of almost suspending their lives (Mackey and Coster-Shultz 1992).
This prompted women in the study to explain bodily changes in terms of 'physiological intuition':

C9: "This pregnancy I view as an illness. Sometimes I get excited... trying not to be too optimistic... it's like an ongoing illness. Never feel well... don't know what's going to happen. Don't feel right today... can feel my cervix pulling. It's hard work as if it needs to be constantly maintained. I don't think I'm going to get very far this time."
HADS-A=12 (moderate) HADS-D=4 (normal)

There was a sense of 'emotional cushioning' where women were protecting themselves emotionally in case it happened again. For some women this was the protection they needed

to get through pregnancy however, there was also an underlying expression that there was an inevitability that it may well happen again because of the physical feelings experienced.

MacKinnon (2006) describes this as the added responsibility women feel of, "keeping the baby in." Women described the physical aspect of pregnancy loss with emotive terms such as "blaming their bodies" and feeling actual physical changes, explaining that their body didn't behave properly.

C180: "Yes, I suffered the loss of my baby girl at 20 weeks. She was a live birth and nothing was wrong with her... just born too soon because of me... because of my cervix."
HADS-A=15 (severe) HADS-D=6 (normal)

C140: "My baby died in October last year. I lost my baby. The birth was premature and I went into labour at 23 weeks, the baby died the next day. They think it was a weakened cervix. It was very traumatic and I had two months off work because I was on maternity leave. It was very strange being off on maternity leave and not having a baby."
HADS-A=8 (mild) HADS-D=5 (normal).

These women felt a shared sense of betrayal by their bodies and shared the sense that they were to blame in some way. Some felt they had to maintain or control the pregnancy in physically even though in reality women were aware that this is beyond their control.
Within this category women had a mixed degree of anxiety and none suffered from depression.

9.9.3 Inability to heal

Despite the passage of time, there was a sense with some women that the healing process had not started. Cote-Arsenault and Bidlack (2001) found that women were worried about their feelings having a negative impact on the baby and of experiencing a constant fear of being given bad news, expressed as "will my body fail me again." This was supported by some responses given:

C9: "It's three years since I lost my son. This pregnancy, every pregnancy brings back that sadness. I went in to premature labour and he was still born. Don't really want to talk about it now... want to go to the ward... too worried it will happen this time... don't want to get upset."
HADS-A=12 (moderate) HADS-D=4 (normal)

Some women were conscious of getting past pregnancy milestones, having guarded emotions and in marking off their progress in terms of safety and development of the baby (Cote-Arsenault and Mahlangu 1999). A sense of self having been affected by past experiences and a distant emotional attachment used by some women as a protective mechanism:

C65: "Yes our baby died in February last year at 22 weeks. It's approaching that time again with this baby and I'm very anxious about it. Mental more than physical symptoms... I keep thinking something's going to go happen again. I can't stop thinking about it... I don't want to say any more today." (started to cry)
HADS-A=13 (moderate) HADS-D=7 (normal)

C18: "I had a miscarriage at 23 weeks last October. I've worried about this pregnancy. I'm trying to look forward... trying to get past 23 weeks... would be good"
HADS-A=12 (moderate) HADS-D=5 (normal)

C25: "I had a late miscarriage last September. It was very stressful because I'm reaching that same day again and I remember what happened last time... don't want to say anymore." (started to cry)
HADS-A=11 (moderate) HADS-D=11 (moderate)

Women's responses epitomized the fact that these pregnancies were fraught with uncertainty. Women seemed to have real difficult investing emotionally in the current pregnancy when their focus was on the previous birth experience. The language used by some women demonstrated their shared emotion of marking the pregnancy off by significant points in time or milestones.

There was also a sense of women trying to look forward but unable to:

C28: "I've been affected in general by my last pregnancy... I worry about everything now since I lost my daughter... I'm more negative about things now than before."
HADS-A=14 (moderate) HADS-D=8 (mild)

C39: "I had a preterm birth last April and the baby died... 24 weeks and 5 days... still very raw and upsetting. I don't feel too stressed about this pregnancy... yet I do get anxious at times"
HADS-A=5 (normal) HADS-D=2 (normal)

C45: "I had a miscarriage at 18 weeks and it's still hard. We had a funeral in April... sometimes it's very hard to bare."
HADS-D=13 (moderate) HADS-D=8 (mild)

C57: "I've been on antidepressants since losing my baby in 2000. I had postnatal depression then and have been on them ever since. I've stopped my medication since I became pregnant... I'm finding it hard at the moment." (became too tearful to continue)
HADS-A=11 (moderate) HADS-D=6 (normal).

Women were experiencing anxiety and uncertainty. They seemed pre-occupied almost reliving the past and at the same time trying to balancing the present. They were very aware of their anxiety and how their worrying had transferred to other aspects of their lives.

One woman felt betrayed by staff, which led to suffering. She felt the sadness of losing the baby with emotional pain and anger targeted towards herself and hospital staff, feeling unprepared for the eventuality of her baby living through the premature birth:

C6: "My marriage broke up... and I went in to preterm labour and it all happened so quickly... I felt devastated and destroyed because the staff told me the baby wouldn't survive labour

and was born alive. I had to go through the process of watching the baby die. I have a great fear for this pregnancy... this has brought it all back to me."
HADS-A=8 (mild) HADS-D=5 (normal)

Sadness and tears were expressed throughout the study when talking about previous births. Women had experienced shattered dreams of a normal pregnancy experience with past losses occurring all along the pregnancy continuum. The commonalities in these women's stories were striking.

Women's belief that there was a link to stress may have been instigated by the focus of this study. However, women were keen to be involved and said they believed there could be a link, describing stress in their lives during a previous preterm birth and came up with reasoning examples of what was happening in their lives at the time of their previous preterm birth. Moreover, there remained many unanswered questions, which were uncovered by the responses. Stress was the most commonly expressed cause for premature birth within this group of women. This perception was confirmed by the women who thought it was at least partly due to stress in their lives and they shared this without being asked this question directly.

The majority of women in this category were identified as having a moderate score for anxiety, however only one woman had a moderate score for depression.

9.10 Damaged Child

Q 2: Has a serious illness, injury or assault happened to a close relative?
9% of women (n=5) wanted to explain that they considered that their children had suffered an injury as a direct consequence of being born premature. They needed to let someone know the impact this "injury" had on their lives and that of their families. Loss of the expected "normal" pregnancy and child had taken priority over every-thing else.

9.10.1 Pre-occupied with suffering child

Those women with ill children responded emotionally to Q5 and related it to their child by describing the stress, uncertainty for the future and the passage of time not erasing the worry felt:

C13: "My little girl is disabled... she has to go into hospital in December for an operation. She has two shunts put in her head already and the worry, anxiety is constant... she's very ill sometimes... she can't walk because of a right-sided hemiplegia and she's in a wheelchair... she's only eight."
HADS-A=11 (moderate) HADS-D=11 (moderate)

C110: "My son's deaf... we just found out on his fourth birthday. It was a shock and he'll need hearing aids and speech therapy and lots of hospital visits. The past few months have been very stressful because of trying to find a school that will take him. It's more settled now... we know the plan and the school is sorted. I feel alright now about it... just upset for him. I know all the help will make a difference though. Don't want to say anymore than that really."
HADS-A=13 (moderate) HADS-D=5 (normal).

Women reported that they had not realised how many concerns and difficult situations they were dealing with at any one time until given the opportunity to discuss their present life situation during the interviews.

9.10.2 Existing day to day

The experience of coping with a damaged child was relayed in the expression of 'existing day to day.' However, for some although resigned to the situation, were still anxious, uncertain and pre-occupied with their thoughts and energy always on that child:

C126: "Yes, my son's disabled and he has operations to put shunts in his head often. He has seizures and the last few he has gone into status. We've spent a lot of time at the hospital over the last few months. He sees the neuro-surgeon... he's only six and when he's ill it's

very stressful for all of us. We just exist on a day to day basis. When he's well he's great... I suppose I'm used to it now."
HADS-A=9 (mild) HADS-D=3 (normal)

For some women the amount of stress they experienced and the responsibility of looking after their damaged children was overwhelming at times.

C34: "My son is registered blind and has cerebral palsy, so I feel he is constantly on the verge of being seriously ill. He's well at the moment but it can change so quickly... constantly assessing the situation... where we can and can't go... whether there is anyone ill in that house, you know."
HADS-A=14 (moderate) HADS-D=6 (normal)

Their future was clearly uncertain:

C41: "My daughter has hydrocephaly and attends hospital frequently to have her head measured. They didn't put a shunt in after birth but made a fourth ventricle inside her head, instead. It allows the fluid to adjust in pressure... it's worked so far, but her head is big. It hasn't affected her intellect at all and she's very bright for her age... mad on science... watches the discovery channel all the time. We'll just have to wait and see. Her future is uncertain and there may come a time where she will need operating on and there is a chance that it will be life threatening. There's no certainty with her future."
HADS-A=6 (normal) HADS-D=5 (normal)

There was a consensus from these few women that the feelings they were experiencing were universal for this group. In this context, women seemed to demonstrate stoicism in the face of adversity, as way of coping with their every-day lives.
The women in this category displayed normal scores for both anxiety and depression.

9.11 Damaged Relationship

Q 5: Have you had a separation due to marital difficulties in the last year?

Twenty-four women (46%) answered this question, some expressed views about their damaged relationships in reference to their previous birth or pregnancy loss others described unstable relationships in general. Seven women (13%) talked directly about the strain of a preterm birth on their relationships and this remained an important source of stress during this pregnancy. Other studies have found that women have discussed the difficulty in preserving the "integrity of self" and the impact the birth experience had on their relationship with the baby and with their partner after a traumatic birth (Moyzakitis 2004).

9.11.1 Relationship overshadowed by loss

13% of women (n=7) reported that their relationship was overshadowed by a loss, loss of normality or actual loss of a pregnancy or child:

C75: "Just the normal stresses of losing babies. Affects the relationship doesn't it? We're still affected by it... especially during this pregnancy."
HADS-A=16 (severe) HADS-D=6 (normal)

C9: "We had a break from each other. Did the world of good... just needed to get away from each other because of what happened before. We are much stronger now. I missed him. This pregnancy is planned and we are happy about it."
HADS-A=12 (moderate) HADS-D=4 (normal)

C19: "We sometimes fall out and I threaten to leave my husband. He goes off for a period of time... sometimes it's very angry and we threaten each other but never physical. Then we phone each other in a couple of days. It stresses me out... the atmosphere in the house is stressful. I have a special needs daughter... which doesn't help. I have trouble as well with my little girl's dad. He gets hot headed and angry and I try to avoid him... he just doesn't deal with things well. Because I'm in a new relationship it's in his face all the time when he comes to pick up his daughter... he'll always be involved with my life because of that."
HADS-A=5 (normal) HADS-D=11 (moderate)

C30: "I'm still feeling stressed after the miscarriage last year. This has put a strain on my relationship... but it is better now... we're more settled now. I was very stressed before it happened"
HADS-A=16 (severe) HADS-D=8 (mild)

C51: "We have just got back together a year ago. We had been together 10 years before that and split up two years after my baby died... four years ago. I'm glad we're back together... we just couldn't cope with the grief I think."
HADS-A=16 (severe) HADS-D=11 (moderate)

Although women were able to suggest some alternate theories for the difficulty in their relationships, a recurring theme in women's narratives was that the strain from the previous preterm birth experience had on their relationships.

C177: "My partner left me after the death of our son."
HADS-A=14 (moderate) HADS-D=4 (normal)

C191: "Yes, I lost my daughter and I moved back to my parent's house. My partner started to drink quite badly... I felt safer there."
HADS-A=12 (moderate) HADS-D=6 (normal)

Problematic relationships were identified by women themselves as being caused by the death of a baby, by explaining that their partners in particular could not cope with the pain and emotional distress.
Most women within this category scored moderate or severe on the HADS scale for anxiety, two women had a moderate score for depression.

9.11.2 Acknowledging instability

19% of women (n=10) described relationship problems during pregnancy, that were unrelated to their previous experience but nevertheless causing anxiety and stress within this pregnancy:

C5: "Yes, he told me he'd been with another woman when I was 3 months pregnant. He only left for a few weeks then came back. You need things to heal. I do feel angry and upset sometimes... we haven't resolved it yet. I feel angry at the other woman not just him. I'm hoping we can sort it out."
HADS-A=8 (mild) HADS-D=6 (normal)

C6: "Marital problems, ongoing... divorced last year... not financially sorted with my half of the house. We've been arguing for the last 2 years. I've got nothing financial from the last relationship. I feel it's ongoing until the financial part is sorted out. I can't finish the previous relationship properly."
HADS-A=8 (mild) HADS-D=5 (normal)

C13: "The father of my daughter is difficult. We separated four years ago and he's been difficult lately. He has her every Sunday for 2 hours. He doesn't see her as much as he used to. She wants to see him more often now... but he's in a new relationship and my daughter doesn't understand that that is more important to him than her."
HADS-A=11 (moderate) HADS-D=11 (moderate)

Some women described life histories wrought with one stressful life experience after another. Women obviously felt a need for self-exposure even though the study was not investigating their relationships as such.

