Determinants of late stillbirth
Auckland 2006-2009

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Abstract

Stillbirth is a devastating and too common outcome of pregnancy; globally there are approximately three million deaths after 28 weeks' gestation every year. In New Zealand, as in other high income countries, more than 1 in 200 babies die before birth, and around 1 in 300 die in the last three months of pregnancy. During the mid twentieth century there was a dramatic decline in the rate of stillbirth, however this improvement has not been sustained in recent years. Previous studies have identified certain causes and risk factors for late stillbirth, but over a third of the deaths remain unexplained. The current variation in the rate of stillbirths both across and within high income countries suggests that it is possible to make further improvements in stillbirth rates. We hypothesised that there would be modifiable, but as yet unidentified risk factors for late stillbirth.

The Auckland Stillbirth Study was the first case control study to select women with ongoing pregnancies as gestation matched controls. This study found that the disparity in rates of late stillbirth in women from different ethnicities in New Zealand could be attributed to associated factors such as high parity, high body mass index and social deprivation. Regular utilisation of antenatal care was found to be protective, and women who attended at least 50% of recommended antenatal visits had a lower risk of stillbirth compared to those who did not. Antenatal identification of sub-optimal fetal growth was found to be a possible aspect of the benefit of regular antenatal attendance. Maternal perception of fetal movements was also identified as an area of importance, with women who perceived their baby's movements to decrease in the last two weeks of the pregnancy being at greater risk of experiencing a stillbirth. In addition this study found an association between maternal sleep practices and risk of late stillbirth. Most strikingly, the study found that women who went to sleep on their left side on the last night (prior to stillbirth/interview) were half as likely to experience a late stillbirth compared to women who went to sleep in any other position.

This study has added a New Zealand perspective to the existing literature on certain known risk factors for late stillbirth (such as high body mass index). It has also identified novel factors that present new possibilities for further research and for the potential for future reductions in the incidence of late stillbirth.

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All scientific work is incomplete - whether it be observational or experimental.
All scientific work is liable to be upset or modified by advancing knowledge.
That does not confer upon us a freedom to ignore the knowledge we already have,
or to postpone the action that it appears to demand at a given time.

A Bradford Hill 1965

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Glossary

Body Mass Index (BMI)	A proxy measure for human body fat based on an individual's height and weight (height in ems/weight in kgs^2). BMI is used as an index to classify underweight, recommended weight, overweight and obesity.
Confidence Interval (CI)	A confidence interval gives a range of values in which an unknown parameter is likely to fall. The confidence level used in this study was 95%.
District Health Board (DHB)	District Health Boards are responsible for providing, or funding the provision of, health and disability services.
Large for gestational age (LGA)	Birthweight more than the 90th percentile for gestation and gender. The customised birth weight centile calculator also takes into account maternal ethnicity, height, weight and parity.
Lead Maternity Carer (LMC)	The Lead Maternity Carer is the health professional (midwife, obstetrician or general practitioner) who is responsible for the coordination of maternity care for the individual woman.
New Zealand Health and Information Service (NZHIS)	The NZHIS were a group within the Ministry of Health responsible for the collection and dissemination of health related information. It was disestablished in 2008 and the roles and responsibilities are now spread across a variety of organisations.
Odds ratio (OR)	The odds ratio is the chance of an event occurring in one group compared to it occurring in another group. It measures the size of the effect.

Perinatal and Maternal Mortality Review Committee (PMMRC)	An independent mortality review committee that advises the Health Quality & Safety Commission on how to reduce the number of deaths of babies and mothers in New Zealand. The PMMRC was established in 2005 and has provided reports on perinatal mortality since 2006.
Perinatal Society of Australia and New Zealand (PSANZ)	A multidisciplinary society dedicated to improving the health and long-term outcomes for mothers and their babies.
Perinatal Society of Australia and New Zealand-Perinatal death Classification (PSANZ-PDC)	The Perinatal Society of Australia and New Zealand-Perinatal Death Classification is the system used in New Zealand for the classification of stillbirth and other perinatal deaths.
Small for gestational age (SGA)	Birthweight less than the 10th percentile for gestation and gender. The customised birth weight centile calculator also takes into account maternal ethnicity, height, weight and parity.

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Chapter 1

Introduction

1.1 Background

Stillbirth, the death of a baby before birth, is a tragedy for the family and the wider community and is also distressing for the clinicians involved. There is considerable international variation in the definition of stillbirth and in the reporting processes, which makes determining both the size of the problem and international comparisons difficult. A recent analysis estimated the worldwide rate of third trimester stillbirth in 2009 to be 18.1/1000, with over 2.64 million stillbirths each year (Cousens, Blencowe et al. 2011). This estimate, although arguably more reliable than previously reported figures, may still be conservative due to under-reporting and unreliable data in many countries, and the uncertainty range is estimated to be from 2.37 to 4.19 million (Stanton, Lawn et al. 2006; Cousens, Blencowe et al. 2011). These numbers compare, internationally, to that of early neonatal deaths, or deaths of one to five year olds and yet stillbirth remains relatively invisible on the international health agenda; a reduction in the rate of stillbirth does not even feature in the Millennium Development Goals (UNICEF 2009).

The vast majority of stillbirths occur in low to middle income countries, accounting for more than 98% of deaths, with the highest rates being in sub-Saharan Africa and South Asia (Lawn, Yakoob et al. 2009; Cousens, Blencowe et al. 2011). Although stillbirth is less common in high income countries, it continues to be a far too frequent outcome of pregnancy.

In many high income countries, the latter half of the twentieth century saw a decline in the perinatal mortality rate due to a reduction in both stillbirths and neonatal deaths (Ward 2003; Craig, Stewart et al. 2004; Woods 2005). There is debate as to the factors which resulted in this reduction, but it is likely that it was due to a combination of effects including: improvements in antenatal and obstetric care, and overall improvement in the health status of women of reproductive age (Vallgarda 2010). Since the early 1990's, the overall improvement in stillbirth rates in high income countries has slowed and even stalled in some areas (Flenady, Middleton et al. 2011). There continues to be a variation in stillbirth rates, however, even amongst high income countries, which suggests that further

reduction in rates of stillbirth is possible (Flenady, Middleton et al. 2011). The reduction in the neonatal death rate has been sustained in recent years, therefore increasing the proportion of perinatal deaths attributable to stillbirth (CMACE 2011; PMMRC 2011). In most high income countries, stillbirth now accounts for over 60% of perinatal mortality (Smith and Fretts 2007).

Although in the last ten years there has been a growing interest in the causes and risk factors for stillbirth amongst academics and clinicians, there is still a relative lack of research into this devastating perinatal complication. Investigation into the causes of stillbirth and strategies for prevention has not been seen as a priority for research funding. Stillbirth has not received the same level of public attention as other tragic perinatal outcomes (such as sudden infant death) (Rose 2005), although there has been a recent increase in public interest with the publication of the *Lancet Stillbirth series* in April 2011.

Late, or third trimester, stillbirth occurs at or after 28 weeks' gestation. At this gestational age the chance of survival if the baby is live born is approximately 95% (ADHB 2010). As pregnancy progresses, the relative risk of stillbirth also increases, as does the proportion of stillbirths that are classified as unexplained (Yudkin, Wood et al. 1987; Huang, Usher et al. 2000). In high income countries, the most common classification of stillbirth in the third trimester is "unexplained/unspecified" (Laws, Li et al. 2010).

New Zealand

There has been no improvement in the rate of stillbirth in New Zealand in the last 10 years (see *Figure 1* below). An apparent rise in the rate of stillbirth needs to be treated with some caution. Since the formation of the Perinatal Mortality Review Committee in 2006, there has been greater ascertainment of cases of fetal death and thus an apparently increased number of deaths; the rise since 2007 is not statistically significant (PMMRC 2011).

There have been no previous prospective studies that have explored the risks factors for stillbirth in New Zealand. The two retrospective studies of risk factors for stillbirth that have been carried out in New Zealand only investigated a limited number of variables. It was not possible to examine a wide range of demographic, medical or novel risk factors in

these former studies. There has therefore been an urgent need for prospective studies to improve the understanding of the determinants of late stillbirth in New Zealand.

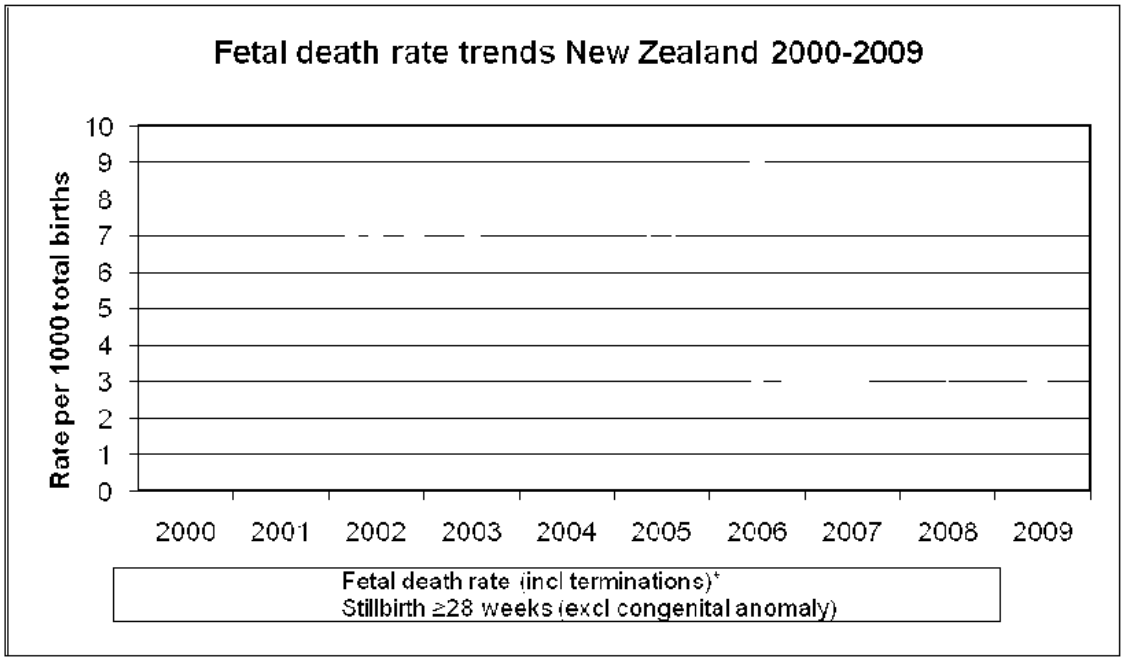

Figure 1 Fetal death rate trends New Zealand 2000-2009.
2000-2005, data obtained from NZIIIS (NZIIIS 2007); 2006-2008 data obtained from PMMRC (PMMRC 2011).

1.2 Aims of the research

The aim of the Auckland Stillbirth Study was to identify modifiable risk factors for late stillbirth.

The broad objectives of this research were:

- To identify and quantify risk factors for late stillbirth in Auckland
- To identify novel, modifiable, risk factors for late stillbirth in order to develop strategies to reduce the incidence.

1.3 Structure of thesis

The thesis begins with an overview of stillbirth; current definition(s), classification systems and known risk factors for stillbirth. This chapter aims to provide a framework for the understanding of stillbirth and provide a context to the research.

The following chapter presents a review of the existing research that has examined risk factors for stillbirth. This review focuses on the literature relating to high income countries and the emphasis is on those factors that are amenable to modification.

The body of this thesis is based on five papers that report on findings from this research. At time of submission, four of these papers have been published/in press and the remaining one has been submitted and is being considered for publication.

The first paper, *The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale (Australian and New Zealand Journal of Obstetrics and Gynaecology, 2011)*, details the methods of the research and provides a rationale for the approach to control selection. It also presents feedback from participants on the impact of being involved in this study.

The second paper, *Relationship between obesity, ethnicity and risk of late stillbirth: a case control study (BMC-Pregnancy and Childbirth, 2011)*, explores the role of socio-demographic factors on risk of late stillbirth. This paper outlines the importance of adjusting for appropriate confounding factors in order to understand the independent contribution of various factors.