C17: "Had a bit of a problem. Split up 3 weeks ago and we're still separated. Still upset a bit... not sure what's going to happen long-term."
HADS-A=15 (severe) HADS-D=9 (mild)

C27: "We are separated now. I am affected by it and I start crying quite a lot. I feel quite resolved and happy with the pregnancy. It has happened since this pregnancy... although it's been a problem long-term... for about 9 years. We've tried to work through it but it's not going to change. I suppose... I'm quite happy now."
HADS-A=7 (normal) HADS-D=0 (normal)

C57: "We've had our ups and downs and have been together for 5 years. I had a drink problem last year... which didn't help. I'm now seeing a psychiatrist. My partner wants to go to work but I don't want him to because I need his support at home with the children when I can't get out of bed."
HADS-A=11 (moderate) HADS-D=6 (normal)

Some women were clearly stressed in this pregnancy because of the relationship problems:
C166: "I'm not married but I've just split up from this baby's dad. We've had problems for a while and it's a very recent split... I'm upset (started to cry). It's causing me a lot of stress. I don't know what's going to happen. He just isn't interested now after the first scan. Don't know what to do about it because he just does what he wants." (too upset to continue)
HADS-A = 14 (moderate) HADS-D = 7 (normal)

C170: "I'm separated from my boyfriend who is the father of my unborn child."
HADS-A=14 (moderate) HADS-D=7 (normal)

With definite uncertainty for the future:
C88: "We have had our ups and downs recently. We are trying to deal with it... it's serious but I hope to get through it... don't know what's going to happen."
HADS-A=8 (mild) HADS-D=11 (moderate)

C108: "Last year when I was pregnant with my son we were living together for 2 years... but he walked out. He told me lies and he had a gambling problem. We had a very stormy relationship last time and in the end we decided not to live together anymore. We were always up and down and it wasn't any good. He does see my little boy often and he is the

father of this baby... but I can't live with him anymore... he tells too many lies and that upsets me."
HADS-A=8 (mild) HADS-D=11 (moderate)

Women in the study reported multiple stresses in their lives with relationship problems one of the main focus of their conversation. Moreover some women had planned their pregnancies despite acknowledging that these ongoing relationship problems existed, resulting in women facing pregnancy and impending birth alone.

19% of women with the shared phenomena of preterm birth and pregnancy loss also shared bad relationships. From a midwifery perspective, the data uncovered gives a glimpse of the complicated relationships some women experience during pregnancy.

HADS scores revealed a mixture of normal to moderate anxiety within this category, with only one woman with a severe anxiety score.

9.11.3 Resignation of relationship

Relationship problems are undeniably an important source of stress and anxiety during pregnancy, however, 15% of women (n=8) seemed somewhat resigned to their current situation and although distressing, they did seem to be relieved that they had come to a decision. Accepting separation as preferable to striving with a relationship that was unlikely to work and may be one way women naturally reduce stress in order to protect the pregnancy. For some there was a positive feeling of being "sorted" and of women being less stressed because the relationship ended:

C49: "I split up from boyfriend 16 weeks ago... I'm made up! I have more money and more time to myself. I'm not as strict on the baby and it's just easier. I don't plan to keep in touch and I was upset at first but not now. I have good support from my family... he was just too hard work."
HADS-A=9 (mild) HADS-D=6 (normal)

C110: "I've split up from my partner now since I was 5 weeks pregnant... he's with a new partner now. It was a great shock... although I didn't really feel upset. I'm strong because I brought up my son on my own and I can do it again. I won't have any more children though. I know I'm having a boy... it will just be me and the two boys and that's it... I'm quite happy about that now."
HADS-A=13 (moderate) HADS-D=3 (normal)

C123: "I've separated from my partner recently. I am coping and I suppose I got to the stage of not caring because he was being so childish. The ultrasound date doesn't fit with my dates so he thinks I got pregnant by some-one else. So I've given up trying to persuade him. We weren't living together and I won't change my mind and have him back. Even his mother is saying the scan can't be wrong and I didn't get pregnant when I thought I did. I don't care anymore. They're just stupid... he won't believe anyone, not my doctor and he wouldn't believe you."
HADS-A=10 (mild) HADS-D=8 (mild)

C61: "Yes, we are always breaking up and having problems. We're still at home with my mum and don't have any privacy. We need our own place... there are too many influences from other people."
HADS-A=8 (mild) HADS-D=5 (normal)

The language used by women demonstrated their detachment to their partner and this was indicative of their uncertainty about the relationship. For some women they were clearly thinking-aloud about the uncertainty of their relationship however they justified this because other children were involved. This resulted in an ongoing stress within this pregnancy:

C127: "I broke up with my partner recently... about 8 weeks ago. I found him in bed with my best friend. I still feel very raw about it all... I feel let down and hurt. I won't have him back because the trust has gone. I'm civil to him because I don't want the children to suffer for his stupidity. When he comes to see the children he begs me to take him back... but I won't. He

has hurt me so much. We will stay friends but he won't be back to live in the house. I can live without him after that... but I want him to be a friend and father to the children."
HADS-A=9 (mild) HADS-D=4 (normal)

C130: "I did split up with my ex-partner who had a serious drug problem. I helped him to stop and we parted on good terms. He isn't the father of this baby... we split up about a year ago. I feel OK about it now... I know I helped him."
HADS-A=11 (moderate) HADS-D=6 (normal)

C151: "Yes, I split up from my partner for a few months after I stabbed him with a butter knife... it wasn't that bad. We are seeing each other some times... we were together for about six and a half years. He can't cope with my mood swings. I already have a psychiatrist and I'm very low at the moment but I saw him last week and he has asked me to try to do without the medication for now and will see me again next week. My support worker is keeping an eye on me. It doesn't help that my children are staying with my boyfriend's mum at the moment. I'm waiting to be re-housed... so I am low because we're all split up and I don't have all my children with me. They must wonder what's going on... they're happy at the new school and I don't want to take them out again when I move... so I'm trying to get a house near the school."
HADS-A=11 (moderate) HADS-D=12 (moderate)

Women with unresolved issues within their relationship seemed to distance themselves from this uncertainty and appeared nonchalant demonstrating stoicism in the face of adversity:

C175: "Our relationship is up and down most of the time... sometimes he's around and sometimes he's not. We are still a couple though. I don't know how long it will last... he comes and goes."
HADS-A=14 (moderate) HADS-D=6 (normal)

The precarious relationships experienced by women during pregnancy were evident in the answers women gave to the questionnaire. Overall some of these women seemed numb when

being interviewed. They seemed to describe their recent PTB as just one more depleting experience in a life filled with such experiences.

Most women in this category had normal anxiety scores and a minority with a moderate score. Two women had a mild to moderate depression score.

9.12 Other findings

Some women (n=4) answered about the death of a baby or a pregnancy loss to question three (Q3).

Q3: Has a parent or spouse died in the last year?

C114: "Yes my baby died at 23 weeks last time... she only lived for a week."
HADS-A=10 (mild) HADS-D=5 (normal)

C119: "I have lost two children."
HADS-A=7 (normal) HADS-D=2 (normal)

C131 "My baby died last year... I can't talk about it. I get too upset... don't ask me any questions please."
HADS-A=11 (moderate) HADS-D=8 (mild)

C175: "My daughter and Nan died, both in April. My daughter died last year and Nan the year before. I'm not sad about my Nan any more as she was old and had a good life. I'm still waiting for counselling because of depression. I did get tablets from the doctor but I didn't take them properly... I don't want to get addicted. I'm still depressed and I do need help. I'm down most of the time. I'm OK when I'm around family and friends but terrible when I'm on my own."
HADS-A=14 (moderate) HADS-D=6 (mild)

Women answered about their previous loss within the context of employment:

Q8: Have you become unemployed or have you seeked work unsuccessfully for more than one month?

C9: "I decided to stop work before I got pregnant... didn't want to risk anything. I love my job but the pregnancy is more important. I will go back to work afterwards definitely."
HADS-A=12 (moderate) HADS-D=4 (normal)

Some women described the stress of working such as being on their feet all day

C175: "I stayed off work this time since I found out I was pregnant. The GP signed me off. I'm going to leave when my sick note runs out. I blame work partly on losing the baby last time... I run around all the time... rushing from one part of the hospital to the other... stressed all the time. I put it down to stress and work... well part of it."
HADS-A=14 (moderate) HADS-D=6 (normal)

C200: "I chose to leave my current job because travelling too much with two young children at home and also being pregnant again. I think that this is what made me deliver early last time... so I wasn't taking any chances this time."
HADS-A=5 (normal) HADS-D=2 (normal)

C87: "I had time off work to have the baby... which didn't survive. I was off work for 4 months. I did try to go back but kept getting too upset... I'm a hairdresser... it was difficult to be happy."
HADS-A=15 (severe) HADS-D=12 (moderate)

However, one woman talked about her the loss of her baby in relation to a burglary at her mother's home:

Q12: Have you had anything you valued, lost or stolen in the last year?

C9: "My son died after being born too early at 26 weeks and his jewellery got stolen last year from my mother's house. We kept it there because we thought it would be safer. I was upset

at the time... cried all the time. I still get angry now... but not as upset. I just couldn't believe it... that some-one could do that after all I'd been through. Very angry at the time... less now... but still angry...it couldn't be replaced."
HADS-A=12 (moderate) HADS-D=4 (normal)

One woman simply answered Q12 by saying:

C14: "The babies were the only thing I lost that I valued."
HADS-A=14 (moderate) HADS-D=13 (moderate)

Overall women in the study seemed happy to be pregnant again. Nevertheless there was an underlying sense that they could not invest themselves fully in the current pregnancy and a positive outcome. They seemed unable to 'jump into the pregnancy with both feet'. This has been described in previous research as 'one foot in and one foot out' (Cote-Arsenault et al 2000) where women leave themselves open to the possibility that the pregnancy will not be successful just as their past experiences had taught them.

LTE-Q was considered the most appropriate tool when considering the objectives of both the SIP Observational study and the SIP Qualitative study. The use LTE-Q was two-fold, providing a predetermined framework enabling the same topics to be covered with each woman and generating a quantitative score. Moreover the use of LTE-Q allowed women to have flexibility in their answers generating qualitative data from the use of interview probes, allowing a 'think-aloud' process of introspection to be uncovered and permitted areas to be identified which may have been neglected by the interviewer. It confirmed the pre-specified topics to be discussed and explored, as well as new areas or ideas being uncovered. By encouraging some freedom within the semi-structured interview schedule women were able to explore and discuss their experiences.

9.13 Conclusion

The primary aim of the qualitative study was to explore the stories women tell within their answers to LTE-Q through the use of framework analysis. The secondary aim was to explore

causation by finding out whether women related stressful life events to their previous preterm birth experience. This part of the thesis has provided insight into women's experiences in a subsequent pregnancy in response to life events and a shared history of a previous preterm birth or pregnancy loss.

The study gives unequivocal insight for midwives and the service they provide within this area of investigation, enabling a greater understanding of women's feelings and views which are grounded in the experience of a preterm birth and / or pregnancy loss.

Multifaceted interventions that consider the complexities of women's behaviour, social environment and life stresses as well as the medically oriented physical assessment, are required to improve both pregnancy experience and outcomes. This qualitative study has therefore provided a key starting point, bridging the gap in current knowledge, generating greater understanding and will lead to future midwifery investigations of women's experience of a preterm birth perhaps using a more explorative in-depth qualitative methodology. It is only when research explores the perceptions of women living with anxiety about past experiences of preterm birth that clinicians can begin to appreciate the challenges that these women face in the next pregnancy and thus practice more empathetically.

Chapter 10

10 DISCUSSION

This chapter will discuss the study in its entirety to conclude the thesis. The study explored the relationship between maternal psychological factors and preterm delivery to provide more information about the relationship of stress in a subsequent pregnancy after a preterm birth. This chapter will discuss briefly the complexities encountered in the study and the difficulty in interpreting the results of the observational study with the many socio-economic, biological and psychological variables linked to premature labour and birth as discussed in the previous chapters. The SIP observational study will be discussed first, followed by the SIP qualitative study and concluding the thesis with implications for midwifery. The SIP study matrix is presented at the end of the chapter (Figure 8).

10.1 The SIP Observational Study

The study consisted of 200 women with a history of at least one idiopathic preterm labour. Women were identified on the evidence that a previous preterm birth is the most strongly correlated risk factor for a recurrence. The women in the study were representative of those referred to the PTL antenatal clinic at the Liverpool Women's Hospital and were screened ruling out infection or biological plausibility to PTB. The sample size calculation was base on a similar patient mix to the established Preterm Labour Clinic at Guy's Hospital, London and from the advice given by the study statistician (GL). The selection of maternal inflammatory / hormonal markers and the gestation for investigation were identified from previous research as discussed in Chapter 2 and from the recognised obstetric expertise in the field (SQ). Psychological testing was undertaken using validated and well established tools used within midwifery research and supported by the study advisor and psychiatrist (DO). The SIP Observational study aimed to identify whether there was an association between maternal stress, maternal immune response and preterm birth using observational methodology.

10.1.1 Unique aspects of the study

As far as is possible to determine this is the first midwifery study investigating the association between stress, immune response, preterm birth and maternal experience of life events using a mixed methods approach. There is a plethora of published epidemiological and laboratory work investigating specific aspects of PTL, maternal stress and immune response however there are few papers which have examined stressful life events, anxiety and depression together with maternal immune response in this group of high risk women with a history of idiopathic preterm deliveries.

Stress, Anxiety and Depression:

The study has reported the prevalence rates of stress, anxiety and depression in women and has compared the results of anxiety scores in a small cross-sectional study with a low risk group of women. These results unsurprisingly found that women with this shared history are more anxious in a subsequent pregnancy.

Within the study 37% of women (n=74) were scored as moderate to severe anxiety at 20 weeks gestation and 30% (n=45) of those women continuing with this score through to 28 weeks. 11% (n=22) of women disclosed a history of depression which again continued through to 28 weeks. However this was not related to PTB despite evidence from other studies supporting this association (Berkowitz et al 1983, Henrickson et al 1994, Copper et al., 1996, Misra et al 2001, Jesse et al 2003).

Within the clinic the researcher (LW) assumed that these levels of anxiety and depression would subside as the pregnancy continued and women surpassed pregnancy loss or preterm birth milestones. However this did not occur in this group of women despite the reassurance from scanning and attendance at the clinic.

Depression rates within the study showed that 1.5% (n=3) of women were reported to be seeing a psychiatrist and all were identified by the midwives through the routine mental health questions within the booking interview, however only those women seeing a psychiatrist were referred to the mental health team at the hospital. Moreover, 7.5% (n=15)

of women were reported to be seeing their GP with 5.5% (n=11) receiving counselling and / or treatment for depression. Within this group there were no referrals made to the mental health team. It is possible that the women themselves felt this was unnecessary and the midwives may also have decided that appropriate care was already in place. However there was no record in the booking history which would determine why these women had not been referred or whether this had in fact been discussed.

One surprising finding however was the remainder of women in the study screened through the use of HADS who were highly stressed, anxious and / or depressed were not identified at all! These findings bring into question whether the recent NICE guidelines (2007) which recommends the use of three mental health questions at the initial antenatal booking appointment is enough and it challenges the need for debate within midwifery for the use of psychological screening tools within the booking interview.

Nevertheless, asking questions about previous mental health will and does identify those women at risk of recurrence and the inclusion of these questions have undoubtedly reduced the risks for those women. Furthermore, it must be acknowledged that not all midwives at the present time will feel able to delve deeper into psychological aspects during the booking history and some may feel uncomfortable using psychological screening tools within the time-frame of a complicated booking process. However, there are a number of psychological screening tools and life event scales in use, and perhaps the antenatal period warrants a tailor-made instrument for midwives to use within the booking history or at other antenatal reviews.

Life Events:

61% (n=121) of women reported significant life events ranging from one event to nine at 20 weeks gestation. This may have impacted on the anxiety scores however it did not impact on the biological response measured within this study despite other studies finding that PTD was nearly doubled in distressed women compared to women with no distress (Hedegaard et al., 1996, Nordentoft et al., 1996) at 20 weeks gestation.

Biological Response:

Determining the impact of biological mechanisms relating stress and preterm labour is complex. The maternal HPA axis and the automatic nervous system are both central in mediating the impact on health and more importantly pregnancy outcomes. CRH produced by the hypothalamus stimulates ACTH which in turn modulates the release of cortisol from the adrenal glands, a key hormone in stress response. However, other factors may amplify the stress response including, the timing of a stressful event, the magnitude, the duration of the event and the numerous social and environmental factors.

In pregnancy, the placenta and fetus produce CRH in addition to maternal CRH and all three regulate the pituitary-adrenal function. Maternal cortisol suppresses CRH release and placental cortisol increases the release of CRH. This positive feedback loop created by the placental CRH may support the maternal and fetal stress response during labour and delivery as the classical HPA axis response to environmental stress is reduced. In contrast, premature elevation of placental CRH may occur in times of chronic fetal stress and lead to preterm birth. High cortisol in the presence of low CRH would be suggestive of an altered placental response to cortisol. Within this study women with chronic stress failed to show increased levels of CRH. A mechanistic / biological explanation was unfortunately not found depicting the CRH status in this high risk group of women.

Results from the laboratory analysis suggest that there may be a placental influence in maternal CRH secretion which may override any alterations in the maternal HPA axis due to maternal stress. Several researchers have investigated the role of CRH in normal and abnormal pregnancies and found high levels associated with PTL (McLean et al., 1998, Hobel et al., 1999, McLean and Smith 2001, Leung et al., 2001, Holzman et al., 2001, Moawad et al., 2002, Wadhwa et al., 2004). The immune response to stress in pregnancy within this study however remains to be unanswered at the present time and is for future research.

Demographic Results:

Despite the evidence relating demographic and socio-economic influences to the risk of PTB through health behaviour during pregnancy (Lobel et al., 1992, Dunkel-Schetter et al., 2001), findings within the SIP study showed no significant results related to age, alcohol consumption, BMI or relationships (married, single, divorced). Only 44% (n=87) of women in this study were married with the remaining 56% (n=113) describing themselves as single or divorced. No information was gathered describing levels of support or stability within relationships. The mean age in the study was 30 years. BMI was recorded for 109 (54.5%) women and ranged from 16.1 to 40.4 with 25.94 as the mean for this population. However 28.5% (n=57), *a* significant number of women in the study smoked. This did not seem to influence the PTB rate and few women had recorded their intention to stop smoking within the booking information despite the risks associated with preterm labour.

Ethnic diversity within this study was not found with 89% of women (n=178) white British, 3.5% (n=7) black British and 7.5% (n=13) women in the study described as other than British ethnicity. 98% (n=196) were recorded as English being their first language with only 2% (n=4) who did not speak English. Socioeconomic factors within different populations of women in the same country are thought to be the main underlying cause rather than actual racial differences, as described by other authors (Meis et al., 2000, Wadhwa et al., 2001, Green et al., 2005).

Socio-economic data gathered using postcodes converted to the Index of Multiple Deprivation Scale (IMD) identified that 87.5% (n=175) of women lived within the Liverpool postcode and 12.5% (n=25) lived out of the area. Within the study 28.5% (n=57) lived within a postcode above the average IMD score of Liverpool. This revealed a significant number of women attending the preterm labour clinic were living in the most deprived areas of Liverpool which is a known factor of premature labour (Smith et al., 2007).

The study results showed that 67% of babies were delivered after 37 weeks, of those 7% (n=14) of women suffered from depression. However because these women had been

identified and were treated this may have had an impact on the associated risk of PTB, depression and the corresponding immune response.

The evidence for an association between maternal stress, anxiety or depression in pregnancy and an adverse outcome of PTB is substantial and has been discussed in the previous chapters, however the underlying placental / biological mechanism responsible is much less defined and it is almost certain other systems are involved. For example, there is little evidence about how the maternal sympathetic nervous system responds to stress and anxiety in pregnancy. The type of stresses and timing in pregnancy, the gestational age and the nature of mediating mechanisms remain unclear. Until more is known about the mechanisms triggering maternal HPA axis in pregnancy and the corresponding placental response, targeting appropriate interventions to reduce maternal stress and influence premature labour will be difficult.

10.1.2 Limitations

There were several limitations associated with the study for the researcher (LW). The first was the time allocated from clinical work in order to help in the laboratory analysis and assay of serum samples. This was recognised at the ethics application and a collaborative approach was agreed with the laboratory staff in the Division of Reproductive and Perinatal Medicine, University of Liverpool.

The second limitation was the time allocated to the interviewing schedule based on the advice from the psychiatrist (DO). This proved to be more time consuming than expected as the LTE-Q was used as semi-structured interview rather than a self completed questionnaire and the complexities of women becoming unexpectedly emotionally upset during this interview meant that the researcher could not recruit other women during that clinic session. This had a significant impact on the length of the study and the recruitment process. Moreover, at the start of the study, the researcher recognised that the anxiety in some women was so great that they often declined recruitment until they had been scanned, the recruitment process was changed and women were only approached after the scan had been completed at both 20 and 28 weeks gestation culminating in less women declining.

Other limitations were recognised in the psychological tools used in particular when researching life events. Life events may not be perceived as equally noxious by all individuals and it may be important to measure the perceived impact of a life event on an individual rather than simply measuring its presence. Retrospective recall of life events, even those arising in the recent past are prone to inaccuracy and may limit observational studies. One of the most basic and critical issues in this research area involves the reliability of maternal recall associated with self-reported measures of life events and makes it difficult to ascertain the degree of distortion involved. There may be a sensitization of measurement and a reactivity effect, where subjects over-report their life experiences as they become unduly sensitized because of the nature of the enquiry.

10.1.3 Implications for future research

Studies aimed at reducing anxiety in women with this shared history are needed in order to determine whether this would decrease the risk of adverse pregnancy outcomes. However, this would be difficult as the heightened anxiety in some women is likely to stem from the previous experience of preterm labour itself as found in the qualitative study.

The concept of reducing stress by using antidepressant medication as a preventative measure for preterm birth in women screening positive for depression is novel and somewhat radical. Currently in the UK there are no RCT's examining the efficacy of any established psychological therapies such as cognitive-behavioural therapy to reduce anxiety during pregnancy. Antenatal stress perhaps warrants a tailor made validated psychological tool before introducing routine antenatal screening can be instigated and this remains to be debated within the midwifery services at this time.

The use of threshold models for analysis may fit the relationship between stress and PTB better than one with no threshold model. These models assume that stress does not affect PTL and PTB until a certain amount of stress has been experienced and that each unit of stress above the threshold adds to the risk of PTB. This model can compare threshold and non-threshold relation between the number of life events and PTB and is suggestive that a threshold model may have fitted better in this study. Future research using this method with

other continuous or ordinal stress measures would be interesting. Such measures may have more consistent results and might clarify whether a threshold effect does exist in the relation to stress and pregnancy outcome.

10.2 The SIP Qualitative Study

The SIP Qualitative Study consisted of 52 women identified from the 200 semi-structured interview responses at 20 weeks gestation in the observational study. Women were selected from the answers they gave to the Life Events questionnaire (LTE-Q) at 20 weeks only, as no new data emerged from the second interview. Women were selected from the description of their experience of PTB as an illness, injury or assault.

The primary aim of the qualitative study was to explore the stories women tell within their answers to LTE-Q, the secondary aim to explore causation by determining whether women related stressful life events to their previous preterm birth experience.

10.2.1 Unique aspects of the study

As far as is possible to determine this was the first midwifery study to explore this group of women's experiences of stress and causality using a psychological screening tool (HADS) and a life events questionnaire (LTE-Q) within the context of a large quantitative midwifery study. Three themes were identified and within the study large numbers of women were undoubtedly stressed, anxious and depressed. In the DS group (n= 23) only two women were found to have normal HADS scores for both anxiety and depression (8%). 69% (n=16) of women in this group scored 11 or above for anxiety (moderate to severe), with a minority of women 17% (n=4) identified with depression. In the DC group (n=5), 60% (n=3) of women had moderate anxiety with one woman found with moderate depression. Finally in the DR group (n=24), 70% (n=17) of women suffered from moderate to severe anxiety and 25% (n=6) with moderate depression.

This level of moderate / severe anxiety may have influenced the responses women gave to LTE-Q and their interpretation of the questions. However there were many more anxious women who were not identified from the answers they gave as they chose to answer yes / no

to the questionnaire without elaborating on the answers. This raises questions about the use of screening for anxiety and depression during pregnancy and the use life events questionnaires as a simple quantitative measure within stress research.

Moreover, the study also found that during pregnancy these women had never been asked about:

- the anxiety they were experiencing
- the stressful life events they dealt with on a daily basis
- the complexities of looking after damaged children from a previous preterm birth
- how they were coping with the current pregnancy

This highlights the finding that much more interesting and thorough information may be gathered through the use of combining this approach with qualitative methodology.

10.2.2 Limitations

The SIP qualitative study was analysed thematically using framework analysis from the answers given to the LTE-Q. The use of the tool limited data collection and only minimal information was gathered because of this, however the use of the tool allowed the researcher to examine 'think-aloud' technique as a method used by women in their cognitive response to the questions. Moreover the findings identified that most women were unable to extend their responses at the time raised by the women themselves because of the questionnaire, however the responses were enhanced through the use of interview probes and some women were able to expand and frame their answers in response to the questions asked. There was clear evidence of women's need to talk and their ability to reflect on prior events as shaping their thoughts through the subsequent pregnancy. Nevertheless the use of LTE-Q limited freedom of women to explore their thoughts and experiences. The limited responses were analysed using framework analysis, which enabled the answers to be explored and contextualised.