The third paper, *Maternal perception of fetal activity and late stillbirth risk - findings from the Auckland Stillbirth Study (Birth-Issues in Perinatal care, In Press)*, examines the significance of maternal perception of fetal activity and risk of late stillbirth. This paper reports a variety of aspects of fetal activity, including maternal perception of strength and frequency of fetal movements as well as perception of fetal hiccups.

The fourth paper, *Antenatal care, identification of suboptimal fetal growth and risk of late stillbirth: findings from the Auckland Stillbirth Study (submitted)*, focuses on antenatal care, in particular the association between utilisation of antenatal care and late stillbirth risk. The relationship between a specific aspect of antenatal care provision (the identification of the small for gestational age (SGA) baby during pregnancy) and risk of late stillbirth is also explored.

The final paper, *Association between maternal sleep position and risk of late stillbirth: a case control study (British Medical Journal, 2011)*, examines the relationship between maternal sleep practices and late stillbirth risk. Although, on average, we spend almost a third of our lives sleeping, there has been very limited research on the role of maternal sleep practices on pregnancy outcome, with no previous research relating to stillbirth risk. This paper describes novel findings in this area.

These papers are followed by a reminder of the context of this research, an examination of the strengths and weaknesses of the study, and thoughts for the future.

Chapter 2

Stillbirth: an overview

2.1 Definition of stillbirth

One of the barriers to understanding the prevalence of stillbirth is the lack of an internationally recognised definition. Stillbirth is a fetal death occurring at greater than a specified gestation (it is the specified gestation that varies with different definitions). Fetal death refers to the death of a baby in-utero "before the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy" (World Health 2004). The World Health Organisation defines stillbirth as a fetal death of 22 completed weeks' gestation or greater (World Health 2006). Due to the range of definitions used in different countries, and the difficulty in obtaining accurate data, for international comparisons stillbirth is generally defined as fetal death that occurs at or after 28 weeks' gestation only. Individual countries, however, apply a range of different definitions (see *Table 1*). In New Zealand, stillbirth is defined as "the death of a fetus born at 20 weeks' gestation or beyond, or weighing at least 400gms, if gestation is not known" (PMMRC 2010).

Country	Inclusion gestation for fetal death
Sweden	≥ 28 weeks' gestation (Macfarlane, Gissler et al. 2003)
UK	≥ 24 weeks' gestation (CMACE 2011)
France	≥ 22 weeks' gestation (Macfarlane, Gissler et al. 2003)
USA	≥ 20 weeks' gestation (McClure, Nalubamba-Phiri et al. 2006)
Netherlands	≥ 16 weeks' gestation (Macfarlane, Gissler et al. 2003)

Table 1 Different definitions of stillbirth in a selection of high-income countries.

Due to this variance in definitions, international comparisons can be difficult and can lead to misconceptions. In addition to the application of different gestational age criteria for the definition of stillbirth, termination of pregnancy (usually for fetal anomalies) is included in some statistics and not in others. This can have a significant impact on the apparent differences in rates of perinatal mortality between countries (Sachs, Fretts et al. 1995).

Definitions of stillbirth (defined by a specific gestational age at birth) are necessary for quality improvement purposes and benchmarking analysis.

2.2 Prevalence

The worldwide incidence of late stillbirth in 2009 has been estimated as approximately 2.64 million, compared to an estimate of 3.03 million in 1995 (Cousens, Blencowe et al. 2011). The global reduction in the rate of stillbirth has been 1.1% on average each year since 1995. Although any improvement is positive, this improvement is half the rate of reduction in childhood deaths (2.3% per annum) during the same period (Cousens, Blencowe et al. 2011). *Table 2* shows rates of late stillbirth in a selection of countries throughout the world. In many countries, birth and death statistics are difficult to capture and therefore even late stillbirth is underreported; the rates in some low income countries may thus be even higher (Setel, Macfarlane et al. 2007).

	Stillbirth rate/1000 total births (≥28 weeks' gestation)	Median year of observation
World (all countries)	18.9	2001
East Asia	9.7	1999
South Asia	26.7	2003
Southeast Asia	13.9	2001
West Asia	12.0	2002
North Africa	13.6	2000
Sub-Saharan Africa	28.3	2002
Latin America/Caribbean	8.7	2002
Oceania	14.5	1996
High income regions	3.1	2002

Table 2: Estimated rates of late (≥ 28 weeks gestation) stillbirth in selected regions (adapted from Cousens, Blencowe et al. 2011)

Stillbirth rate and stillbirth risk by gestational age

The rate of stillbirth at a given gestational age is calculated by dividing the number of stillbirths by the number of total births at the same gestational period. This does not however describe the *risk* of stillbirth. It has now been well established that the most

appropriate way of assessing risk of stillbirth by gestational age is derived from the number of stillbirths at a given gestation as a proportion of the total number of undelivered babies (Yudkin, Wood et al. 1987; Smith 2001). The rate of stillbirth is therefore higher in the preterm period, but the risk of stillbirth increases with advancing gestational age.

2.3 Causes of stillbirth

The causes of and risk factors associated with stillbirth in low to middle income countries differ considerably to those in high income countries. *Table 3* outlines the main causes and risk factors for stillbirth in both settings.

Low to middle income countries	High income countries
• Obstructed labour	• Congenital abnormalities
• Congenitally acquired infection: in particular syphilis	• Fetal growth restriction
	• Medical diseases such as diabetes
• Hypertensive disease	• Hypertensive diseases
• Poor maternal nutritional status	• Smoking
• Previous stillbirth	• Multiple gestation
• Congenital abnormalities	• High body mass index
• Malaria	• Previous stillbirth
• Sickle cell disease	• Maternal age over 40

Table 3: Main causes of and risk factors for stillbirth in high and low income countries (adapted from Smith and Fretts 2007).

Risk factors, confounding and causes

A risk factor is an epidemiological variable, or 'exposure' that is associated with an increased risk of a given outcome. Confounding is considered to be a 'third' factor that is associated with the exposure and is also related to the outcome, but is not on the causal pathway to the outcome. Confounding factors can lead to a misinterpretation of the relationship between a given risk factor and outcome and it is therefore necessary to adjust for this in the statistical analysis. Risk factors are not necessarily causal (although some are), but rather correlational. All causative factors are therefore risk factors, but not all risk factors are causal.

2.4 Classification of stillbirth

There are a number of ways of classifying stillbirth, including: by gestational age at death, timing of the death (antepartum or intrapartum) or by presumed cause of death. When applying gestational age, two or three periods are generally defined: early (prior to 28 weeks gestation) and late (≥ 28 weeks gestation), and sometimes, term (> 37 weeks gestation). Although simplistic, the implication of the gestation of fetal death is clinically significant, in that late stillbirths are potentially viable (as opposed to stillbirths that occur prior to viability, or during the early weeks of viability, where the prognosis for live-born infants is guarded). The timing of stillbirth in relation to labour is also of clinical relevance. Worldwide 45% of stillbirths occur during labour (intrapartum), whereas in high-income countries less than 14% of stillbirths occur in labour (PMMRC 2010; Lawn, Blencowe et al. 2011). Intrapartum stillbirths are more likely to be preventable with appropriate obstetric care; Kiely and others suggest that intrapartum stillbirth can be used as an indicator for quality of obstetric care (Kiely, Paneth et al. 1985).

Systems for clinical surveillance of perinatal death, in order to identify causal factors, have existed since the early 20th century. One of the earliest published systems of perinatal death classification was developed by Baird in Scotland in the 1940s, and published in 1954 (Baird, Walker et al. 1954); since then many diverse systems have emerged. Flenady et al found that there are now 33 distinct systems, and 12 further modifications, for the classification of causes of perinatal death (Flenady, Froen et al. 2009). The underlying aim of all classification systems is to reduce perinatal death: determining the cause of stillbirth using a systematic approach assists clinicians to identify avoidable stillbirths and improve quality of care. The development of diverse systems has been driven by different philosophical approaches and needs. The requirements underlying the respective classification systems (whether it be to identify deficiencies in perinatal care, for audit and benchmarking, research or new developments in care) determines, to some degree, the focus of the system.

For a system to be effective it needs to be:

- Easily applied
- Have high inter-observer agreement
- Based on clinical factors and post-mortem findings

- Able to capture the underlying cause of death
- Have a high percentage of classifiable cases (low percentage of unexplained)
- Identify deficiencies in the provision of care

(Whitfield, Smith et al. 1986; de Galan-Roosen, Kuijpers et al. 2002).

New Zealand

New Zealand uses the Perinatal Society of Australia and New Zealand Perinatal Death Classification System (PSANZ-PDC) to classify perinatal deaths (Chan, King et al. 2004). This semi-hierarchical system, which is also used in Australia, aims to identify the obstetric origins that precede the sequence of events leading to the death and is based on modifications of the Aberdeen and Whitfield classification systems (Baird, Walker et al. 1954; Whitfield, Smith et al. 1986). The system has been shown to be easy to use and have high inter-observer agreement (Flenady, Froen et al. 2009). *Table 4* compares a selection of other perinatal death classification systems developed in high income countries.

Most classification systems aim to identify the underlying cause of stillbirth; however the distinction between causal factors and associated factors is not always clear. There continues to be debate as to whether certain factors. such as fetal growth restriction or hypertension, are causes or associated factors, and whether they should be included as such in classification systems. Unsurprisingly, when death is attributed to these factors, especially fetal growth restriction, the proportion of unexplained stillbirth is lower (Gardosi and others 2005; Korteweg and others 2006).

Unexplained or unexplored

Unexplained stillbirth is a common classification for cause of death, accounting for between a quarter and a third of all stillbirths, (Froen, Arnestad et al. 2001; PMMRC 2010; CMACE 2011). As pregnancy progresses this proportion becomes even higher (Huang, Usher et al. 2000; PMMRC 2010). The classification of unexplained stillbirth usually also includes a proportion of deaths that have not been fully investigated; 'unexplored' stillbirths. As both Froen and Measey argue, 'unexplored' is not the same as 'unexplained', and in order to accurately assess distinct risk factors for unexplained stillbirth (as opposed to other causes of stillbirth) a clearer distinction should be made (Froen, Arnestad et al. 2001; Froen 2002; Measey, Charles et al. 2007). Froen suggests that

this could be achieved by including the requirement for autopsy in the definition of unexplained stillbirth, in the same way that the definition of sudden infant death syndrome necessitates the performing of an autopsy (Froen, Arnestad et al. 2001).

In New Zealand in 2008, 33% of fetal deaths that were classified as unexplained were not investigated, with no post-mortem, placental pathology or karyotyping, and were therefore unexplored (PMMRC 2010). The distinction between fully investigated unexplained stillbirth and unexplored stillbirth can be captured in the PSANZ-PDC classification system.

Classification system	**Key points**	**Strengths**	**Weaknesses**
Wigglesworth United Kingdom (Wigglesworth 1980)	Hierarchical system Identifies a single underlying cause Clinical based categories	Easy to use Clear implications for clinical management	Strict hierarchical system, does not allow for the capturing of associated factors. High proportion of unexplained cases
ReCoDe (Relevant Conditions at Death) United Kingdom (Gardosi, Kady et al. 2005)	Hierarchical system Clinical based categories Defines conditions *associated* with death as opposed to a cause	Easy to use Helps with provision of care and directing of services to those babies that are more at risk	Confuses risk/associated conditions with cause. A high proportion of deaths attributed to fetal growth restriction
TULIP The Netherlands (Korteweg, Gordijn et al. 2006)	Semi-hierarchical Identifies pathological entities initiating the chain of events that led to death	Easy to use High inter-observer agreement. Explores mechanism of death as well as associations	Over concentration on mechanism and confusion with cause of death reduces clinical usefulness
PSANZ-PDC Australia and New Zealand (Chan, King et al. 2004)	Semi-hierarchical Identifies obstetric origins that precede death	Easy to use High inter-observer agreement	Higher proportion of unexplained stillbirths compared to some other systems
CODAC (Cause of Death and Associated Conditions International (Froen, Pinar et al. 2009)	Non hierarchical (except for termination of pregnancy) Identifies cause of death and associated conditions	Easy to use Can also be applied in low income countries Low level of unexplained cases	Not currently adopted in a clinical setting

Table 4: A comparison of selected classification systems for perinatal mortality developed in high income countries

2.4.1 Classification of stillbirths using the Perinatal Society of Australia and New Zealand Perinatal Death Classification System

The gestational age cut off for stillbirth in New Zealand is 20 weeks' gestation or beyond

Congenital abnormality

Congenital abnormality remains one of the major causes of stillbirth: whether associated with a spontaneous death or due to therapeutic termination. Faye-Petersen et al found that 35% of all babies who underwent a post mortem, had a structural abnormality (Faye-Petersen, Guinn et al. 1999). Cytogenetic abnormalities may account for up to 25% of these anomalies, but the underlying cause of many abnormalities remains unknown (Goldenberg, Kirby et al. 2004).