Women framing their answers with the prior preterm delivery to the first question both as a quantitative measure but also as common theme made this study possible. Nevertheless,

within the clinic setting, there was limited time available for exploring the answers given and some women became unexpectedly upset and unable to carry on.

10.3 Implications for future research

Future research should explore the experiences of women and the perceived impact having a previous preterm birth has on the next pregnancy. The research design would be best as a hermeneutic phenomenological approach, exploring perceptions of women with one to one in-depth interviews and may benefit from being conducted in women's homes to enable a deeper exploration of meaning with interviews tape recorded and transcribed verbatim. Preparation and information beforehand would help women to feel ready to disclose and may reduce the heightened emotional response and inability to continue observed in this study. An interpretive analytical approach could be conducted with a purposive sample of women recruited from the Preterm Labour Clinic at the hospital. The value of further research in this group would help develop strategies to ensure the next pregnancy focus is a positive experience as well as a positive outcome.

10.4 Discussion

This may be the first midwifery study to explore women's experiences of a previous premature birth within a specialist antenatal clinic within the context of a larger quantitative midwifery study. For some, this pregnancy was clearly overshadowed by their previous experience and the definition of a preterm birth or miscarriage to women themselves was irrelevant. They described their experience as the loss of a baby regardless of gestation. Women were determined to express their feelings of loss to whichever question they could relate it to. Some perceived life events to have an impact on their last pregnancy however they did feel less stressed during this pregnancy. This may be due to their attendance at the clinic and the care offered through consultant expertise, ultrasound scanning and midwifery support.

10.5 Conclusions

This midwifery study has added important information to the complex phenomena of preterm birth in women with a history of idiopathic preterm labour. Living with a previous PTB or pregnancy loss is a discourse of disruption which has assemblages of physical and psychological disturbance in the next pregnancy. Other compelling concerns such as daily living stresses, economic struggles, problematic relationships, may or may not be associated with preterm birth. This study did not find a clear association with stress and PTB. However stress represents an event, perhaps one of multiple events that disrupts normal pregnancy and can result in preterm birth which in turn damages individual lives. Within the qualitative study the nature of the questions asked undoubtedly influenced women's responses. The outcome from a previous experience, loss of a baby, damaged child and damaged relationship would undeniably impact on how women perceived the current pregnancy. Overwhelmingly however the women interviewed welcomed being involved in the study.

10.6 Implications for midwifery

Mental health problems in pregnancy are distressing and may have a huge impact on pregnancy outcome in terms of negative maternal experience or adverse pregnancy events. The subjective description of labour being more painful and leading to more requests for epidural has been found in women with high anxiety levels and higher serum cortisol have been found in women with a more positive labour experience (Mahomed et al 1995, Dayan et al 2002). Women who have antenatal depression have also been found to be more likely to have children with behavioural problems (O'Connor et al 2002) moreover suicide in pregnancy is now recognised as a significant cause of maternal mortality (CEMACH 2004). Many maternity services have implemented recommendations in order to improve mental health and reduce maternal risk by taking into account the NICE guideline (NICE 2007) recommendations to enquire about past or present severe mental illness. However, asking these questions and sign-posting women who need to be reviewed from the mental health team does not identify women who may be highly anxious, stressed or depressed. The MAPPIM midwifery team at Guys Hospital, London, asks women whether there is anything that would make pregnancy difficult for them at that time in their lives, within the booking history, enabling the identification of women who are highly anxious at that time (Elliott et al

2007). This goes some way to recognise that anxious and depressed women may not be identified through NICE guideline questions alone. However the implementation of psychological screening tools to detect current anxiety or depression during pregnancy still needs to be addressed and should only be instigated if midwives are trained, can institute extra visits and support. Moreover, screening could only be planned when perinatal or primary care therapy and counselling services have the capacity to provide quick access for women with moderate problems. At present, most midwives have inadequate training to fulfil this role. Alternatively if services wanted to be compliant with NICE guidelines (2007) from the outset, women should be screened and those with moderate problems should be routinely referred to their GP. Ignoring antenatal distress will lead to opportunities for preventative measures being missed during a time when women are engaged closely with health services through midwifery care.

The government's strategy (DOH 2002) suggests that having a mental health practitioner in each specialist service with an interest in perinatal mental health will lead to the improvement of local service provision both at primary and specialist levels and care pathways for mental health fall in to the agenda of the National Services Framework (DOH 2004). Within the Liverpool Women's Hospital this is already an established antenatal service, however there were only three women within the SIP study identified at the booking visit who needed this levels of expertise despite moderate to severe levels of anxiety and depression found through screening. If women can be identified they could be targeted for more intensive antenatal surveillance and perhaps prophylactic interventions which may ultimately reduce the incidence of PTB.

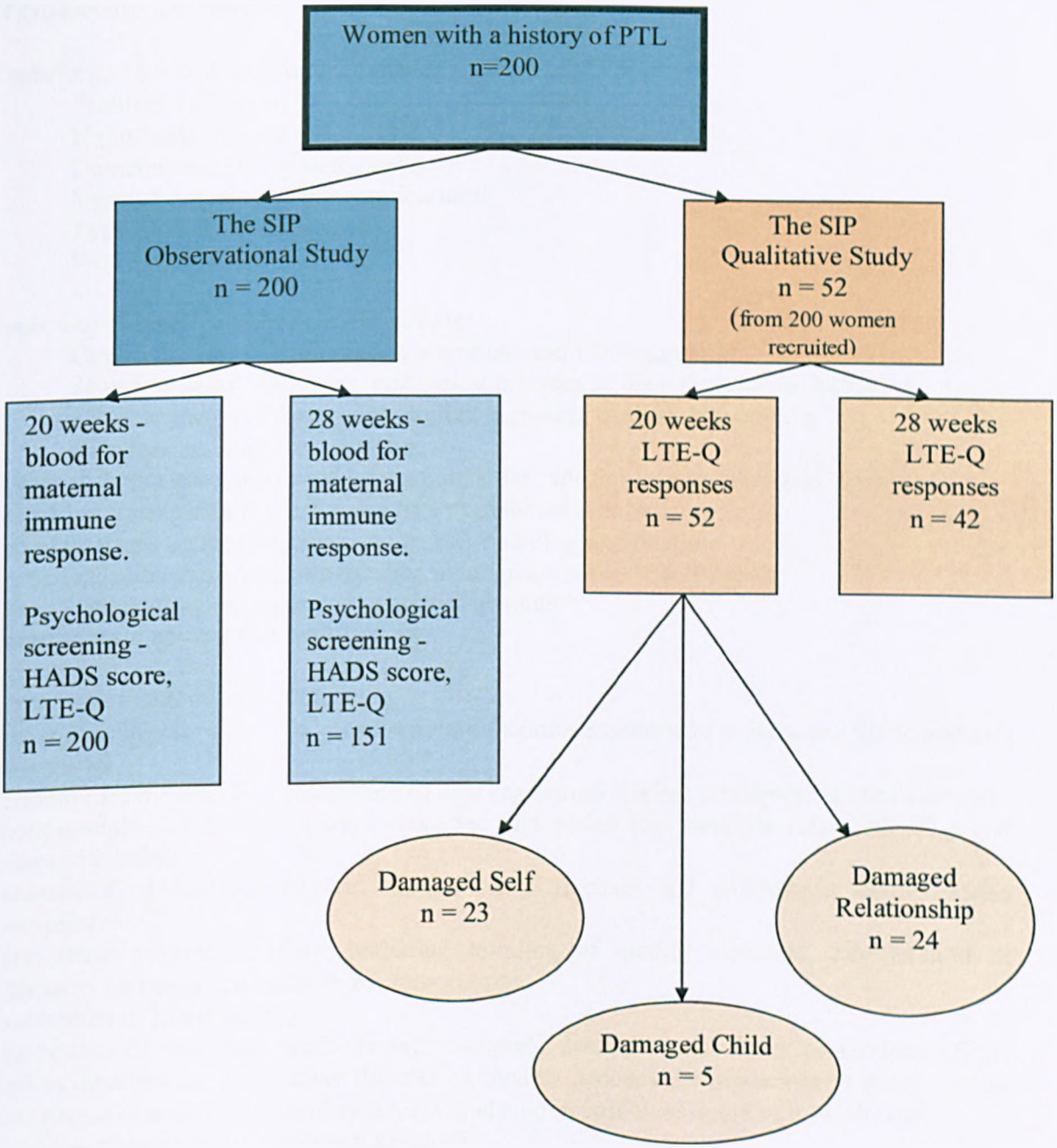
It is more likely in the future that midwives will have an increasing role to play in the care of women identified with antenatal anxiety and depression. The NMC (2004) states that midwives should have the skills and knowledge to monitor and support all women and are the key professionals in predicting those mothers at risk of perinatal mental health disorders thereby reducing the effects on the mothers, the fetus and the family (NICE 2007). However having these skills is subjective and individual midwives may not feel adequately equipped to deal with this in the current climate.

The use of medication to treat women with depression remains a common obstetric dilemma; however, antidepressant administration is associated with reduced cytokine levels (Scheipers et al 2005) and could provide a novel, though controversial way to reduce the risk of PTD. Psychotropic agents freely cross the placenta (Marcus et al 2001) and minimising risk to the fetus is paramount. Nevertheless, the effects of anxiety and depressive symptoms during pregnancy are also important and need to be urgently addressed.

Currently there is a false dichotomy between the non-treatment therapies and traditional drug treatment and clinicians should be encouraged to consider non-medication treatments wherever possible. Clinical trials are proving that there are excellent forms of psychological treatment for anxiety such as programs for relationship support, stress reduction with cognitive analytic therapy (Hunot et al 2006), yoga (Naredran et al 2005, Satyapriya et al 2009) and relaxation therapy (Khianman et al 2008). An immediate need to screen for maternal emotional problems during pregnancy, institute appropriate interventions and evaluate their efficacy is needed and midwives interested in this aspect of care are well placed to play a central role in this. Moreover, in pregnancy, any mechanism that translates social adversity into pathophysiology would implicate that intervention strategies would be possible.

To conclude, this study will help to inform future midwifery research in terms of a framework for thought and enquiry and through being better informed about the sensitivity of research in this area. It may also help in the dialogue for developing future diagnostic and predictive tests. These findings however cannot be extrapolated to women with other problematic pregnancies. Nevertheless this research represents an important element in the exploration of the association between stress, the impact on pregnancy and the outcome of preterm birth.

Figure 8 (10)
THE SIP STUDY MATRIX



Appendix 1 (4.7)

MOOSE Checklist

The Proposed Reporting Checklist for Authors, Editors and Reviewers of Meta-analysis of Observational Studies.

Reporting of background should include:

- Problem definition
- Hypothesis statement
- Description of study outcome(s)
- Type of exposure or intervention used
- Type of study designs used
- Study population

Reporting of search strategy should include:

- Qualifications of searchers (eg. librarians and investigators)
- Search strategy, including time period included in the synthesis and keywords
- Effort to include all available studies, including contact with authors
- Database and registries searched

Search software used, name and version, including special features used (eg. explosion)
Use of hand searching (eg. reference lists of obtained articles)
List of citations located and those excluded, including justification
Method of addressing articles published in languages other than English
Method of handling abstracts and unpublished studies
Description of any contact with authors

Reporting of methods should include:
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
Rationale for the selection and coding of data (eg. sound clinical principles, or convenience)
Documentation of how data were classified and coded (eg. multiple raters, blinding and interrater reliability)
Assessment of confounding (eg. comparability of cases and controls in studies where appropriate)
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results
Assessment of heterogeneity
Description of statistical methods (eg. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose response models or cumulative meta-analysis) in sufficient detail to be replicated
Provision of appropriate tables and graphics

Reporting of results should include:

- Graphic summarizing individual study estimates and overall estimate
- Table giving descriptive information for each study included
- Results of sensitivity testing (eg. subgroup analysis)
- Indication of statistical uncertainty of findings

Reporting of discussion should include:

- Quantitative assessment of bias (eg. publication bias)
- Justification for exclusion (eg. exclusion of non-English language citations)
- Assessment of quality of included studies

Reporting of conclusions should include:

- Consideration of alternative explanations for observed results

Generalization of the conclusions (ie. appropriate for the data presented and within the domain of the literature review)
Guidelines for future research
Disclosure of funding source

Appendix 2 (5.4.2.1) (7.4.2)

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Scoring sheet for researcher

This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you feeling in the past week.
Don't spend too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

Tick only one box in each section

A
I feel tense or "wound up":

Most of the time	☐	3
A lot of the time	☐	2
Time to time. Occasionally	☐	1
Not at all	☐	0

D
I feel as if I am slowed down:

Nearly all the time	☐	3
Very often	☐	2
Sometimes	☐	1
Not at all	☐	0

D
I still enjoy the things I used to enjoy:

Definitely as much	☐	0
Not quite so much	☐	1
Only a little	☐	2
Hardly at all	☐	3

A
I get sort of frightened feeling like "butterflies" in my stomach:

Not at all	☐	0
Occasionally	☐	1
Quite often	☐	2
Very often	☐	3

A
I get sort of frightened feeling as if something awful is going to happen:

Very definitely and quite badly	☐	3
Yes, but not too badly	☐	2
A little, but it doesn't worry me	☐	1
Not at all	☐	0

D
I have lost interest in my appearance:

Definitely	☐	3
I don't take so much care as I should	☐	2
I may not take quite as much care	☐	1
I take just as much care as ever	☐	0

D
I can laugh and see the funny side things:

As much as I always could	☐	0
Not quite as much now	☐	1
Definitely not so much now	☐	2
Not at all	☐	3

A
I feel restless as if I have to be on the move:

Very much indeed	☐	3
Quite a lot	☐	2
Not very much	☐	1
Not at all	☐	0

A
Worrying thoughts go through my mind:

A great deal of the time	☐	3
A lot of the time	☐	2
From time to time	☐	1
Only occasionally	☐	0

D
I look forward with enjoyment to things:

As much as ever I did	☐	0
Rather less than I used to	☐	1
Definitely less than I used to	☐	2
Hardly at all	☐	3

D
I feel cheerful:

Not at all	☐	3
Not often	☐	2
Sometimes	☐	1
Most of the time	☐	0

A
I get sudden feelings of panic

Very often indeed	☐	3
Quite often	☐	2
Not very often	☐	1
No at all	☐	0

A
I can sit at ease and feel relaxed:

Definitely	☐	0
Usually	☐	1
Not often	☐	2
Not at all	☐	3

D
I can enjoy a good book or radio or TV programme:

Often	☐	0
Sometimes	☐	1
Not often	☐	2
Very seldom	☐	3

Thank you

Appendix 3 (5.4.2.2) (7.2)

LIST OF THREATENING EXPERIENCES QUESTIONNAIRE (LTE – Q)

This is a conversational enquiry about events within the last year.

Please answer all 12 questions.

1. Have you suffered a serious illness, injury or assault in the last year?
2. Has a serious illness, injury or assault happened to a close relative in the last year?
3. Has a parent or spouse died in the last year?
4. Has a close family or friend or another relative died n the last year?
5. Have you had a separation due to marital difficulties in the last year?
6. Have you broken off a steady relationship in the last year?
7. Have you had a serious problem with a close friend, neighbour or relative in the last year?
8. Have you become unemployed or have you seeked work unsuccessfully for more than one month?
9. Were you sacked from your job in the last year?
10. Have you had a major financial crisis?
11. Have you had a problem with the police and a court appearance in the last year?
12. Have you had anything you valued, lost or stolen in the last year?

Appendix 4 (5.4.3.2)

STANDARD OPERATING PROCEDURE (SOP) FOR ELISA PLATE READER USE

This SOP will explain how to use the Multiskan Ascent ELISA plate reader and Ascent software.

Health and Safety Precautions:
The main health and safety risks to this procedure arise from the use of sulphuric acid, and display screen equipment (DSE). Sulphuric acid causes severe burns on contact and damages mucous membranes on inhalation. Laboratory coat, protective gloves and safety glasses should be worn. DSE risks are the possibility of upper limb disorders (e.g. repetitive strain injury (RSI)), eye strain and eye fatigue and the effects of mental stress. In order to minimise these risks, users should endeavour to create a comfortable work position and layout of work, ensure that the screen is regularly cleaned and avoids glare and reflections, take short breaks or changes of activity, report problems straight away and arrange to have eyesight checks. Users should have a copy of the HSE leaflet "Working with VDUs" if they work on DSEs for at least one continuous hour on 10 occasions.

Equipment Information:
Plate reader:
Multiskan Ascent (Thermo Electron Corporation) connected to Dell PC running Thermo Ascent software.
Plate shaker/incubator:
Dynatech Varishaker~Incubator
Microtiter plates (Corning, 3369)
Plate sealers (Anachem 100-SEAL-PLT)

Instructions:
1. Turn on Dell PC and Multiskan Ascent plate reader.
2. Open Ascent software by double clicking on the desktop icon.
3. Open previous file.
4. Save as: new file name.
5. From procedure tab, open Comments sheet and modify accordingly.
6. Open area sheet and ensure that the analysis area is correctly highlighted.
7. Open layout sheet.
8. If necessary clear all previous data. If standard curve information is correct, keep this.
9. If new standard curve data is required: Click on "Fill"
10. Enter the following settings: For position A1, type= Blank, replicates = 2, filling order ↓⊙ O
11. Eg. For position B1, type=Calibr, name cal_1, concentration= 7.8125, replicates = 2, fill replicates and blanks O⊙→, generate dilution series, number of dilutions = 7, Operators= multiply by 2. "Apply" and close when completed.
12. Enter the appropriate sample identification information onto the remainder of the plate plan.
13. Save the file

14. Read OD_{450} (and OD_{540}) by clicking "Start" from the main menu of the Ascent software.
15. Click on the results tab to access the results data.
16. A standard curve is prepared by clicking on the graph icon from the main menu. The fit type should be "linear regression". Results are calculated automatically by the software. Ensure that all results fall within the linear portion of the standard curve.

Appendix 5 (5.5.2)

Liverpool Women's NHS
NHS Foundation Trust

PATIENT INFORMATION SHEET

Crown Street
Liverpool
Tel:

Stress, Immunity and Preterm Birth Study
Liverpool Women's Hospital

Information Sheet

Stress, Immunity and Preterm Birth.

You are being invited to take part in a research project. Here is some information to help you decide whether or not to take part. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything you do not understand or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Some women go into labour early so that they deliver their babies before they are properly mature. Doctors think that stress may trigger some of these early labours. We wish to study the mother's response to stress whilst she is pregnant. We will study the substances (cytokines) released by the white blood cells. These cytokines may trigger preterm labour. We wish to see whether women who have early labours produce extra cytokines and white blood cells in response to stress.

Why have I been chosen?

You have been chosen because you have had an early labour in a past pregnancy, which could not be explained by routine hospital investigations. There is also an increased chance that you could have an early labour again.

A maximum of 200 other patients will be studied.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

You will be visiting the preterm labour clinic at 20 and 28 weeks gestation for internal ultrasound scans to measure the length of the cervix (opening to the womb). Taking part in this study will mean that we would also like to take a blood sample (10mls = 2 tsp) from you at this time for the research project. We would also like you to fill in two questionnaires to assess your levels of stress (this will take about 10 minutes).

Visiting you at home:
If for some reason the research midwife is unable to see you at the time of your routine visit to the hospital, with your permission, you may be contacted at home where the questionnaires and blood tests can be taken at your convenience.

What are the possible benefits of taking part?
The information we get from this study may help us understand the immune response (the body's defences) to stress in pregnancy. This new information may then help us design better treatments aimed at preventing preterm labour. If in the unlikely event we were to find that you may have a depression we would discuss this with you and only inform your G.P. with your consent. All such information would be strictly confidential.

What if something goes wrong?
If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

Will my taking part in this study be kept confidential?
All information collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The results will be published in scientific journals and presented at conferences to further our understanding of the immune response to stress.

Who is organising and funding the research?
Medical charities are funding the laboratory experiments.

Who has reviewed the study?
The Liverpool Research Ethics Committee.

Contact for Further Information
Specialist Midwife Lorna Wood
Tel: Bleep 410
or
Dr. S. Quenby's secretary
Liverpool Women's Hospital

Tel:

Thank you for reading this.
You will be given a copy of the information sheet and a signed consent form to keep.
Sept 2004

Appendix 6 (5.5.2)

CONSENT FORM

Liverpool Women's NHS
NHS Foundation Trust

Stress, Immunity and Preterm Birth Study
Liverpool Women's Hospital

Title of Project: **Stress, Immunity and Preterm Birth**
Name of Researchers: Lorna Wood and Siobhan Quenby

Please initial box

1. I confirm that I have read and understand the information sheet dated 1/3/03 (version1) for the above study ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from Liverpool Women's Hospital. I give permission for these individuals to have access to my records ☐
4. I agree to take part in the above study ☐

Name of Patient	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature

Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 7

ETHICS FORM (5.5.2)

LIVERPOOL (ADULT) RESEARCH ETHICS COMMITTEE APPLICATION FORM

For Ethics Committee use only Number: .....Date received: .....

Outcome: .....Applicant informed: .....

INSTRUCTIONS: Please complete this form in typescript. Select Yes/No options as appropriate. It is essential that this form is completed fully and the relevant enclosures are received if the study is to receive proper scrutiny by the Ethics Committee. Please refer to the Guidance Notes when completing the form.

1. **CHECKLIST:** The following checklist must be completed. Please indicate if the following have been enclosed by selecting Yes/No/Not applicable option below.

	Yes	No	Not Applicable
19 copies of the application form (double-sided if possible)	☐4	☐	
2 copies of the protocol	☐	☐	4
19 copies of the patient information sheet	☐4	☐	
19 copies of the patient consent form	☐4	☐	
19 copies of the GP Letter	☐	☐	4
19 copies of advertisements/posters		☐	4
19 copies of Questionnaire*	☐4	☐	
Please attach the additional information above, stapled to the application form.			
Fee (cheque for £500 made payable to Cheshire & Merseyside Health Authority) – commercially sponsored studies	☐	☐	4
2 copies of manufacturer's data sheet for all drugs	☐	☐	4
1 copy of the Clinical Investigator's Brochure	☐	☐	4
2 copies of the manufacturer's indemnity	☐	☐	4
2 copies of CTX/CTL/DDX	☐	☐	4
Annexe A**	☐	☐	4
Annexe B***	☐	☐	4
Annexe CH	☐	☐	4

* Please indicate if not yet finalised. Include an interview schedule if used.

** If the study involves the use of a medicinal product or medical device.

*** If the study includes the use of ionising or non-ionising radiation, radioactive substances or X-rays

H For research in general practice

Please return your completed application to: Mrs K Simons, Administrator, Liverpool Research Ethics Committee, Hamilton House, 24 Pall Mall, Liverpool, L3 6AL. Tel: 0151 285 209

SECTION 1	Details of applicant(s)

1. **Short title of project** *(in not more than 6 words)*

Stress immunity and preterm labour

Full title

2. **Are the psycho-neuro-immunological pathways in miscarriage present in preterm labour?**

Summary of practical benefits/improvements in patient care which are envisaged

An understanding of the relationship between the immune response to stress in pregnancy and preterm labour.

2. **Applicant** *(all correspondence will be sent to this address unless otherwise indicated)*

Surname: Wood Forename: Lorna Title: Mrs

Present appointment of applicant: Specialist Midwife

Qualifications: BA Hons., RGN., RM

Address: 88 Magazine Lane, Wallasey, Merseyside.

Tel: 0151 638 4854 Fax: Out of hours tel:

Email Address: Lorna.wood@lwh-tr.nwest.nhs.uk

Please note that a brief CV of head applicant must be attached with proposal (if one has not been submitted in the last 12 months)

3. **Other workers and departments/institutions involved** *(please supply names and addresses)*

Dr G. Vince, Department of Immunology, Duncan Building, University of Liverpool, L69 3BX

Dr. S. Quenby, Liverpool Women's Hospital, Liverpool, L8 7SS

Dr. D. Owen, Liverpool Women's Hospital, Liverpool, L8 7SS

Prof. J. Neilson, Liverpool Women's Hospital, Liverpool, L8 7SS

Dr. G. Lancaster, School of Health Sciences, University of Liverpool, L69 3BX.

4. **Signature of relevant bodies**

The information supplied in this application form is to the best of my knowledge and belief accurate. I have read the Guidance Notes and clearly understand my obligations and the rights of the subject, particularly with regard to obtaining freely-given informed consent. I undertake to carry out the work in accordance with the principles of the Declaration of Helsinki (South Africa October 1996).

Signature of applicant .....Date

Signature of Head of Department/Supervisor/Principal in General Practice with overall responsibility for the project ..... Date

Name and Title in capitals .....

I am fully aware of the details of this project and happy for it to continue as outlined here.

Signature(s) of relevant Clinical Director(s) where study is being conducted/Medical Director(s) signing on behalf of Trust(s) involved *(where appropriate)*

..... Date

Name and Title in capitals

SECTION 2	Details of project

This section must be completed. Two copies of the protocol should be supplied, but it is not sufficient to complete questions by referring to the protocol.

5. Aims and objectives of project *(i.e. what is the intention of the project ?)*

The aim of the study is to test the following hypothesis:

2.1. Does the host immune response and stress determine the risk of preterm delivery in women?

2.2. Study endpoints: The incidence of preterm labour.

6. Scientific background of study *[Committee members, who do not receive a full protocol each, use this section to decide if the research is significant, valid and novel – See also Guidance Notes]*

Despite advances in fetal medicine, the incidence of preterm labour (PTL) and preterm delivery has remained constant between 5 and 10% and is the major cause of perinatal mortality and morbidity in the developed world. New evidence emerging from North America has suggested that this incidence may actually be increasing. Preterm birth is a major cause of neonatal morbidity and mortality, accounting for 65% of neonatal deaths and 50% of childhood neurological disabilities. There is reliable evidence that the incidence of preterm births is increasing, especially births before 28 weeks gestation. Contributing factors include births following assisted reproduction, especially multiple births and the increasing proportion of births among women >34 years. Preterm prelabour rupture of the membranes (PPROM) and spontaneous preterm labour (PTL) account for 80% of preterm deliveries. The remaining 20% are indicated deliveries for maternal or fetal reasons (Terizdou and Bennett 2002). Approximately 50% of preterm labours have no identified aetiology (Recent LWH audit).

Stress

It has been acknowledged that pregnancy can be a stressful time for women. The sources of stress can be psychological or physical, external or internal in origin and possibly associated with personality traits. Stress is associated with anxiety and depression and it is unknown whether preterm delivery is caused by anxiety, depression, life events or a combination of factors. Increasingly, psychosocial factors are being implicated in the aetiology of some adverse outcomes in pregnancy such as intrauterine growth retardation, low birth weight and preterm delivery (Whitehead et al 2002, Dole et al., 2003, Mulder et al., 2003).

Leucocytes

Approximately 25% of the decidua in normal pregnancy consists of leucocytes (Bulmer, 1996). Changes in endometrial leucocyte populations have been associated with recurrent miscarriage, differing population of leucocytes existing in the pre-implantation endometrium of women with recurrent miscarriage compared to those with successful pregnancy (Lachapelle et al., 1996, Quenby et al., 1999, Clifford et al., 1999). Thus, the endometrial leucocyte population has been linked to adverse pregnancy outcome. Similarly the peripheral leucocyte population has been associated with preterm labour (Gervasi et al., Sendag et al. 2002)

Cytokines

An important feature of early pregnancy is the establishment of a connection between pregnancy tissues and the lining of the womb. These communication pathways play an important role in ensuring the appropriate development of the placenta and baby. The signals that travel along these communication pathways are substances produced by both fetal and maternal cells. These signals include a group of factors known as cytokines. T helper (Th) cells can differentiate into subsets with distinctive patterns of cytokine release and it has been proposed that Th1-type responses (e.g. the production of IL-2 and IFN-γ) are systemically suppressed in murine pregnancy and that local expression of Th2-type cytokines (e.g. IL-4, IL-6, IL-10) in placental tissue might be beneficial for fetal survival (Wegmann *et al.*, 1993). A similar situation may exist in human pregnancy (Marzi et al., 1996, Raghupathy et al., 1999, Makhseed et al., 1999, Raghupathy et al., 2000, Bates et al, 2002). Other cytokines eg TNF-α, IL-1β, 6 and 8 have been associated with pre term labour (Amory et al, 2001, Taylor et al.,
1996).

Immune response to stress in pregnancy

A previous study investigated decidual leuocytes and cytokines in women having first trimester miscarriages (Arck et al., 2001). They found women with high stress scores had higher numbers of $CD8^+$ T cells, mast cells and cells that stained positive for TNF· in their decidua than women with lower stress scores (Arck et al., 2001).
This study will investigate the involvement of cytokine signals and leucocyte populations in women at high risk of preterm labour and the relationship to stress. We will investigate the hypothesis:
The host immune response to stress determines the risk of preterm delivery in women at high risk of pretem labour.
It is hoped it will be possible to provide women with better information about the risk of subsequent preterm labour. This research may also help develop diagnostic and predictive tests and possibly to discover a means to prevent recurrent preterm labour.

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Brief outline of project *(i.e. what do you intend to do?)*

3. Patients

Patients will be recruited from the newly formed preterm labour clinic at Liverpool Women's Hospital.

Inclusion criteria

1. A history of at least one idiopathic preterm delivery between, 24-32 weeks gestation (i.e. could not be explained by routine hospital investigations: blood tests for full blood count, rubella, syphilis, blood group and rhesus, hepatitis B, HIV, urine sample for infection and ultrasound scan for fetal anatomy).

Samples will be taken in the preterm labour clinic at 20 and 28 weeks gestation at the time of routine clinic visits for transvaginal ultrasonography to measure cervical length.

Exclusion Criteria

Women whose previous preterm delivery was elective or was associated with abruption, intra-uterine growth restriction, thrombophilia, multiple pregnancy or fetal anomaly.

Information sheets will be provided at the antenatal booking clinic for those women who are suitable and they will be approached to consider participating in the study when they attend for their 20 week preterm labour clinic appointment. At this visit the research midwife will discuss the study and a written consent will be obtained.

Numbers – We aim to recruit 200 patients over a maximum of 5 years.

4. Stress Questionnaires

Patients will be given two standard questionnaires to fill in:

1. Hospital Anxiety and Depression Score (HADS)
2. List of Threatening Experiences questionnaire (LTE).

5. Systemic host response

Venous blood will be sampled, centrifuged and assayed for the following cytokines using enzyme linked immunoabsorbant assay (ELISA) for IL-10, IFN-γ, TNF-α, IL-8, IL4, IL12, IL2, IL-1,, IL-18

Flow cytometry will be used to measure the peripheral leucocytes populations for cells expressing CD45, CD3, CD4, CD8, CD14, CD16, CD21, CD56, CD69, using the appropriate isotype control antibodies.

8. Study design *(e.g. cohort, case control)*
This is an Observational Study.

---

9. (i) How was the size of the study determined ?

We estimate that 25% of women will have a preterm labour (event), as we have estimated a similar patient mix to the established Preterm Labour Clinic at Guy's Hospital, London. In order to obtain 10 events per explanatory variable in the regression analysis model, we intend to study 200 women which will enable us will to include 5 explanatory variables in a regression analysis.

(ii) Was there formal statistical input into the overall study design?

4Yes No

If *Yes*, please give name of adviser: Dr. G. Lancaster.

(ii) What method of analysis will be used:

An initial exploratory analysis will be done to determine potential predictor variables for the Regression Analysis. Only variables significant to the outcome ($p < 0.25$) will be included.

---

10. Does the study fall into any of the following categories?

Pilot	Yes	No4
Multi-centre study	Yes	No4
Student project	4Yes	No

If this study is to be conducted at centre(s) other than that named in Question 11, please complete the following:

(i) Which centres are involved? (please include addresses)

(ii) Which Local Research Ethics Committees have been approached and what is the outcome to date?

(iii) Who will have overall responsibility for the study?

(iv) Who has control of the data generated?

---

11. Where will the study take place and in what setting?
The study will take place in the preterm labour antenatal clinic in Liverpool Women's Hospital. Women will be recruited and questionnaires and samples will be obtained.

12. Is any payment being made, or actively being sought by the investigator or department/unit in respect of this study ***(include research grants)*****?**

4Yes ☐
No

If *Yes*, complete the section below; if *No*, go to Question 13

(i) Is the payment:

(a) A block grant 4Yes ☐
No

If *Yes*, give details, including amount & source of funding £ 15000

Name of funding body/sponsor We will apply to various medical / midwifery charities.

(b) Based on number of subjects recruited Yes No4

If *Yes*, give name of funding body/sponsor .....

If payment is based on number of subjects recruited (per capita/payment), state total sum payable for each subject completing the study

£.....
State number of subjects agreed for centre named in Q11 .....

Will patients have their travel costs paid? ☐ Yes ☐ No

If more than one UK centre is involved, state <u>total</u> number of subjects to be recruited

(ii) Is the payment made in order to: If *Yes*, state sum

(a)	Pay a salary(ies)	Yes	No4	£.....
(b)	Fund equipment	Yes	No4	£.....
(c)	To support further departmental research	Yes	No4	£.....
(d)	Other (state) consumable costs	4Yes	No	£15000

11. **Who will have control of the funds? (e.g. Charitable Trust etc)**
University of Liverpool

(iv) Does the investigator(s) have any direct personal involvement? (e.g. financial, shareholding, etc.) in the sponsoring organisation?
(If *Yes*, give details) Yes No4

(v) Will all the costs incurred by the institution be covered by the grant/sponsorship? 4Yes No

---

13. If the project is to be carried out in a Trust has the R & D Lead the Trust been notified of the project? If No/NA, give reasons 4Yes ☐ No ☐ NA in

---

14. Schedule
Proposed starting date:1/9/03 Proposed duration: 5 years

SECTION 3	Recruitment of subjects

15. How will the patients or subjects in the study be selected, approached and recruited; what inclusion and exclusion criteria will be used? ***State if they are the subject of therapeutic or non-therapeutic research.***

Patients will be recruited in the preterm labour clinic in Liverpool Women's Hospital and be the subject of non-therapeutic research. 200 women as a consecutive sample of women attending the preterm labour clinic

Inclusion Criteria

Women with a singleton pregnancy and with a past history of at least one idiopathic preterm labour (delivery between 24 – 32 weeks of pregnancy).

Exclusion Criteria

Women whose previous preterm delivery was elective or was associated with abruption, intra-uterine growth restriction, thrombophilia, twins or fetal anomaly.

16. How many subjects will be recruited and of what age group?

200 women will be recruited from age 18-45. With a 25% incidence of preterm labour we estimate that 50 women out of 200 will have another preterm labour (delivery between 24 – 32 weeks of pregnancy).

17. How will the control group (if used) be selected, approached and recruited; what inclusion and exclusion criteria will be used? Type *N/A* if no controls

We estimate that 150 women will not have a preterm labour.

18. How many controls will be recruited and of what age group? Type *N/A* if no controls

The control will be the Preterm Labour Clinic attendees who do not have a preterm labour.

19. Are the subjects or controls included in this study involved in any other research investigation at the present time?

4Yes No

If *Yes,* please give details

Women will be approached at the booking visit and recruited only on a Tuesday afternoon in the antenatal clinic. The "Mothering Orientation and Attachment in Pregnancy" Study will also be recruiting in the Antenatal Clinic, on a Wednesday only.

20. Will healthy volunteers be used? Yes No4

If *Yes*, complete details below. If *No,* go to Question 21.

(i) What is their relationship to the investigator?

(ii) Will they receive any payment and, if so, what is the source of the funding? ☐ Yes ☐ No

5.1.1. If *Yes*, give details of payment per subject

Applicants must undertake to explain to volunteers that the researcher will contact their GP to ask about any drug therapy and that they must inform the researcher if they consult another doctor during the study, and that this doctor will be informed of this study.

SECTION 4 Consent

21. Is written consent to be obtained? 4Yes ☐No

If *Yes*, please attach a copy of the consent form to be used.
(Please see our standard consent form in the Guidance Notes)

If no written consent is to be obtained is it because one of the following methods of research is employed?

No	Postal questionnaire	☐ Yes	☐
No	Interview	☐ Yes	☐
No	Other	☐ Yes	☐

If *Other*, please justify.

---

22. Does the study include subjects for whom English is not a first language?

If *Yes*, give details of arrangements made; if *No*, please justify. 4Yes No

Interpreters will be used to obtain informed consent from women for whom English is not their first language.

---

23. Are the subjects or controls in one of the following vulnerable groups?

People with learning difficulties	Yes	No4
Other vulnerable groups, e.g. mental illness, dementia	Yes	No4

If *Yes*, please complete the details below, *otherwise* go to Question 24

(i) What special arrangements have been made to deal with the issues of consent and assent?
i.e. how and from whom will informed consent/assent be obtained?

(ii) In what way, if any, can the proposed study be expected to benefit the individual patient/subject on whom it is performed?

---

24. Will the patient/subject be given a written information sheet or letter? 4Yes ☐
No

(Please see Guidance Notes on suggested format)

Note: The Patient Information Sheet/Letter must be separate from the Consent Form

If *Yes*, please attach a copy to each application form. If *No*, please justify.
NOTE: If you, as investigator, are not responsible for the overall care of the subject, you must ensure that the Clinician responsible is given a copy of the Patient Information Sheet and signed Consent Form (for any patient/subject under the care of a Consultant at an NHS Trust)

SECTION 5	Details of interventions

25. Does the study involve the use of a medicinal product or medical device?
Yes No4
If *Yes,* please complete Annexe A, *otherwise* go to Question 26.

26. Will any ionising or non-ionising radiation, or radioactive substances or X-Rays be administered to a patient or volunteer?

Yes No4

If *Yes,* please complete Annexe B, *otherwise* go to Question 26.
Please ensure that information in Question 15 includes exclusion criteria with regard to ionising radiation if appropriate.