In New Zealand between 2007 and 2009, 92 (28%) fetal deaths were attributed to congenital abnormality; 79% of these were terminations of pregnancy (see *Table 5* below), and the majority of these deaths occurred between 20 and 28 weeks (PMMRC 2011).

Perinatal infection

Although the relationship between maternal infection and stillbirth is not always clear, in high income countries 10-25% of stillbirths have been attributed to infection (Goldenberg, McClure et al. 2010). In low income countries the role of infection is likely to be even greater (Smith and Fretts 2007). Determining that infection is the cause of death can be problematic: finding histological evidence of infection does not prove causation, and some micro-organisms that have been associated with stillbirth, such as ureaplasma urealyticum, are hard to identify and often not looked for in routine perinatal death investigations (Goldenberg, Kirby et al. 2004).

In New Zealand between 2007 and 2009 only 4% of stillbirths are attributable to infection (*Table 5*). This may be due to the requirement in the classification for evidence of fetal infection, that there is either histological confirmation of infection in the cord or the fetus, or convincing clinical evidence of a primary maternal infection, or positive cultures from the placenta or the mother.

Hypertension

Hypertension, both chronic hypertension and gestational hypertensive disorders, has long been associated with increased risk of poor pregnancy outcomes, including stillbirth (Smulian, Ananth et al. 2002; Ananth and Basso 2010). The improvement in obstetric care for high risk women in the latter half of the twentieth century may well be partly responsible for the improvement in stillbirth rates seen during that time (Silver 2007). There has however been an increase in the incidence of hypertensive disorders of pregnancy in some locations and hypertension continues to contribute to stillbirth numbers (Ananth and Basso 2010).

4% of New Zealand stillbirths are attributed to maternal hypertension (*Table 5*)

Antepartum haemorrhage

Antepartum haemorrhage includes abruption, as well as other causes of haemorrhage. Abruption occurs in < 1% of pregnancies but accounts for 10-20% of stillbirths (Ananth, Berkowitz et al. 1999). Abruption is associated with smoking, illicit drug use, hypertension, fetal growth restriction and placental pathology.

Antepartum haemorrhage (in addition to specific perinatal conditions) is the second most common classification for stillbirth in New Zealand (*Table 5*). Women who live in the most deprived areas in New Zealand have been found to have the highest rates of antepartum haemorrhage (PMMRC 2011).

Maternal conditions

Maternal diabetes, inherited thrombophilia and termination of pregnancy for psychosocial reasons are included in this classification. Along with hypertension, diabetes is one of the most common medical disorders of pregnancy, affecting 3-5% of pregnant women (Mokdad, Ford et al. 2003); with the rising levels of obesity and increasing age of childbearing in the western world there is a corresponding increase in rates of diabetes in pregnancy. Impaired glucose tolerance has long been associated with poor perinatal outcomes, including an increase in the rate of stillbirth (Mondestin, Ananth et al. 2002; Simpson 2002). However, improvement in pre-conception care and diabetic management has improved outcomes for diabetic women (Fretts, Schmittdiel et al. 1995; Wahabi, Alziedan et al. 2010).

The role of blood clotting disorders in perinatal mortality risk is not well established. Some studies suggest that there is an association between inherited thrombophilias and stillbirth, however the lack of consistency in study populations, the range of disorders that are investigated and the nature of study designs makes it difficult to reach clear conclusions (Saade and McLintock 2002; Werner and Lockwood 2010).

In New Zealand in 2009, 25 stillbirths were attributed to maternal conditions, 9 of which were due to maternal diabetes and only 4 related to blood clotting disorders (PMMRC 2011)

Specific perinatal conditions

The broad category of specific perinatal conditions includes twin to twin transfusion, feto-maternal haemorrhage, cord complications and uterine abnormalities.

Feto-maternal haemorrhage is relatively rare, but has a high rate of fatal outcome and is thought to be under-recognised and under-reported (Wylie and D'Alton 2010). Umbilical cord abnormalities and cord accidents can cause fetal death, although the degree to which they contribute to the overall rate of perinatal death is debateable (Collins 2002). Thinner cords have been associated with poor outcome (Roche, Skurnick et al. 2008), and have been identified as a predictor of fetal size (Goynumer, Ozdemir et al. 2008). The coiling index has also been shown to be associated with poor outcomes, with both under-coiled and hyper-coiled cords being associated with an increased risk of stillbirth (de Laat, Franx et al. 2006), in particular when combined with a deficiency of Warton's jelly (Peng, Levitin-Smith et al. 2006). It is difficult, however to determine whether these structural cord anomalies are just an association or are causally related to stillbirth.

Without full autopsy, it is difficult to attribute the cause of stillbirth to cord accidents (other than in the case of cord prolapse), as true knots and nuchal cords are common in live births and denominator data on the true prevalence in the general population has not been available.

Feto-maternal haemorrhage was classified as the cause of death for 11 babies in New Zealand in 2009 (PMMRC 2011).

Hypoxic peripartum

This category includes deaths where the baby is alive at the onset of labour, and generally includes normally formed babies of over 24 weeks' gestation. It also incorporates cord prolapse, shoulder dystocia and uterine rupture. In high income countries, intrapartum death (where the cause of stillbirth is considered to be related to the intrapartum period), is rare. Four percent of stillbirths in New Zealand were considered to be hypoxic peripartum deaths (*Table 5*), which is consistent with rates from reports from other countries (Flenady, Middleton et al. 2011).

Fetal growth restriction

This classification includes babies born with a birthweight below the 10th percentile for gestational age, and where growth restriction has been identified antenatally, or there is evidence of fetal growth restriction at post-mortem. The association between fetal growth restriction and poor perinatal outcome has been well established, in particular when customised birthweight centiles are used in preference to population centiles (Froen, Gardosi et al. 2004; McCowan, George-Haddad et al. 2007; PMMRC 2010; CMACE 2011). Customised birthweight centiles adjust for gender, gestation, ethnicity, maternal age, parity and BMI (Gardosi, Clausson et al. 2009). Classification systems differ in the extent to which they attribute cause of stillbirth to fetal growth restriction (Chan, King et al. 2004; Gardosi, Kady et al. 2005). Poor fetal growth is thought to be associated with placental function, but whether it is a marker of placental dysfunction, or causally associated with fetal death, is unclear (Smith and Fretts 2007).

12% stillbirths were classified as being caused by fetal growth restriction in New Zealand (*Table 5*). In the PSANZ-PDC classification system, for a fetal death to be classified as due to growth restriction, fetal growth restriction needs to have been identified antenatally, or there was clear evidence of fetal growth restriction at autopsy (PSANZ 2009). In 2009, 48% of all stillbirths weighed less than the 10th customised centile at birth (PMMRC 2011).

Spontaneous preterm birth

Normally formed and appropriately grown babies (without signs of fetal infection) who die following spontaneous onset of preterm labour, or spontaneous rupture of membranes, are captured in this classification.

Spontaneous preterm birth accounts for 10% of fetal deaths in New Zealand (*Table 5*)

Unexplained antepartum death

This classification incorporates both unexplained and unexplored or under-investigated deaths. In New Zealand in 2009 22% of stillbirths that were classified as unexplained were not investigated , not having a post mortem, placental pathology or karyotype undertaken (PMMRC 2011). Unexplained antepartum death is the most common classification of cause of stillbirth in New Zealand (*Table 5*)

Perinatal death classification	**Termination n=426**		**Stillbirth n=1146**		**All fetal deaths n=1572**	
	n	%	n	%	n	%*
Congenital abnormality	350	82%	92	8%	442	28%
Perinatal infection	4	1%	49	4%	53	3%
Hypertension	10	2%	48	4%	58	4%
Antepartum haemorrhage	8	2%	144	13%	152	10%
Maternal conditions	17	4%	58	5%	75	5%
Specific perinatal conditions	8	2%	149	13%	157	10%
Hypoxic peripartum death	-	-	43	4%	43	3%
Fetal growth restriction	12	3%	137	12%	149	10%
Spontaneous preterm birth	17	4%	119	10%	136	9%
Unexplained antepartum death	-	-	307	27%	307	20%

Table 5: Classification for fetal deaths in New Zealand 2007-9 (PMMRC 2011)

*Adds up to >100 due to rounding

The following chapter will provide a review of the literature relating to risk factors for stillbirth.

Chapter 3

Literature review: Risk factors for stillbirth

The risk factors for stillbirth in high income and low to middle income countries differ considerably; as this study is set in a high income country, the following review will concentrate on factors relating to these settings.

3.1 Maternal age

Over the last 10 to 15 years there has been growing evidence of a link between advanced maternal age (generally defined as equal to or over 35 years) and risk of stillbirth (Fretts, Schmittdiel et al. 1995; Huang, Usher et al. 2000; Froen, Arnestad et al. 2001; Canterino, Ananth et al. 2004; Jacobsson, Ladfors et al. 2004; Miller 2005). The table below (*Table 6*) provides a summary of key studies in this area. Although there was heterogeneity in the design of these studies, the association between advanced maternal age and risk of stillbirth is consistent, thus suggesting a real and valid relationship.

Effect of increasing age

The magnitude of risk appears to vary between studies; the reason for the variation in magnitude may in part be due to differences in categorisations. As the relationship between maternal age and stillbirth risk is not linear, most studies have categorised age rather than used it as a continuous variable; the categorisations, however, are not always consistent. Some studies have applied just two categories: women over 35 years old and women less than 35 years old (Raymond, Cnattingius et al. 1994; Astolfi and Zonta 2002). As greater understanding of the issue has developed, and as the proportion of women over 35 years and over 40 years having babies has increased, narrower categorisations have been made. These studies have shown that the risk of stillbirth does not suddenly increase as a woman reaches 35 years old, and then stay consistent, but increases gradually from the mid 30s and then more rapidly after the age of 40 (Fretts, Schmittdiel et al. 1995; Nybo Andersen, Wohlfahrt et al. 2000; Astolfi and Zonta 2002; Jacobsson, Ladfors et al. 2004).