27. What investigations and/or interventions will subjects and/or control have over and above routine care?
Please complete (a) and (b) by selecting YES/NO option as appropriate. If YES, give details

(a)

Self completion questionnaires	4Yes	No
Interviews/interview administered questionnaires	Yes	No4
Video/audio taping	Yes	No4
Physical examination	Yes	No4
Internal physical examination	Yes	No4
Imaging investigations (not radiation)	Yes	No4
Other investigations not part of normal care	Yes	No4
Additional outpatients attendances	Yes	No4
Longer inpatient stays	Yes	No4
Local anaesthetic	Yes	No4
General anaesthesia	Yes	No4
Other	Yes	No4

Details:

Patients will be given Hospital Anxiety and Depression Score and List of Threatening Life Experiences questionnaires to complete with the assistance of the research midwife Lorna Wood.

(b) **Blood sampling, biopsies, tissue samples** Yes No

	Samples Cannula	Indwelling[1]	Repeated Puncture	Total Volume		
Venepuncture*	4	□	□	□	□	...10....ml

Arterial* ☐ ☐ ☐ ☐ ☐ .....ml

[[1]If an indwelling cannula is utilised, please give details of the quantity, site, size of cannula and duration]

Biopsy* ☐Yes ☐No 4

[If *Yes*, please give details of the site, size, number, method used and whether local/general anaesthesia]

Other tissue/ Body sample* 4Yes No
If Yes, please give details

A cytobrush will be rotated in the endo-cervical canal as part of the preterm clinic investigations by the Consultant Obstetrician.

***If *Yes*, will samples be retained beyond the end of the study for testing for other factors beyond that in this study?** 4Yes No

If *Yes*, will the samples be anonymised? 4Yes No

5.2. If *No*, please justify

If additional investigations or tests are involved with revenue consequences for the NHS, all of the relevant head(s) of department(s) must be contacted.

Signature of Head of Department ..... Date.....

Name in capitals ..... Position.....

Please provide further signatures, if appropriate.

SECTION 6	Risks and ethical problems

28. Are there ethical problems or considerations that the investigators consider to be important or difficult with the proposed study?

4Yes No

If *Yes*, please give details:

The HADS questionnaire is not diagnostic, it is only a strong indicator, therefore with consent, and women would be referred to their GP who has the expertise and knowledge of the local support services. The research midwife would aim to avoid labelling as some women may feel this is stigmatising and detrimental to their mental state. All difficult cases will be discussed with Dr. David Owen (Psychiatrist and advisor) and the Consultant Obstetrician and supervisor Dr. Quenby. *

There is an issue of confidentiality and consent, which will be an important factor in the referral of women.

(i) Is it possible that the trial medication will not be available at the end of the trial?

☐ Yes ☐ No NA4

(ii) If *Yes*, is this made clear in the patient information sheet? ☐ Yes ☐ No

If *No*, give reasons:

29. Are there any potential hazards to subjects or patients? Yes No4

If *Yes*, please give details, and give the likelihood and details of precautions taken to meet them, and arrangements to deal with adverse events and overdoses, including reporting to the relevant authorities

34. Is this study likely to cause discomfort or distress to subjects/patients?

4Yes No

If *Yes*, estimate the degree and likelihood of discomfort or distress entailed.

Women may feel slight discomfort from the venepuncture. There is always a slight risk of a haematoma occurring after venepuncture, the usual preventative measure of applying and maintaining digital pressure until haemostasis is achieved will be employed. A strict aseptic technique will be used and women will be advised to report pain and / or swelling in the venepuncture site to the GP. The research midwife Lorna Wood is very experienced and highly skilled in this technique.

31. Will information be given to the patient's General Practitioner (especially if a drug is to be given or an invasive procedure is undertaken)?

Yes No4

If *Yes*, please enclose a copy of the GP information sheet/letter

If *No*, please justify

This study will have no effect on the other care in the preterm labour clinic.

If the study is on patients under the care of a Consultant at an NHS Trust, has the consent of all consultants whose patients are involved in this research been obtained?

4Yes ☐ No

If the study is in general practice, has the consent of all the partners been obtained?

☐ Yes☐ No

Where available, please enclose an information sheet for consultants or GPS

32. If, during the course of the study, an unexpected but clinically significant result is found, what course of action will you take? *Please give full details.*

The HADS score will be followed up within one week and those women who are found to have severe symptoms of depression antenatally will be asked to consent for referral to the GP or Consultant Obstetrician whichever is appropriate. All difficult cases will be discussed with Dr. David Owen (Psychiatrist and advisor) and the consultant Obstetrician and supervisor Dr. Quenby. *

SECTION 7 Indemnity and confidentiality

Product liability and consumer protection legislation make the supplier and producer (manufacturer) or any person changing the nature of a substance, e.g. by dilution, strictly liable for any harm resulting from a consumer's (subject or patient) use of the product.

33. (i) If you are not a member of staff of an NHS Trust or Health Authority what arrangements have been made to provide indemnification and/or compensation in the event of a claim by, or on behalf of, a subject for negligent harm?

(ii) What arrangements have been made to provide indemnification and/or compensation in the event of a claim by, or on behalf of, a subject for non-negligent harm?

If the study is commercially-sponsored, please supply two copies of the Indemnity Form.

(iii) Will a medical student be involved directly in the project? 4Yes ☐No

34. Has a manufacturer provided any equipment or medical devices?
☐YesNo4 ☐NA

If Yes, what arrangements have been made with the manufacturer to provide indemnity? Please enclose two copies of any appropriate documentation.

35. (i) Has the relevant Data Protection Officer been notified of the study?
4Yes ☐No

Give name of Data Protection Officer:
Sheila Nealey - IT Department Liverpool Women's Hospital

(ii) If *No*, give reasons:

36. Will the patient's medical records be examined? 4Yes ☐No

If *Yes*, will information relevant to this study only be extracted? 4Yes ☐No

If extra information is extracted, please justify.

What, if any, additional steps have been taken to safeguard confidentiality of personal records?

37. Will the study include the use of any of the following?

Audio/video tape recording?	Yes	No4
Observation of patients?	Yes	No4

If Yes to either,

(a) How are confidentiality and anonymity to be ensured?

(b) What arrangements have been made to obtain consent?

(c) How long will the tapes be kept, where will they be stored and what will happen to them at the end of the study?

Please note that audio tapes should be transcribed and destroyed within 6 weeks. If audio tapes are to be kept longer than 6 weeks, please justify

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38. Will medical records be examined by research worker(s) outside the employment of the NHS?

Yes No4

If *Yes,* it is the responsibility of the principal investigator to ensure that research workers understand that they must:

(i) undertake never to divulge information about patients or research subjects, recorded or otherwise, to anyone without the authority of the Consultant/GP under whose care the patient is;

(ii) also understand that the names, addresses and places of work of patients or research subjects are confidential and must not be divulged.

Appendix 8 (5.6)

DATA COLLECTION FORM

Stress, Immunity & Preterm Birth Study
Lorna Wood 22/07/04
Patient I.D.
Serial no:

Demographic data from booking history:
Age in years
Postcode

Medical History:

Yes=1 / No=0 / NK=9

Smoker
Alcohol
Previous H/O Depression
Treatment
GP
Psychiatrist
On Medication
Type:.....

Obstetric history:

Gravida
Para
Number of Preterm Births (> 24 wks)
Number of Miscs (< 24 wks)

Gestational age in weeks:
Pregnancy 1.
Pregnancy 2.
Pregnancy 3.
Pregnancy 4.
Pregnancy 5.
Pregnancy 6.
Pregnancy 7.
Pregnancy 8.
Pregnancy 9.
Pregnancy 10.

Obstetric Intervention this pregnancy:
Cervical suture
Yes=1 / No=0 / NK=

Psychological Data

Patient I.D. ☐☐☐☐☐☐☐☐

Serial no: ☐☐☐☐

Stress and Anxiety scores:

Gestation in wks HADS ☐☐ ANXIETY ☐ LTE-Q ☐☐
DEPRESSION ☐

Gestation in wks HADS ☐☐ ANXIETY ☐ LTE-Q ☐☐
DEPRESSION ☐

Pregnancy Outcome Data ☐
NK=9

Gestation at birth in weeks ☐☐

Onset of labour:

Spontaneous ☐ **Yes=1 / No=0 /**
NK=9

Reason for elective delivery.....
.....
...

Live/Still Birth ☐ **LB=1/SB = 2**

Birth Weight in grams ☐☐☐☐

Sex of baby ☐ **Male=1/Female =2**

Apgar score:
1 min ☐☐
5 min ☐☐

No sample = 99
No HADS = 99
No LTE-Q = 99
No spec = 99

Coding:
NO SAMPLE = 99
NO HADS = 99
NO LTE-Q = 99

Laboratory Data

NO SPEC = 99

Patient I.D.

Serial no:

Lab label = C

Cytokines:

Leucocytes:

Gestation in wks

IL-10		CD 45	
IFN-Y		CD3	
TNF-a		CD4	
IL-8		CD8	
IL-4		CD14	
IL12		CD16	
IL2		CD20/22	
IL-1		CD56	
IL-18		CD69	

Lab label = CC

Cytokines:

Leucocytes:

Gestation in wks

IL-10		CD	
IFN-Y		CD3	
TNF-a		CD4	
IL-8		CD8	
IL-4		CD14	
IL12		CD16	
IL2		CD20/22	
IL-1		CD56	
IL-18		CD69	

Coding:

NO SAMPLE = 99

Sample code C = Levels at 20 weeks (+ / - 2 weeks) = 18 – 22 weeks

NO HADS = 99

Sample code CC = Levels at 28 weeks (+ / - 2 weeks) = 26 – 30 weeks

NO LEDS = 99

Appendix 9 (9.5)

HAD SCORES AT 20 WEEKS FOR THE SIP QUALITATIVE STUDY (N=52)

ANXIETY SCORES (HADS-A) RELATED TO THEMES

Damaged Relationship (n=24):

0-7=4 (16%) normal

8-10=5 (20%) mild and a possible clinical disorder.

11-14=12 (50%) moderate and a probable clinical disorder

15-21= 5 (20%) severe anxiety.

Damaged Self (n=23):

0-7= 2 (8%) normal

8-10=5 (22%) mild and a possible clinical disorder.

11-14=12 (52%) moderate and a probable clinical disorder

15-21=4 (17%) severe anxiety.

Damaged Child (n=5):

0-7= 1 (20%) normal

8-10= 1 (20%) mild and a possible clinical disorder.

11-14= 3 (60%) moderate and a probable clinical disorder

15-21= 0

Appendix 10 (9.5)

DEPRESSION SCORES (HADS-D) RELATED TO THEMES

Damaged Relationship (n=24):

0-7 =11 (45%) normal

8-10=7 (29%) mild and a possible clinical disorder.

11-14=6 (25%) moderate and a probable clinical disorder

15-21=0

Damaged Self (n=23)

0-7 = 16 (70%) normal

8-10= 3 (13%) mild and a possible clinical disorder.

11-14=4 (17%) moderate and a probable clinical disorder

15-21=0

Damaged Child (n=5)

0-7 = 4 (80%) normal

8-10= 0

11-14=1(20%) moderate and a probable clinical disorder

15-21=0

Appendix 11 (9.5)

ANXIETY SCORES (HADS-A) AT 28 WEEKS RELATED TO THEMES

Damaged Self (n=15) (not seen=8)

0-7 = 3 (20%)

8-10= 7 (47%) mild and a possible clinical disorder.

11-14=5 (33%) moderate and a probable clinical disorder

15-21=0

Damaged Child (n=4) (not seen=1)

0-7 = 0

8-10= 2 (50%)

11-14=2 (50%) moderate and a probable clinical disorder

15-21=0

Damaged Relationship (n=23) (not seen=3)

0-7 =6 (26%) normal

8-10=7 (30%) mild and a possible clinical disorder.

11-14=7 (30%) moderate and a probable clinical disorder

15-21=3 (13%) severe anxiety.

Appendix 12 (9.5)

DEPRESSION SCORES (HADS-D) AT 28 WEEKS RELATED TO THEMES

Damaged Self (n=15) (not seen=8)

0-7 = 11 (73%) normal

8-10= 2 (13%) mild and a possible clinical disorder.

11-14=2 (13%) moderate and a probable clinical disorder

15-21=0

Damaged Relationship (n=23) (not seen=3)

0-7 =14 (60%) normal

8-10=3 (13%) mild and a possible clinical disorder.

11-14=5 (22%) moderate and a probable clinical disorder

15-21=1 (4%) severe depression.

Damaged Child (n=4) (not seen=1)

0-7 = 3 (75%) normal

8-10= 0

11-14=1(25%) moderate and a probable clinical disorder

15-21=0

Appendix 13 (9.6)

LIFE EVENTS AT 20 WEEKS RELATED TO THEMES (N=52)

Damaged Self group life events at 20 weeks (n=23)

5 women had 1 life event (21%)

8 had 2 (34%)

2 had 3 (9%)

3 had 4 (13%)

1 had 5 (4%)

2 had 8 (9%)

Zero women having more than 8

Damaged Child group life events at 20 weeks (n=5)

2 had 1 (40%)

1 had 3 (20%)

1 had 4 (20%)

1 had 5 (20%)

Damaged Relationship group life events at 20 weeks (n=24)

1 had 0 life events

3 had 1(12%)

10 had 2 (4%)

7 had 3 (30%)

3 had 4 (12%)

1 had 7 (4%)

Zero women had more than7

Appendix 14 (9.6)

LIFE EVENTS AT 28 WEEKS RELATED TO THEMES (N=42)

Damaged Self group life events at 28 weeks (n=15) (not seen=8)

4 women had between zero and two life events

1 had 3 (7%)

1 had 4 (7%)

1 had 5 (7%)

1 had 7 (7%)

Zero had 6

Zero more than 7 life events.