	Number of participants Age: SB/Total	**Key findings OR (95% CI)**	**Comments**
(Raymond, Chattingius et al. 1994)	20-34:1811/563180 ≥35: 349/75062	≥35: 1.5 (1.4-1.7)	*Country*: Sweden *Stillbirth defined*: ≥28 weeks *Adjusted for*: nulliparity and smoking and excluded diabetes, hypertension, IUGR and placental complications
(Fretts, Schmittdiel et al. 1995)	<35: 561/82376 ≥35: 127/11942	35-39: 1.9 (1.3, 2.7) ≥40: 2.4 (1.3, 4.5)	*Country*: Canada *Stillbirth defined*: Weight >500gms *Adjusted for*: Past perinatal death, diabetes, hypertension, placenta previa, abruption and marital status
(Conde-Agudelo, Belizan et al. 2000)	<20 : 2638/170780 20-34: 9400/579389 ≥35: 2675/87063	<20: 1.2 (1.0, 1.1) ≥35: 1.5 (1.4, 1.6)	Country: Latin America Stillbirth defined: ≥20 weeks Adjusted for:BMI, maternal education, smoking, antenatl care attendance
(Astolfi and Zonta 2002)	<35: 8455/2089070 ≥35: 1174/202054	≥35: 1.4 (1.4, 1.5)	*Country*: Italy *Stillbirth defined*: Weight >500gms *Adjusted for*: Marital status, parity
(Rasmussen, Albrechtsen et al. 2003)	<35: 2669/1509529 35-39: 352/13436 ≥40: 105/29646	35-39: 1.7 (1.4, 2.1) ≥40: 2.0 (1.5, 7.0)	*Country*: Norway *Stillbirth defined*: Unexplained stillbirth ≥28weeks *Adjusted for*: unadjusted Note : used <20 years as the reference
(Canterino, Ananth et al. 2004)	<35: 15061/5440685 >35: 8177/2470005	35-39: 1.2 (1.2, 1.3) 40-44: 1.6 (1.5, 1.8) >44: 2.4 (1.8, 3.3)	*Country*: USA *Stillbirth defined*: >24 weeks *Adjusted for*: gravidity, race, marital status, prenatal care, education, smoking
(Jacobsson, Ladfors et al. 2004)	20-29: 2785/876361 40-44: 203/31662 >45: 14 /1205	40-44: 1.7 (1.5, 1.9) ≥45: 2.4 (1.5, 4.0)	*Country*: Sweden *Stillbirth defined*: ≥28 weeks *Adjusted for*: diabetes, hypertension, placenta previa, pregnancy complications, parity, marital status, smoking, malformations, multiple pregnancy.
(Reddy, Ko et al. 2006)	<35: 479594 35-39:567708 ≥40: 120092	35-39: 1.3 (1.2, 1.4) ≥40: 1.9 (1.6, 2.2) (at 37-41 weeks)	*Country: USA* *Stillbirth defined*: ≥20 weeks (without congenital abnormality) *Adjusted for*: maternal disease , parity, ethnicity
(Haavaldsen, Sarfraz et al. 2010)	<35: 19263/1958771 ≥35: 3491/223985	35-39: 1.9 (1.7, 2.1)	*Country*: Norway *Stillbirth defined*: ≥16 weeks *Adjusted for*: Parity, plurality, preeclampsia and paternal age
(Lisonkova, Janssen et al. 2010)	20-29: 295/68728 35-39: 139/24919 ≥40: 30/4786	35-39: 1.5 (1.2, 1.9) >40: 1.5 (1.0, 2.4)	*Country*: Canada *Stillbirth defined*: >20 weeks *Adjusted for*: Parity, suboptimal antenatal care, marital status, low socio-economic area, smoking, drug/alcohol, previous obstetric history

Table 6: Summary table of key papers relating to maternal age and stillbirth risk

Gestation and maternal age

The risk of stillbirth in older women also appears to increase with gestational age (see *Figure 2* below). As early as 1994, Raymond and others suggested that length of gestation may compound the risk of stillbirth for older women (Raymond, Cnattingius et al. 1994). A recent study by Haavaldsen specifically explored the relationship between length of gestation and risk of stillbirth in older women (Haavaldsen, Sarfraz et al. 2010). This Norwegian population based study, which included more than 2 million pregnancies, examined the relative rates of stillbirth for women of different ages by length of gestation. They report that at the earlier gestational periods there was relatively little difference in the risk of stillbirth between the different age groups (OR 1.14 for women aged 35 to 39 and 1.25 for women aged 40 to 44 years). However by 40 weeks' gestation the magnitude of difference was substantially higher OR 2.07 (95% CI: 1.72, 2.52) for women aged 35 to 39 and OR 2.66 (95% CI: 1.98, 3.57) for women aged 40 to 44 years). The one limitation of this study was that they only adjusted for a few potential confounders (year of delivery, parity, plurality, paternal age and preeclampsia).

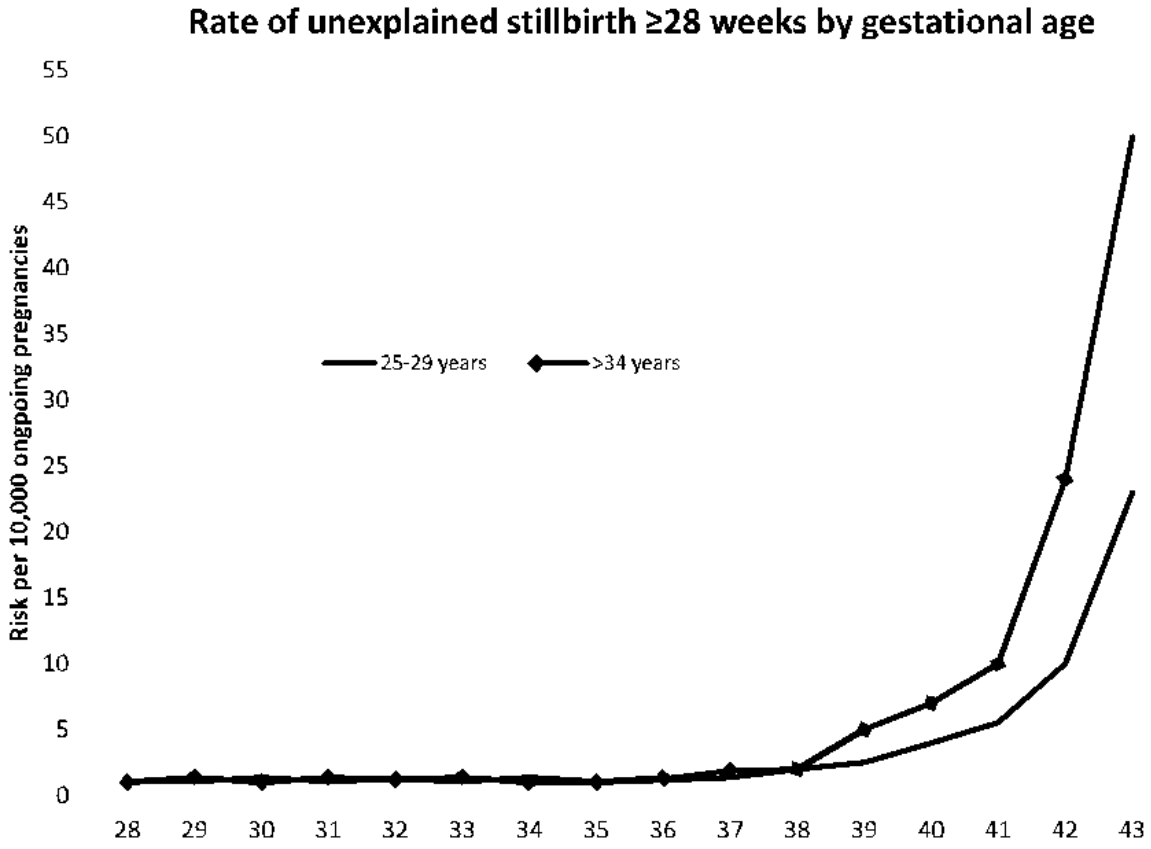

Figure 2: Rate of unexplained stillbirth ≥ 28 weeks by gestational age in weeks and maternal age. (Adapted from Rasmussen, Albrechtsen et al. 2003)

Parity and maternal age

Few studies have examined the risk of stillbirth in older women for nulliparous and multiparous women separately. Studies that have considered an interaction between parity and age have not produced consistent findings; Kiely (1986) found no interaction (Kiely, Paneth et al. 1986), whereas Raymond in 1994 showed that older nulliparous women had an increased risk of stillbirth, post-term, compared to multiparous women (Raymond, Cnattingius et al. 1994). Both these studies had limitations in that they did not adjust for potential confounders such as past medical or obstetric history. Recently, Lisonkova and others conducted an analysis of births in Canada specifically to address the question of the role of parity on risk of stillbirth in older women (Lisonkova, Janssen et al. 2010). This population based retrospective cohort study examined approximately 100,000 births including 464 stillbirths, and supported Raymond's finding that older nulliparous women had an added degree of increased risk of stillbirth compared to older multiparous women, again specifically after 40 weeks gestation. Although this study adjusted for more variables than some previous studies considering the same issue, they did not adjust for maternal BMI or maternal medical conditions. As the authors themselves state, chronic diseases such as asthma, diabetes and hypertension are more common in older women, and they found that nulliparous women had an even higher prevalence of these conditions than older multiparous women (Lisonkova, Janssen et al. 2010).

Unexplained stillbirth and maternal age

Unexplained stillbirth generally occurs at later gestational periods (Rasmussen, Albrechtsen et al. 2003). Froen and others explored risk factors for unexplained stillbirth (≥22 weeks' gestation) in Norway (Froen, Arnestad et al. 2001); 291 stillbirths were included in the study, 26% of which were unexplained, even after post mortem examination. This study found that women over 35 had a fivefold increased risk of unexplained stillbirth, aOR 5.02 (95% CI: 1.32, 19.57) compared to women under 35 years old. This is a considerably higher magnitude of risk than found in other studies which have explored the relationship between maternal age and all causes of stillbirth, and may suggest an increased strength of association between maternal age and unexplained stillbirth in particular. Froen's study was however relatively small, as shown by the wide confidence interval, and other studies that have also specifically explored unexplained stillbirth have not found the same magnitude of association. Huang and others, for instance, in their cohort of 196 unexplained stillbirths (>500gms at birth), 97% of whom

had full post mortem examination, found that women between 35 and 39 years old only had a 25% increased risk of unexplained stillbirth compared to women aged between 20 and 24 (Huang. Usher et al. 2000). The magnitude of effect may be debateable, but these findings suggest that the association between maternal age and risk of stillbirth is real and independent of other confounding factors such as an increased fetal anomaly rate in older women, or higher incidence of specific medical conditions.

Young maternal age

The impact of young maternal age is sometimes difficult to assess as researchers have used a range of reference values when evaluating the relationship between maternal age and stillbirth risk, with some including women under 20 years old in the reference group (Astolfi and Zonta 2002; Rasmussen, Albrechtsen et al. 2003; Sutan, Campbell et al. 2010). Many studies have shown, in crude analysis, that there is a J shaped curve which describes the relationship between maternal age and stillbirth risk (Conde-Agudelo, Belizan et al. 2000; Nybo Andersen, Wohlfahrt et al. 2000; Ananth, Liu et al. 2005). However once adjustment is made for lifestyle and socio-economic factors, such as smoking and social deprivation, an independent association has not usually been found (Huang, Usher et al. 2000; McCowan, George-Haddad et al. 2007). The analysis conducted by Smith and others on a large cohort of Scottish pregnancies is one of the few studies that show an association between young maternal age and risk of stillbirth (>24 weeks' gestation) after adjustment of known confounders (Smith and Pell 2001). This study, however, only found an independent association in young women aged between 15 and 19 years old having their second babies, not young women having their first baby.

Possible causal mechanisms

The mechanism(s) by which older women are more likely to experience a stillbirth is unclear. A review of the relationship between maternal age and risk of stillbirth conducted by Huang and others suggests that due to the relatively small effect of adjusting for known confounders in many studies, it is likely that the association between maternal age and stillbirth risk is independent of many known confounding factors that are likely to increase with age (Huang, Sauve et al. 2008).

"Uteroplacental insufficiency" has been speculated as a mechanism for the increased risk of stillbirth in older women (Naeye 1983; Jolly, Sebire et al. 2000). However, Miller found

that older women did not have any significantly increased markers for uteroplacental insufficiency, such as fetal growth restriction or fetal distress in labour, compared to younger women (Miller 2005).

Women who have had a history of infertility have also been shown to have an increased rate of stillbirth (Whitley, Doyle et al. 1999, Wisborg, Ingerslev et al. 2010). It is likely that more women with a history of infertility are included in the cohorts of women over 35; a history of infertility, or receiving infertility treatment are not usually accounted for in the analysis of published studies.

Medical complications of pregnancy, such as gestational diabetes and hypertension are also more common in older women (Jolly, Sebire et al. 2000; Joseph, Allen et al. 2005). As medical complications may be on the causal pathway between exposure and outcome, it may not be appropriate to consider them as confounding factors and adjust for them in analysis; there has not been a consistent approach to which factors are included in the current literature as potential confounders. The possible contribution of chronic and pregnancy related medical conditions to the increased risk of stillbirth in older women needs further investigation. However, as previously noted, the association between advanced maternal age and increased stillbirth risk remains, or is arguably increased, in the event of an unexplained stillbirth, thus suggesting that the mechanism is unlikely to be solely related to increased maternal disease in older women.

New Zealand

National reports have shown a J or U shaped association between maternal age and risk of stillbirth (PMMRC 2011). However, the only two previous studies conducted in New Zealand that have explored a relationship between maternal age and risk of stillbirth (Craig, Stewart et al. 2004; McCowan, George-Haddad et al. 2007) showed a significant, independent, association between maternal age and risk of stillbirth.

Summary

Older maternal age is associated with an increased risk of stillbirth, in particular at later gestational ages. The mechanism for this increase in risk remains unclear. There is no strong evidence that young maternal age is independently associated with an increased risk of stillbirth

3.2 Maternal ethnicity

The association between ethnicity and pregnancy outcomes is a complex issue fraught with controversy. Ethnicity itself is not well defined and different studies have used a variety of definitions and categorisations depending on the accepted norms of the country in which the research has taken place. In some countries, such as Australia and New Zealand, an ethnic minority may be indigenous to the country, whereas in other parts of the world (such as the United States) certain ethnic or racial minorities have a specific history within that country. Women from ethnic and racial minorities may be born in the country, or be new immigrants. All these factors may impact on a woman's overall health and pregnancy outcome. There is a strong association between minority ethnic or racial groups and socio-economic disadvantage; it can be hard to disentangle the respective influence of these factors on perinatal outcome.

A disparity in rates of stillbirth between different races and ethnicities has been described in many parts of the world. Salihu and others conducted a large retrospective cohort study in the United States which included more than 14 million singleton and more than 400,000 multiple pregnancies (Salihu, Kinniburgh et al. 2004). This study showed a significant, almost threefold, disparity in risk of stillbirth over 24 weeks' gestation for Black Americans compared to White Americans, aOR 2.9 (95% CI: 2.8, 3.0). These findings have been supported by other American studies (Ananth, Liu et al. 2005; MacDorman, Hoyert et al. 2007; Reddy, Laughon et al. 2010).

In a review of racial disparities and pregnancy outcomes, Bryant and others found that Black Americans, in particular, were more at risk of experiencing a perinatal death compared to any other ethnic or racial groups in the USA (Bryant, Worjoloh et al. 2010). The Hispanic population in the United States is now the second largest racial minority, and while there is similar socio-economic disadvantage for Hispanic and non-Hispanic Black American women, Hispanic women do not have the same rate of poor perinatal outcome as Black Americans (Brown, Chireau et al. 2007). Although one study has suggested that this may be due to a systematic underreporting of Hispanic fetal deaths, further investigation of these possible differences in outcome is required (Wingate and Alexander 2006).

In the UK, South Asian women have been shown to be at disproportionate risk of experiencing stillbirth compared to European women, and are at greater risk than Black British women (Balchin, Whittaker et al. 2007). A study of almost 200,000 nulliparous women found that South Asian women had the highest rate of stillbirth compared to European and Black British women (Balchin, Whittaker et al. 2007). In univariable analysis, Black women had an increased rate of stillbirth compared to European women after 32 weeks gestation, but this association did not remain once adjustment was made for possible confounding factors such as BMI. In contrast, the risk amongst South Asian women persisted. The reasons for these reported ethnic disparities have not yet been determined.

Differences in risk factors

Clarke and others in 1988 published a study that explored the differences in risk factors for perinatal death between South Asian and European women in Leicestershire in the UK (Clarke, Clayton et al. 1988). This case control study, which included 1342 perinatal deaths and 1342 live births, found that South Asian women had an increased risk of perinatal death compared to European women, and also that the associated risk factors differed. For South Asian women parity (both primiparity and parity greater than 3) and history of infertility were associated with increased risk of perinatal mortality; no such association was seen for European women. This analysis was not adjusted for gestational age at birth and therefore may indicate that there was a greater association between preterm birth and stillbirth in the South Asian and Black women, rather than a relationship with fetal growth restriction as suggested by the authors. They also saw a greater risk of term stillbirth for South Asian women who by 42 weeks had a risk 3.8 times that of European women, OR 4.6 (95% CI: 1.8, 7.3) compared to OR 1.2 (95% CI: 0.3, 1.6).

Ethnicity and antenatal care

In the United States, Black women have been found to be less likely to receive antenatal care than White Americans (Vintzileos, Ananth et al. 2002; Park, Vincent et al. 2007). It has been suggested that this is one of the reasons for the apparent disparity in perinatal mortality rates between White and Black Americans. In order to explore this issue, Healy and others from the Faster Trial Research Consortium analysed over 35,000 pregnancies of women who accessed antenatal within the first trimester (Healy, Malone et al. 2006). This study found that even amongst women who accessed early antenatal care and after

adjustment for a range of known confounders (including BMI, smoking and drug use), Black American women still had a threefold increased risk of stillbirth (≥ 24 weeks gestation) compared to White American women.

A study conducted in the Netherlands to explore the relationship between ethnic disparity in perinatal mortality rates and substandard care, found that in an analysis of 137 perinatal deaths, there was an increased rate of substandard care for non-Western women (Alderliesten, Stronks et al. 2008).

Ethnicity and obesity

A study by Salihu and others using the Missouri maternally linked dataset explored the relationship between obesity and ethnicity (Salihu, Dunlop et al. 2007). This study found that obesity increased the disparity between Black and White Americans. Other studies have suggested that Black women in the United States are more at risk of being obese than white women; it may therefore be that increased obesity in Black women is one of the reasons for this apparent racial disparity. However Reddy's recent retrospective cohort study showed that even when adjustment was made for maternal BMI, Black women still had a twofold increased risk of stillbirth compared to White women (Reddy, Laughon et al. 2010).

New Zealand

In New Zealand, there have been a number of audits and retrospective studies that have suggested a difference in rates of stillbirth by maternal ethnic origin. In 1989 Becroft and Gunn described an increased stillbirth rate amongst Pacific Island women in Auckland (Becroft and Gunn 1989). This retrospective audit showed that Pacific Island women were 60% more likely to experience a stillbirth compared to European or Māori women. Becroft and Gunn speculated this increase was associated with the unusually high occurrence of intracranial haemorrhages in many of the stillborn babies of Pacific Island ethnicity and may be due to the practice of traditional massage.

Ekeroma and others examined the causes of fetal death in New Zealand using birth and death registration data (Craig, Stewart et al. 2004; Ekeroma, Craig et al. 2004). This retrospective study also found a disparity in risk of stillbirth between women of Pacific Island ethnicity and European women, aOR 1.26 (95% CI: 1.01, 1.60) adjusted for a

limited number of variables and therefore an exploration of whether ethnicity was independently associated with risk of stillbirth could not be firmly established. The only other New Zealand study, conducted by McCowan, that explored such a relationship was able to explore more potential confounding factors (such as smoking habits, parity and marital status) but was still limited in the variables available. McCowan and others analysed the possible risk factors associated with stillbirth in Auckland and found that both Indian and Pacific women were significantly more likely to experience a stillbirth compared to European women, aOR 1.85 (95% CI: 1.18, 2.91 and aOR 1.65 (95% CI: 1.27, 2.14) respectively (McCowan, George-Haddad et al. 2007).

Summary

Ethnic/racial disparity has been identified as a risk factor for stillbirth in a number of high income countries. It is still unclear however whether there is a causal relationship between ethnicity and stillbirth risk. Research studies have been limited in their ability to collect a full range of potential confounding factors that are inherent to race and cultural practice that may impact on risk of stillbirth.

3.3 Parity

In the obstetric literature, parity has often been classified as a dichotomous variable, that is either nulliparous or multiparous. In considering the relationship between parity and stillbirth, Bai and colleagues have shown that the degree of multiparity can significantly affect perinatal outcomes, and therefore argue against the use of a dichotomous categorisation (Bai, Wong et al. 2002). This study of over half a million singleton births in Australia explored in detail the effect of different parity groups on a number of pregnancy outcomes, including perinatal mortality. The authors found that the effect of parity on pregnancy outcome is J shaped: with a slightly increased risk of adverse outcomes for nulliparous women and an increasing risk for women of parity greater than three, compared to low parity (1-3). They therefore suggest that, when assessing risk, it is appropriate to classify parity into three groups, nulliparity, low multiparity and grandmultiparity (Bai, Wong et al. 2002).

Nulliparity

Nulliparity is associated with an increased risk of a number of adverse perinatal outcomes; it has also been associated with an increased risk of stillbirth (Raymond, Cnattingius et al. 1994; Cnattingius, Haglund et al. 1998; Bai, Wong et al. 2002; Reddy, Laughon et al. 2010). Cnattingius' population based cohort study included over a million singleton pregnancies from the Swedish birth register; this study found that nulliparous women had a 40% increased risk of experiencing a late stillbirth, aOR 1.5 (95% CI: 1.3, 1.5) (Cnattingius, Haglund et al. 1998). An Australian study which examined all stillbirths over 20 weeks' gestation, also found an increased risk of stillbirth for first time mothers, aOR 1.17 (95% CI: 1.07, 1.28) (Bai, Wong et al. 2002); both these studies adjusted for known risk factors associated with stillbirth, such as age, smoking and socio-economic status. In studies that have not found such an association (Conde-Agudelo, Belizan et al. 2000; Froen, Arnestad et al. 2001), nulliparity was either used as the reference value, or a dichotomous classification was applied (nulliparity versus parity) therefore possibly distorting the analysis (see following discussion of grandmultiparity).

Grandmultiparity

In those studies that do distinguish between degrees of multiparity, a range of different definitions have been used for grandmultiparity, or risk threshold, ranging in general from

parity three to five, or even higher (Rasmussen, Albrechtsen et al. 2003; Roman, Robillard et al. 2004; Aliyu, Salihu et al. 2005; McCowan, George-Haddad et al. 2007; Shechter, Levy et al. 2010). However, even with this heterogeneity in definition, there has been an almost consistent association found between high degrees of parity and risk of stillbirth, independent of maternal age. In an early study into risk factors for stillbirth, Kiely and others describe an association between grandmultiparity (four or more previous births) and intrapartum stillbirth (Kiely, Paneth et al. 1986). This association between high parity and stillbirth risk has been replicated in many further studies (Conde-Agudelo, Belizan et al. 2000; Oron, Sheiner et al. 2001; Bai, Wong et al. 2002; Shechter, Levy et al. 2010).

Bai describes a rising level of risk for perinatal death after parity three, rising from an aOR of 1.57 (95% CI: 1.27, 1.93) for women who have had four previous pregnancies of greater than 20 weeks, to aOR 2.89 (95% CI: 1.86, 4.50) in women of parity seven and eight; adjustment was made for maternal age and other known confounders (Bai, Wong et al. 2002). A similar rise in magnitude of risk associated with increasing parity was also shown by Aliyu and others in their study of over 27 million births in the United States (Aliyu, Salihu et al. 2005).

Possible mechanisms

The mechanisms that might underlie the relationship between high parity and stillbirth risk are not well understood. A speculation by Aliyu and others is that "uterine exhaustion" is reached and the uterus becomes less effective in its nurturing of the fetus (Aliyu, Salihu et al. 2005), although there has been no confirmation of this speculation. Grandmultiparity is also associated with advanced maternal age, low socio-economic status, reduced access of antenatal care services, obesity and anaemia (Babinszki, Kerenyi et al. 1999; Bai, Wong et al. 2002; Aliyu, Salihu et al. 2005; Akwuruoha, Kamanu et al. 2009). Although studies have often been able to adjust for maternal age, obesity and aspects of socio-economic disadvantage, there may be residual confounding from these or other factors.

New Zealand

In New Zealand, McCowan et al found that nulliparous women had an increased risk of stillbirth, but that women of parity three and above did not (once adjustment had been made for known confounders) (McCowan, George-Haddad et al. 2007). Unexpectedly they also found that women who had had two previous babies had a significantly increased risk

of stillbirth. This is not consistent with previous studies and the authors did not have an explanation for this finding.

Summary

Both nulliparity and grandmultiparity are associated with an increased risk of stillbirth; once parity is greater than three, there appears to be a dose-effect to the relationship. Grandmultiparous women are more likely to be of low socio-economic status, of advanced maternal age and have high BMI. It is not clear however whether there is a causal relationship between parity and stillbirth risk

3.4 Past obstetric history

Although past obstetric history is not modifiable, other than delivery by caesarean section, understanding the relationship between past history and future outcome can assist both parents and clinicians in their decisions and clinical management. Previous fetal death, as well as other adverse pregnancy outcomes (including preterm birth, small for gestational age (SGA), pre-eclampsia and caesarean section) has been associated with an increased risk of future stillbirth (Samueloff, Xenakis et al. 1993; Greenwood, Samms-Vaughan et al. 1994; Salihu, Sharma et al. 2006; Smith, Shah et al. 2007).