Damaged Child group life events at 28 weeks (n=4) (not seen=1)

2 women had 1(50%),

1 had 2 (25%)

1 had 5 (25%),

1 woman not seen

Damaged Relationship group life events at 28 weeks (n=23) (not seen=3)

5 women had zero life events (22%),

5 had 1(22%),

6 had 2(26%),

2 had 3 (9%) and

5 had 4 (22%).

Zero had more than 4

3 women not seen (13%)

Appendix 15 (9.7)

C6 First interview at 20 (18 – 22) weeks

LW. *Have you suffered a serious illness, injury or an assault in the last year?*
C6. Can I talk about my last pregnancy?
LW. *Yes, if you see that as fitting in to an illness, injury or an assault to you.*
C6. Yes I do. The last pregnancy was 1 year and 4 months ago. It all happened so quickly. I felt devastated. I'm still grieving. Felt destroyed because staff told me the baby wouldn't survive labour and was born alive. Had to go through the process of watching baby die. I have a great fear for this pregnancy; this has brought it all back to me. It's reassuring to attend this clinic. I think There is a link to stress with the previous Pregnancy, My marriage broke up, I was going to court to get a settlement, then I was divorced and the children and the house was a constant argument to get access settled. I've had financial problems ever since. I'm more settled this pregnancy but the problems with the house and the money with my ex husband is ongoing.
Partner started to cry while she was re-counting this. He said he wasn't upset but just couldn't stop the tears. I suggested that we stop but both wanted to carry on with the questionnaire. C6 wanted to continue to talk about how she felt about being 21 weeks pregnant and having this very traumatic experience last time.
LW. *Has a serious illness, injury or an assault happened to a close relative in the last year?*
C6. My sister had a baby last year, anencephalic and the baby's death was very traumatic for every-one. I felt I couldn't really grieve for my sister because I was still grieving for myself. I feel guilty feel sorry for her but sorry for myself more. I had two funerals to go to and can't help thinking that this pregnancy will lead to another one.
LW *Has a parent or spouse died in the last year?*
C6 No
LW *Has a close family or friend or another family member died in the last year?*
C6 No

LW *Have you had a separation due to marital difficulties in he last year?* **C6** Yes, marital problems ongoing. Divorced last year. Not financially sorted with the half of the house. We've been arguing for the last 2 years. **LW** *Have you broken of a steady relationship in the last year?* **C6** Nothing financial from the last relationship. I feel it's ongoing until the financial part is sorted out. I can't finish the previous relationship properly. **LW** *Have you had a serious problem with close friend, neighbour or relative in the last year?* **C6** In my previous pregnancy, I had noisy neighbours. We moved house and schools last November. No problems now. **LW** *Have you become unemployed or have you seeked work unsuccessfully for more than one month?* **C6** I have a stressful job. I'm a nurse in the A & E department. The pressures of the job and the nature of the work, you have to accept it. I enjoy it, but it's stressful. **LW** *Were you sacked from your job in the last year?* **C6** No never. **LW** *Have you had any major financial crisis?* **C6** Yes, ongoing divorce settlement, having to go to court to get money for the house. We have money problems with the mortgage, because starting again without money from the divorce. It's taken more than two years **LW** *Have you had a problem with the police and a court appearance in the last year?* **C6** Only to get settlement from divorce. Taken ex-husband to court to make him pay is ongoing. **LW** *Have you had anything you valued lost or stolen in the last year?* **C6** Not recently *Comment: very talkative.* *Didn't get upset. Husband did at one point. We talked about grief and fears for this pregnancy. She thought the split in her relationship last time and the divorce contributed to the PTB last pregnancy. She thought she would have had a high stress score if this research had been done last pregnancy.*	

Appendix 16 (9.7)

CC6 Second interview at 28 (26 – 30) weeks.

Given transcript for verification – member checking.

LW *Have you suffered a serious illness, injury or an assault in the last year?* **CC6** Pelvic problems since 22 weeks and gradually worsening **LW** *Has a serious illness, injury or an assault happened to a close relative in the last year?* **CC6** My uncle died last month we weren't very close. **LW** *Has a parent or spouse died in the last year*? **CC6** Uncle **LW** *Has a close family or friend or another family member died in the last year?* **CC6** Uncle **LW** *Have you had a separation due to marital difficulties in he last year* **CC6** On gong problem from last marriage **LW** *Have you broken of a steady relationship in the last year* **CC6** Same as before **LW** *Have you had a serious problem with close friend, neighbour or relative in the last year?* **CC6** No **LW** *Have you become unemployed or have you seeked work unsuccessfully for more than one month?* **CC6** I've been off sick since Christmas. No hassle. If I wasn't in the NHS I'd be worried. **LW** *Were you sacked from your job in the last year?* **CC6** No. **LW** *Have you had any major financial crisis?* **CC6** We've moved house. I'm excited about it; it's a nice new house, nearer to school. **LW** *Have you had a problem with the police and a court appearance in the last year?* **CC6** No **LW** *Have you had anything you valued lost or stolen in the last year?* **CC6** More frustration, since I got my new car and I can't drive yet since I had a suture (cervical) put in.	*Comment: On her own this time. Happy with the scan and the news that there were no signs of impending PTL. Seemed much happier this time and less talkative.*

Appendix 17 (9.7)

C26 First interview at 20 (18 – 22) weeks

LW. *Have you suffered a serious illness, injury or an assault in the last year?* **C26** No **LW.** *Has a serious illness, injury or an assault happened to a close relative in the last year?* **C26** No **LW** *Has a parent or spouse died in the last year?* **C26** No, I couldn't be bothered who died. I don't know what I mean. I can't explain that statement. **LW** *Has a close family or friend or another family member died in the last year?* **C26** No **LW** *Have you had a separation due to marital difficulties in he last year?* **C26** No **LW** *Have you broken of a steady relationship in the last Year?* **C26** No **LW** *Have you had a serious problem with close friend, Neighbour or relative in the last year?* **C26** I did have bother with my neighbours before they moved out. Racial harassment last March. I was very stressed about it. I am fine now. No problems. They used to put hate letters through my door and break in to the house, damaged my car and bully the kids. I have made lots of statements to the police and they haven't done anything. They don't act. I think the kids do your head in as well though. **LW** *Have you become unemployed or have you seeked work Unsuccessfully for more than one month?* **C26** No **LW** *Were you sacked from your job in the last year?* **C26** No **LW** *Have you had any major financial crisis?* **C26** No **LW** *Have you had a problem with the police and a court Appearance in the last year?* **C26.** I only had dealings with the police because of the neighbours. **LW** *Have you had anything you valued lost or stolen in the*	

Last year? **C26** I had all my gold jewellery stolen; £4000 worth I was very upset at the time. Now I think as long as the kids are OK, the money doesn't matter to me. *Comment: Seemed very depressed / body language and was really fed up didn't know why as her scan was OK. Couldn't explain why she felt so low. Had very high stress scores on HADS questionnaire. I ask her to see the GP or to speak to the consultant in clinic. She was already seeing her GP weekly. Didn't want any help from anyone else. I offered her referral to Health Visitor or Family liaison at the hospital but she declined.*	

Appendix 18 (9.7)

CC26 Second interview at 28 (26 – 30) weeks.

Given transcript for verification – member checking.

LW *Have you suffered a serious illness, Injury or an assault in the last year?* **CC** **LW** *Has a serious illness, injury or an assault happened to a close relative in the last year?* **CC** **LW** *Has a parent or spouse died in the last year?* **CC** **LW** *Has a close family or friend or another family member Died in the last year?* **CC** **LW** *Have you had a separation due to marital difficulties in He last year?* **CC** **LW** *Have you broken of a steady relationship in the last Year* **CC** **LW** *Have you had a serious problem with close friend, Neighbour or relative in the last year?* **CC** **LW** *Have you become unemployed or have you seeked work Unsuccessfully for more than one month?* **CC** **LW** *Were you sacked from your job in the last year?* **CC** **LW** *Have you had any major financial crisis?* **CC** **LW** *Have you had a problem with the police and a court Appearance in the last year?* **CC** **LW** *Have you had anything you valued lost or stolen in the Last year?* **CC**	*Comment:* *No change from last interview. Has been seeing the GP. Feels a bit better. Looked at the answers from last time and agreed with my comments. Doesn't feel as depressed now and not on any medication.* *Doesn't want to add anything.*

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LIST OF ABBREVATIONS

ACTH	Adrenocorticotropic hormone
ANS	Automatic nervous system
A&W	Alive and well
BV	Bacterial vaginosis
CG	Control group
CL	Cervical length
CRF	Corticotrophin Releasing Factor
CRH	Corticotrophin Releasing Hormone
CRHBP	Corticotrophin Releasing Hormone Binding Protein
CS	Ceasarian section
DC	Damaged child
DR	Damaged relationship
DS	Damaged self
EDC	Expected date of confinement
EDTA	Ethylenediamine tetra acetic acid
ELISA	Enzyme linked immunosorbent assay
FFN	Fetal fibronectin
G	Gravida
GAD	General Adaptation Syndrome
GCS-F	Granulocyte colony-stimulating factor
HADS	Hospital Anxiety and Depression Scale
HADS -A	Anxiety
HADS -D	Depression
HPA	Hypothalamic-pituitary-adrenal
HRP	Horseradish peroxidase
HVS	High vaginal swab
IFN-γ	Interferon-γ
IL	Interleukin
IMD	Index of Multiple Deprivation

IOL	Induction of labour
LE	Life events
LTE-Q	List of Threatening Experiences Questionnaire
NK	Natural killer
P	Primip
PBS	Phosphate buffered saline
PND	Postnatal depression
PROM	Prelabour rupture of membranes
PPROM	Preterm prelabour rupture of membranes
PTB	Preterm birth
PTD	Preterm delivery
PTL	Preterm labour
PTS	Post traumatic stress
RCT	Randomised Control Trials
RDS	Respiratory distress syndrome
ROM	Rupture of membranes
SES	Socioeconomic status
SIP	Stress, immunity and Preterm birth
SIPPS	Stress, immunity and Preterm birth Pilot Study
TNF-a	Tumour necrosing factor- alpha
TVU	Transvaginal ultrasound
VLBW	Very low birth weight
Wks	Weeks

CODES

C	20 weeks gestation
CC	28 weeks gestation

PUBLISHED PAPERS

Wood L., Quenby S (2010) A review of qualitative studies exploring views and emotions of women in a subsequent pregnancy with a history of preterm birth or pregnancy loss. British Journal of Midwifery 18 (6)

Abstract

This is the first of two papers. The first paper outlines the literature review that informed the qualitative study; the second describes the qualitative study: Stress, Immunity and Preterm birth Study (SIPS).

The review examined qualitative research to understand the area of investigation and determine whether this corresponded with the findings of the qualitative study. The SIP Study used semi-structured interviews exploring women's answers to a life events questionnaire as part of a larger quantitative prospective observational study, the stress, immunity and preterm birth (SIPS) study. The SIP Study examined the association between maternal stress, maternal immune response and pregnancy outcome in women with a history of recurrent idiopathic preterm labour. The review evolved into three broad themes: the impact of perinatal loss on a subsequent pregnancy; the preterm labour experience; and disenfranchised grief.

PUBLISHED PAPERS

Wood L., Quenby S (2011) Women's perceptions of stressful life events in relation to a previous preterm birth: the SIP Study. British Journal of Midwifery 19 (2)

Abstract

This is the second of two articles exploring the views and emotions of women in a subsequent pregnancy with a history of preterm birth or pregnancy loss. The first article outlined the preliminary literature review that informed this study. In the literature review it was found that women who had experienced preterm birth or pregnancy loss were anxious throughout a subsequent pregnancy; that pregnancy milestones were important to get past; that grief resurfaces during a subsequent pregnancy; and that the psychological effects of a past experience could alter women's locus of control and ability to deal with the next the pregnancy. In light of these findings, a qualitative study was undertaken—the Stress, Immunity and Preterm birth (SIPS) Study.

Data from the List of Threatening Experiences Questionnaire (LTE-Q) from a larger quantitative prospective observational study (n = 200), the SIP Study was used to explore stressful life events. 'Think-aloud' methods were explored because of the structured format of data collection and 26% of women's responses (n=52) were analysed thematically using 'framework analysis'. Themes are described in relation to 'damage', that is, damage to self, damage to the child and damage to relationships as a result of experiences of preterm birth or pregnancy loss.