Prior fetal death

Although there is a clear risk for recurrent stillbirth, the magnitude of risk depends to a considerable extent on the aetiology of the initial death. For causes of stillbirth such as abruption and hypertensive disorders there is an increased likelihood of recurrence. However there has been conflicting evidence as to whether other causes of stillbirth (including unexplained stillbirth) are also associated with a risk of recurrence (Samueloff, Xenakis et al. 1993; Heinonen and Kirkinen 2000; Black, Shetty et al. 2008).

Samueloff et al found a tenfold increased risk of experiencing a stillbirth in a subsequent pregnancy following an initial stillbirth, however all causes of death were included and adjustment was made for only a limited number of potential confounders that may have also contributed to the initial death (Samueloff, Xenakis et al. 1993). These findings were supported by Sharma and others who used the Missouri Maternal Linked dataset, and found a relationship between stillbirth in a first pregnancy and risk of future stillbirth, with a hazard ratio of 5.8 for recurrence (Sharma, Salihu et al. 2007). A recent study by Bhattacharya and others also found a recurrence risk of stillbirth in the second pregnancy, with an aOR of 1.94 (99% CI: 1.29, 2.92) compared to women who had a live birth in their first pregnancy (Bhattacharya, Prescott et al. 2010). This large retrospective cohort study included all women delivering in Scotland between 1981 and 2000 and included 3094 women who had a stillbirth in their first pregnancy. Adjustment was made for age, social deprivation, smoking, placental abruption, pre-eclampsia, preterm birth and low birthweight. The lower odds ratio in Bhattacharya's study may be due to the ability of the study to adjust for a broad range of potential confounding factors. Other studies that have

not shown such a relationship have generally been smaller and not had the power to demonstrate an association (Black, Shetty et al. 2008).

Previous small for gestational age and previous preterm birth

Small for gestational age (SGA) in a first pregnancy has been shown not only to be associated with a risk of recurrence of SGA but also to a twofold greater risk of future stillbirth (Surkan, Stephansson et al. 2004; McCowan, George-Haddad et al. 2007; Rasmussen, Irgens et al. 2009). Similarly, prior preterm birth has also been found to be associated with subsequent stillbirth risk. Surkan and colleagues, in a large Swedish study, found that women who had delivered a preterm baby (<32 weeks) had a twofold increased risk of experiencing a stillbirth in their subsequent pregnancy. aOR 2.0 (95% CI: 1.0, 3.8), even after adjustment for known confounding factors such as smoking (Surkan, Stephansson et al. 2004). If the first baby was preterm and also small for gestational age, then the risk of future stillbirth was fivefold compared to a women whose first baby had been born at term and not small for gestational age, aOR 5.0 (95% CI: 2.5, 9.8). For discussion of SGA in the index pregnancy, see section 3.12.

Previous Caesarean Section

In studies powered to detect an effect, prior caesarean section has been found to be associated with subsequent stillbirth in some studies (Smith, Pell et al. 2003; Kennare, Tucker et al. 2007; Reddy, Laughon et al. 2010). This association appears stronger for subsequent unexplained stillbirth. In Kennare's Australian study of over 35,000 women having their second birth, previous caesarean section was associated with a 60% increase in stillbirth overall, OR 1.56 (95% CI: 1.04, 2.32), and more than twofold for unexplained stillbirth, OR 2.32 (95% CI: 1.26, 4.37) (Kennare, Tucker et al. 2007). Smith and others conducted a large retrospective cohort study in Scotland to investigate specifically whether there was an association between caesarean section and subsequent risk of unexplained stillbirth (Smith, Pell et al. 2003). They found that women whose first baby was delivered by caesarean section were significantly more likely to experience an unexplained stillbirth in their second pregnancy after 34 weeks gestation, HR 2.23 (95% CI: 1.48 to 3.36). The authors speculate that there could be a biological explanation for this finding, and that it may be a combination of abnormal placentation caused by uterine scarring and possibly in extreme cases the ligation of uterine arteries at the time of surgery leading to impaired blood flow in subsequent pregnancies (Smith, Pell et al. 2003). Adjustment in this study

was made for maternal height, smoking status and area of deprivation, but not for maternal obesity.

Wood and others, on the other hand, did not find any association between unexplained stillbirth and previous caesarean section (Wood, Chen et al. 2008). This was a large retrospective cohort study conducted in Canada, with over 158,000 second births; the perinatal database included demographic data as well as maternal medical conditions and pregnancy outcomes. This study found that once adjustment had been made for number of maternal characteristics including maternal weight over 91 kg, smoking and maternal medical conditions, there was no association between previous caesarean section and subsequent stillbirth risk, aOR 1.27 (95% CI: 0.92, 1.77).

New Zealand

The one previous study conducted in New Zealand that examined the relationship between past obstetric outcomes and risk of stillbirth also found a strong relationship between previous low birthweight and future risk of stillbirth (McCowan, George-Haddad et al. 2007). A relationship was not seen between caesarean section and subsequent stillbirth but this study was underpowered to detect an effect of caesarean section.

Summary

The association between previous adverse pregnancy outcomes and subsequent risk of stillbirth is well established. There may be a common mechanism for the association between this range of previous obstetric outcomes and subsequent stillbirth risk, which may be placental in origin.

3.5 Socio-economic factors

Socio-economic deprivation has long been associated with poor pregnancy outcomes, including stillbirth (Baird and Wyper 1941; Gray 1982; Morrison, Najman et al. 1989). Many obstetric studies that have explored risk factors for stillbirth have used measures of socio-economic status as potential confounding factors in the relationship between other factors and perinatal outcome; a few others have specifically explored the relationship between socio-economic status itself and risk of stillbirth (Stephansson, Dickman et al. 2001; Devlieger, Martens et al. 2005). The interpretation of these analyses is complicated by the range of measures used for determining socio-economic status (White 1982).

The most common measures utilised for evaluating socio-economic status are: an index of income, level of education or occupational status (frequently that of the father). However as Braveman et al. argue, socio-economic status is complex and different factors may affect health in different ways and at different times in life (Braveman, Cubbin et al. 2005). A more accurate understanding of any relationship between socio-economic status and health outcomes may be obtained through using a combination of individual and neighbourhood social characteristics (Braveman, Cubbin et al. 2005).

3.5.1 Family Income

Income can be a difficult variable to assess accurately; Salmond has identified the complexities of interpreting income as a way of describing socio-economic status (Salmond, Crampton et al. 2006):

> In practice, the measurement of income has proved to be too complicated for it to be achieved in a few simple questions because it is necessary, also, to establish certain contextual features, such as the numbers of people who are dependent upon a particular income, or the possession of assets which affect the potential utility of a particular level of income. Income also often derives from more than one source, and consumption needs vary over the life course, so recorded income should be adjusted to account for this. (Salmond 2006, p1478)

Family income, however, remains an important measure of socio-economic status. In a Canadian study that compared the association between three measures of socio-economic status (maternal education, occupational status and family income) and risk of stillbirth,

family income was the only measure found to be a significant predictor of stillbirth (Goy, Dodds et al. 2008). A small study in Lithuania also found low income to be the only measure of socio-economic status that was significantly associated with stillbirth risk (Maleckiene, Nadisauskiene et al. 2001).

3.5.2 Maternal education

The level, or amount, of maternal education is also commonly used as an indicator of socio-economic status. However there are inconsistent findings regarding the relationship between level of maternal education and stillbirth risk; this is compounded by the different definitions of low educational attainment/attendance that are used.

A number of studies have found an association between women who have spent fewer years in education and increased stillbirth risk (Petridou, Kotsifakis et al. 1996; Huang, Usher et al. 2000; Froen, Arnestad et al. 2001; Cammu, Martens et al. 2009). Fewer years in school was found to be significantly associated with unexplained stillbirth in Norway (Froen, Arnestad et al. 2001; Winbo, Serenius et al. 2001). Froen compared women who had less than 10 years education to women with more than 12 years, and found that women who had had fewer years in education had an almost four fold increased risk of unexplained stillbirth, aOR 3.77 (95%CI: 1.50, 9.48) (Froen, Arnestad et al. 2001). In contrast to Goy above, Devlieger and others, who also specifically examined the relationship between risk of stillbirth and a range of socio-economic measures (maternal education, maternal employment and paternal professional skill level), found that maternal education level was the most important socio-economic determinant of stillbirth risk (Devlieger, Martens et al. 2005). Other studies have found no association between maternal education and stillbirth risk (Olsen and Madsen 1999; Goy, Dodds et al. 2008).

3.5.3 Occupation

Maternal or paternal occupational status has also been used as a measure for socio-economic status. Some studies have found a significant association between occupational status of the mother or father and risk of stillbirth (Parsons, Duley et al. 1990; Stephansson, Dickman et al. 2001). Stephansson and others conducted a case control study in Sweden with 702 cases of stillbirth at 28 weeks' gestation or greater and 702 controls (Stephansson, Dickman et al. 2001). They found that blue collar workers were twice as likely to experience a stillbirth compared to high level white collar workers, aOR 2.2 (95%

CI: 1.3, 3.7) (the association was even stronger for intrapartum stillbirths, aOR 3.3 (95% CI: 1.3,2, 9.3).

3.5.4 Neighbourhood social characteristics

Braveman argues that neighbourhood social characteristics play an important role in the health behaviours and outcomes of an individual and therefore should be considered in the exploration of the association between socio-economic status and health outcomes (including stillbirth) (Braveman, Cubbin et al. 2005). Local characteristics are sometimes easier to collect than individual characteristics and a wider range of factors can be taken into account. Guildea conducted a study in Wales, and found that living in an area of social disadvantage was associated with a fourfold increase in stillbirth risk, OR 4.4 (95% CI: 2.5, 6.1) and was particularly associated with unexplained stillbirth, and infection (Guildea, Fone et al. 2001).

3.5.6 Marital status

Some studies have used marital status as a proxy for socio-economic status, or as a way of identifying social cohesion, stability and support. Marital status has therefore in general been applied as a confounding factor, rather than a variable of specific interest. In most studies, marital status has been categorised as a dichotomous variable. Young and Declercq, however, argue that marital status should be categorised into three groups: married, unmarried with partner, and unmarried without partner, as these categories show a gradient of risk (Young and Declercq 2010).

Being unmarried has been associated with increased risk of stillbirth (Arntzen, Moum et al. 1996; Raatikainen, Heiskanen, & Heinonen, 2005; Luo, Wilkins et al. 2004; MacDorman, Hoyert et al. 2007). However, this association has not always remained once adjustment was made for related confounders (Petridou, Kotsifakis et al. 1996).

Possible mechanisms

The potential pathway(s) by which socio-economic status is associated with stillbirth risk is likely to be complex and multifaceted. The mechanisms by which socio-economic status impacts health are complicated by other closely related lifestyle factors such as smoking, access to antenatal care, body mass index and nutrition (Freisling, Elmadfa et al. 2006; Raatikainen, Heiskanen et al. 2007). It is therefore difficult to unravel the essential factors

that might influence health outcome. Stephansson and others found that high BMI, attendance at antenatal care and smoking only accounted for a small part of the increased risk of stillbirth (Stephansson, Dickman et al. 2001). Goy and others suggest that health risk behaviours are a pathway by which socio-economic status contributes to stillbirth outcomes; they found that adjusting for smoking resulted in an 18.5% reduction in the association between household income and stillbirth risk, but a residual effect remained (Goy, Dodds et al. 2008). It is likely that smoking is just one of the health risk behaviours that contribute to the outcomes in perinatal mortality; others may be more difficult to capture. It is possible that stress associated with socio-economic deprivation is also a contributory factor.

New Zealand

In New Zealand, Craig and others found that those women who lived in the lowest decile areas were 68% more likely to experience a stillbirth compared to those who lived in the highest decile areas aOR 1.68 (95% CI: 1.23, 2.31), although this study was not able to adjust for health risk behaviours such as smoking and antenatal care attendance (Craig, Stewart et al. 2004).

Summary

Socio-economic disadvantage, in whatever form it is described, appears to be associated with poor health outcomes, including an increase in rates of stillbirth. It is likely that the reasons for this are related to a number of contributory factors including lifestyle and behaviour (such as smoking). Clear pathways have however not been established and therefore strategies to close the gap in stillbirth risk between different social groups have remained limited.

3.6 Maternal Body Mass Index

Body Mass Index and definitions of obesity

An individual's BMI is calculated by taking their weight in kilograms and dividing it by the square of their height in metres. This tool is used to approximate an individual's level of body fat and subsequent risks of cardiovascular disease and diabetes. The World Health Organisation (WHO) has established standard criteria for categorising BMI: underweight (< 18.5 kg/m^2), normal weight (18.5 kg/m^2-24.9 kg/m^2),overweight (25 kg/m^2 -29.9 kg/m^2) and obese (≥ 30 kg/m^2) (WHO 2000). These are the generally accepted definitions used for overweight and obesity within the obstetric literature; even though these criteria were established for a non-pregnant population.

There has been debate as to whether these WHO criteria are appropriate when applied to a multi ethnic population. It is argued that appropriate cut off points for overweight and obesity differ between ethnic groups as the BMI and body fat ratios differ (Swinburn, Ley et al. 1999; Deurenberg 2002) and consequently ethnic specific BMI categories have been developed for use in multi ethnic populations (Razak, Anand et al. 2007). South Asians have been found to have a more centralised distribution of body fat compared to Europeans, and in Asian populations increased mortality and morbidity occur in people with lower BMIs (WHO Expert Consultation 2004). In contrast Polynesians with high body mass indexes were leaner than Europeans (they had a higher lean mass:fat mass ratio) (Swinburn, Ley et al. 1999). It has therefore been suggested that the definition of overweight/obese for Asians be lower than that for Europeans: overweight (≥ 23 kg/m^2) and obese (≥ 27.5 kg/m^2) and higher for Polynesians: overweight (≥ 26 kg/m^2) and obese (≥ 32 kg/m^2) (WHO Expert Consultation 2004). To date, these ethnic specific criteria have not been used in the literature relating to obesity and perinatal mortality.

Obesity is increasing globally in high income countries. In 2007 over 57% of New Zealanders were overweight or obese, a similar prevalence to the United Kingdom, Australia and Canada (OECD 2010). Obesity is associated with a wide range of poor health outcomes, including poor pregnancy outcomes. Pregnant women who are obese are more likely to: be diagnosed with gestational diabetes, develop pre-eclampsia, require a caesarean section, experience an induction of labour and experience a maternal death (Leung, Leung et al. 2008). Pregnant women who are underweight (in high income

countries) are more likely to bear a small for gestational age baby and deliver preterm than women who are of normal weight (Sebire, Jolly et al. 2001; Khashan and Kenny 2009).

Pre-pregnancy obesity

There is now a large body of evidence that links pre-pregnancy obesity with an increased risk of stillbirth. Little and Weinberg (1993), in their case control study of risk factors for stillbirth, were possibly the first to identify an independent association between increasing BMI levels and risk of stillbirth (Little and Weinberg 1993). This study was followed by a number of studies from Scandinavia which confirmed the relationship (Cnattingius, Bergstrom et al. 1998; Stephansson, Dickman et al. 2001; Cnattingius and Lambe 2002; Kristensen, Vestergaard et al. 2005; Nohr, Bech et al. 2005); studies from England (Sebire, Harris et al. 2001; Tennant, Rankin et al. 2011); and a large study conducted by Salihu and others in the United States (Salihu, Dunlop et al. 2007). Meta-analysis of six studies thatassessed pre-pregnancy obesity, showed that a BMI of $\geq$ 30 kg/m^2 was associated with a 60% increase in risk of stillbirth, OR 1.61 (95%CI: 1.53, 1.70) (*Figure 3).*

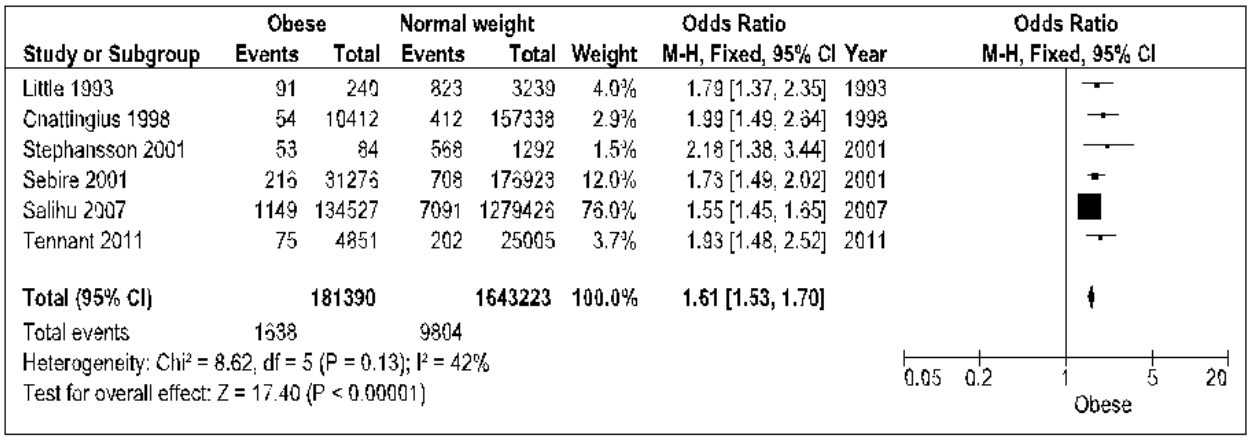

Figure 3: Association between maternal obesity and risk of stillbirth

Dose dependant relationship

Studies have found that there is a dose dependant relationship between obesity and stillbirth risk (Cedergren 2004; Salihu, Lynch et al. 2009). Lean (or underweight) women have been generally found to have the lowest risk of stillbirth (Cnattingius, Bergstrom et al. 1998), although some have shown no difference in risk between lean and normal weight women (Nohr, Bech et al. 2005; Salihu, Mbah et al. 2009), or excluded women with a low

BMI from their analysis (Sebire, Jolly et al. 2001). Salihu and others explored the relationship between stillbirth risk and extreme obesity; using the Missouri Linked database, they had access to over 1.4 million pregnancies, including 134,527 to women who were classified as obese (Salihu, Dunlop et al. 2007). A similar pattern was found by Cedergren in her exploration of the effect of morbid obesity on stillbirth risk (Cedergren 2004).

Weight gain in pregnancy

The role of weight gain in pregnancy has not been as well researched and any relationship with stillbirth risk is not clearly established. Stephansson, in one of the few studies that has explored the impact of pregnancy weight gain, did not find any association between weight gain in pregnancy and risk of stillbirth (Stephansson, Dickman et al. 2001). This is an area that requires further study.

Inter-pregnancy weight gain

Villamor and Cnattingius, in their study on inter-pregnancy weight gain, showed that women whose BMI increased by three or more units (compared to a change of -0.9 to 1 unit) had an increased risk of experiencing adverse outcomes, including stillbirth, in the subsequent pregnancy; this effect was also dose-related (Villamor and Cnattingius 2006). These data suggest that there is likely to be a causal link between increasing BMI and stillbirth risk.

Gestational age of stillbirth and Body Mass Index

Studies that have specifically explored the impact of gestational age on the relationship between increasing BMI and stillbirth risk have suggested that the risk of stillbirth in obese women increases with gestational age (Stephansson, Dickman et al. 2001; Nohr, Bech et al. 2005). Nohr and others found that by 40 weeks gestation, the hazard ratio (HR) for women with a BMI of 30 or greater was more than twice that at 20-27 weeks gestation, aHR 4.6 (95% CI: 1.6, 13.4) at 40 weeks and aHR of 1.9 (95% CI: 1.2, 3.3) at 20-27 weeks (Nohr, Bech et al. 2005). Stephansson and others found that if they limited their analysis to term pregnancies only, the increased risk of stillbirth for obese women increased by 70% from an OR of 2.1 (95% CI: 1.2 , 3.6) for all gestations to an OR of 2.8 (95% CI: 1.3, 6.0) at term (Stephansson, Dickman et al. 2001).

Possible mechanisms

The mechanism(s) by which obesity increases the risk of stillbirth is not clear and is likely multi-factorial. Metabolic disorders such as diabetes and pre-eclampsia are associated with obesity (Leung, Leung et al. 2008), and are in turn associated with an increased risk of stillbirth (Smulian, Ananth et al. 2002). Obese pregnant women have altered metabolic profiles compared with non obese women, including higher glucose levels (even when not meeting the criteria for diabetes), altered lipids and a pro-inflammatory milieu (Sheehan and Jensen 2000). In high income countries, obesity is associated with lower socio-economic status, and women who do not have access to micronutrient rich food have been found to be more likely to be overweight or obese (Asfaw 2007).

Obese pregnant women also have significantly more sleep-related disordered breathing than normal weight women and subsequently are likely to experience a greater incidence of sleep apnea and hypoxemia (Maasilta, Bachour et al. 2001). Snoring has been associated with fetal growth restriction and pregnancy-induced hypertension (Franklin, Ake Holmgren et al. 2000), but there has been only one case study reported that suggested a link between obstructive sleep apnoea and stillbirth (Brain, Thornton et al. 2001).

Obesity has also been associated with altered perception of fetal movements, with more overweight and obese women presenting with reduced fetal movements compared with women of normal weight (Holm Tveit, Saastad et al. 2009). It is possible that the increased rate of stillbirth in obese women is due to a combination of these (and possibly other as yet unidentified) factors.

New Zealand

New Zealand has one of the highest rates of obesity in the world, with almost 40% of women in New Zealand having a BMI of ≥ 30 kg/m^2 (WHO 2011). There is considerable variance in the rates of obesity across ethnic populations within New Zealand, with Māori and Pacific Islanders having a higher mean BMI than European women and higher overall rates of obesity (Metcalf, Scragg et al. 2000). The New Zealand Health Survey of the New Zealand population in 2006/7 found that Pacific men and women were 2.5 times more likely to be obese than people in the total population (Ministry of Health 2008). Māori men and women were 1.7 times more likely to be obese than those in the total population

(Ministry of Health 2008). The New Zealand Health Survey also found that women who lived in the most deprived areas were significantly more likely to be obese than women living in more affluent areas (Ministry of Health 2008). There have been no studies in New Zealand to date that have specifically explored a relationship between perinatal mortality and obesity.

Summary

Maternal overweight and obesity is associated with increased risk of stillbirth. This relationship has a dose gradient and appears to increase with gestational age. The impact of gestational weight gain remains uncertain. Although a causal link is suspected, the mechanisms are still not clearly established.

3.7 Personal habits

This section will explore the association between risk of stillbirth and smoking, alcohol and drug use in pregnancy. It will also examine the effect of caffeine intake in pregnancy.

3.7.1 Smoking

The relationship between smoking and poor perinatal outcomes is well established (Meyer, Tonascia et al. 1974; Cnattingius, Haglund et al. 1988; Wisborg, Kesmodel et al. 2001; Mitchell, Thompson et al. 2002; Salihu, Sharma et al. 2008). Smoking has consistently been found to be associated with an increased risk of stillbirth, see *Table 7* for a summary of key studies. The relationship has been shown to be dose dependant (Stephansson, Dickman et al. 2001; Aliyu, Salihu et al. 2007; Salihu, Sharma et al. 2008). It has also been found that stopping smoking in the first four months of pregnancy can prevent the adverse effect of tobacco use (Butler, Goldstein et al. 1972; Raymond, Cnattingius et al. 1994; Cnattingius 2004; McCowan, Dekker et al. 2009).

	Study design and size	**Outcome**	**Findings** **Adjusted OR (95%CI)**
Raymond, Cnattingius et al. 1994 Sweden	*Population based cohort study* 638242 births	Stillbirth ≥28 weeks	aOR 1.4 (1.2, 1.5) *Adjusted for*: Maternal age, parity
Wisborg, Kesmodel et al. 2001 Denmark	*Propsective hospital based cohort* 25,102 births	Stillbirth ≥28 weeks	aOR 1.9 (1.3, 2.9) *Adjusted for*: fetal sex, maternal age, height, weight, parity, years of education, marital status, occupation, alcohol and caffeine
Aliyu, Salihu et al. 2007 USA	*Retrospective cohort study* 1436725 births	Intrapartum stillbirth ≥20 weeks	aOR: 1.5 (1.3, 1.7) *Adjusted for*: Maternal age, ethnicity, parity, educational achievement, marital status, fetal sex, prenatal care attendance
Salihu, Sharma et al. 2008 USA	*Case control* 1787 stillbirths/445438 controls	Stillbirth ≥20 weeks	aOR: 1.3 (1.3, 1.4) *Adjusted for*: Maternal age, parity, marital status, educational status, BMI, adequacy of antenatal care
Reddy, Laughon et al. 2010 USA	*Retrospective cohort study* 174109 births	Stillbirth ≥20 weeks	aOR: 1.6 (1.2, 2.1) *Adjusted for*: Maternal age, parity, ethnicity, marital status, insurance, previous obstetric outcome, pre-existing medical conditions, alcohol, BMI

Table 7: Selected studies on smoking and stillbirth risk

Gestational age of stillbirth and smoking

Studies have found that the risk of stillbirth related to smoking appears to be predominantly associated with preterm stillbirth (Raymond, Cnattingius et al. 1994; Stephansson, Dickman et al. 2001). Raymond and others found that the risk due to smoking decreased through the third trimester and by 40 weeks' gestation there was no increased risk of stillbirth for smokers (Raymond, Cnattingius et al. 1994).

Environmental smoke exposure

Although less well researched, an association has also been found between environmental smoke exposure in pregnancy and stillbirth risk (Kharrazi, DeLorenze et al. 2004). Exposure to environmental smoke has also been found to increase the risk of fetal growth restriction (Abu-Baker, Haddad et al. 2010).

Possible mechanisms

Smoking is associated with placental abruption (Cnattingius 2004; Salihu and Wilson 2007). It has also been found to be causally related to fetal growth restriction (Cnattingius 2004; Salihu and Wilson 2007). These factors may to some extent explain the association between smoking in pregnancy and increased risk of stillbirth, although a causal relationship may be confounded by other maternal characteristics such as age, ethnicity and socio-economic factors. There is growing evidence that smoking is a risk factor for the development of placental pathology (Aliyu, Lynch et al. 2010). At 20 weeks' gestation, women who smoke have been shown to have a higher umbilical resistance index than non smokers, which may contribute to the development of fetal growth restriction in smokers (Kho, North et al. 2009).

New Zealand

McCowan's study in New Zealand showed a 30% increased risk of stillbirth for women who smoked in their pregnancy (McCowan, George-Haddad et al. 2007). The study also found that women of 'unknown' smoking status had an even greater risk OR 2.87 (95% CI: 2.21, 3.59), which may suggest that they had other related risks that were not captured in the study; such as late booking, transfer from out of the area or poor antenatal care attendance.

Summary

Smoking is a well established risk for most adverse perinatal outcomes, including stillbirth, and the risk is particularly evident for early stillbirths.

3.7.2 Alcohol

A number of studies have explored the relationship between alcohol use in pregnancy and adverse pregnancy outcomes, in particular fetal growth and development (Marbury, Linn et al. 1983; Barrison and Wright 1984; Burd, Roberts et al. 2007; Aliyu, Wilson et al. 2009). There have been fewer studies that have specifically examined the relationship between alcohol consumption and stillbirth (Little and Weinberg 1993; Tolo and Little 1993; Kesmodel, Wisborg et al. 2002; Aliyu, Wilson et al. 2008). These studies have varied in design and classification of exposure and the findings have not been consistent. Self reported retrospective drug and alcohol consumption has the potential to be unreliable, with a likelihood of underreporting. The use of simple questions regarding the total number of weekly drinks has, however, been validated against more indepth data collection methods (Kesmodel and Olsen 2001).

Kesmodel and others conducted a prospective cohort study in Denmark and analysed the impact of alcohol use in pregnancy based on self-administered questionnaires and hospital files (Kesmodel, Wisborg et al. 2002). This study included 24768 singleton pregnancies and found that risk of late stillbirth increased with increasing alcohol intake. Women who drank five or more units of alcohol a week had an almost threefold increased risk of stillbirth aOR 2.66 (95% CI: 1.18, 5.97).

A large retrospective cohort study, using the Missouri database, found that alcohol consumption in pregnancy was particularly associated with early (20-28 weeks) stillbirth, aHR 1.8 (95% CI: 1.3, 2.3), whereas the association was much smaller when the analysis was confined to late (≥ 28 weeks) stillbirth, aHR 1.2 (95% CI: 1.0, 1.6) (Aliyu, Wilson et al. 2008). In a recent study by Reddy and others it was found that women who drank alcohol prior to or during pregnancy had a 70% increased risk of stillbirth, aOR 1.7 (95% CI: 1.1, 2.6) (Reddy, Laughon et al. 2010). It is worth noting that only 1.8% of controls in this study were classified as having any alcohol prior to or during pregnancy, which would be far lower than rates of alcohol consumption in many other pregnant populations (Kesmodel, Wisborg et al. 2002).

Alcohol consumption is also related to other potentially harmful behaviours in pregnancy, including smoking and marijuana use (Tolo and Little 1993); many studies have been able to adjust for smoking, but few have adjusted for other drug use in pregnancy.

A number of studies have reported the combined effect of smoking and alcohol intake and stressed the importance of public health strategies to reduce the incidence of both behaviours (Odendaal, Steyn et al. 2009). Brooke found that once adjustment had been made for smoking, alcohol was not associated with increased risk of fetal growth restriction (Brooke, Anderson et al. 1989).

New Zealand

There have been no studies to date that have explored an association between alcohol intake in pregnancy and stillbirth risk in New Zealand.

Summary

Alcohol intake in pregnancy appears to be related to poor perinatal outcome (including stillbirth). However variations in study design and population norms make it hard to assess the estimate of effect.

3.7.3 Illicit drug use

Illicit drug use in pregnancy has been associated with a number of adverse fetal outcomes, in particular preterm birth and fetal growth restriction (Chasnoff, Burns et al. 1987; Keith, MacGregor et al. 1989; Singer, Arendt et al. 1994; Sherwood, Keating et al. 1999; Pinto, Dodd et al. 2010). Marijuana is the most common illicit drug used in pregnancy (Sherwood, Keating et al. 1999; Ebrahim and Gfroerer 2003) and most studies have concentrated on either marijuana or cocaine use in pregnancy. These studies have shown similar findings, although the association with placental abruption and preterm birth appears to be stronger for cocaine users (Chasnoff, Burns et al. 1987). The few studies that have specifically explored the relationship between illicit drug use and risk of stillbirth have generally found that an association exists (Martinez, Larrabee et al. 1996; McDonald, Vermeulen et al. 2007). One study that did not find any relationship between stillbirth and marijuana use was not powered to detect an association with a relatively rare outcome such as stillbirth (Fergusson, Horwood et al. 2002). In general, although there are considerable

differences in the study designs and the prevalence of illicit drug use in different populations, the association between illicit drug use and adverse pregnancy outcomes, including stillbirth, is fairly consistent.

Illicit drug use is associated with a number of other health risk behaviours such as smoking and alcohol use (Witter and Niebyl 1990; Bauer, Shankaran et al. 2002), lack of attendance at antenatal care (Maupin, Lyman et al. 2004; Schempf and Strobino 2008) and poor nutritional intake (Knight, James et al. 1994). Although most studies were able to adjust for some of these factors, not all are taken into account, and therefore the association between illicit drug use and poor perinatal outcome may be overestimated.

New Zealand

No previous studies have been conducted in New Zealand looking at the association between illicit drug use and stillbirth risk. McCowan et al found in the SCOPE study (conducted in New Zealand, Australia and the United Kingdom) that recreational drug use was associated with a twofold increased risk of SGA (McCowan, Roberts et al. 2010).

Summary

Illicit drug use is associated with poor perinatal outcomes, including stillbirth. Due to the complex set of factors associated with recreational drug use (including social, psychosocial, behavioural and medical factors), and the difficulty in accurately ascertaining frequency and amount of drug intake, the magnitude of risk is unclear.

3.7.4 Caffeine

Caffeine is a stimulant that is consumed regularly by a large proportion of pregnant women. Caffeine intake in pregnancy has been associated with fetal growth restriction (Boylan, Cade et al. 2009). This association appears to be dose dependant and most studies show that it is only with high levels of caffeine intake (generally defined as more than 5 cups of coffee per day) that such an association is found (Bracken, Triche et al. 2003; Bakker, Steegers et al. 2010). A link between caffeine intake before and in the early stages of pregnancy, and miscarriage has also been found (Cnattingius, Signorello et al. 2000; Weng, Odouli et al. 2008). An association between caffeine consumption and stillbirth, however, has been less well explored.

As part of the large prospective Danish Cohort study, Bech and others examined the relationship between caffeine intake in pregnancy and risk of late stillbirth (≥28 weeks' gestation)(Bech, Nohr et al. 2005). They found that there was a dose dependent relationship between caffeine intake and risk of stillbirth, and that women who drank four or more cups of coffee a day had an increased risk of stillbirth; 4-7 cups, aOR 1.33 (95% CI: 1.08, 1.63), and eight cups or more, aOR 1.59 (95% CI: 1.19, 2.13). An earlier Danish study also showed a threefold increased risk of stillbirth amongst women who regularly drank more than eight cups of coffee a day during pregnancy (Wisborg, Kesmodel et al. 2003). Other studies have also found a relationship with high caffeine intake and increased risk of stillbirth (Greenwood, Alwan et al. 2010); (Matijasevich, Barros et al. 2006). Due to smaller sample sizes, these studies had differing magnitudes of effect with wide confidence intervals.

New Zealand

No studies have explored the relationship between caffeine intake and perinatal outcomes in New Zealand.

Summary

A high consumption of caffeine in pregnancy is associated with miscarriage, fetal growth restriction and stillbirth. The magnitude of effect is uncertain and may depend on the quantity of caffeine consumed.

3.7.5 Diet

There are many aspects of dietary intake during pregnancy that could potentially impact on perinatal outcome. However, there are few studies that have assessed the impact of maternal diet during pregnancy; this may be due to the difficulty in accurate assessment. Studies have shown that retrospective studies of health behaviours can be difficult to conduct and may have poor validity (Gollenberg, Mumford et al. 2011).

Maternal weight has been used, at times, as a proxy for maternal nutritional status, and yet in high income countries obesity is also related to poor nutritional status (Asfaw 2007; Rifas-Shiman, Rich-Edwards et al. 2009). Women, who have poor nutritional intake, in high income countries, are more likely to be: young, from socially disadvantaged areas,

have high body mass index and be of high parity (Rifas-Shiman, Rich-Edwards et al. 2009).

Baker et al found that low micronutrient intake (specifically folate and iron levels) was associated with an increased risk of SGA in pregnant teenagers in the United Kingdom (Baker, Wheeler et al. 2009). Micronutrient status was assessed by blood biomarkers in the third trimester of pregnancy and dietary status was assessed during three periods of recall. This study found that low levels of dietary folate or iron intake and poor folate status were associated with an increased risk of SGA. Catov et al found, in their analysis of data from the Danish Birth Cohort, that periconceptual intake of low dose multivitamins was associated with a reduced risk of SGA amongst non-obese women (Catov, Bodnar et al. 2007). El-Bastawissi et al also found that women who took part in the Washington Special Supplemental Nutrition Program for Women, Infants and Children were less likely to experience preterm birth, SGA or fetal death, compared to women who were eligible to take part, but did not. The effect on fetal death was strongest for women with low levels of education OR 0.2; (95% CI: 0.1, 0.3) for women with <12 years education).

Dietary supplementation in pregnancy has not, however, been consistently shown to improve perinatal outcomes. Some studies that have looked at dietary supplementation (with multivitamins, iron and/or folic acid) found that supplementation did not impact positively on perinatal outcome (Mathews, Yudkin et al. 1999; Kramer and Kakuma 2003; Alwan, Greenwood et al. 2010). It may be that the timing of the nutritional supplementation and baseline nutritional status are crucial to the effect of the intervention. Further studies in this area are needed for there to be a fuller understanding of the role of nutritional status and the possibility of modification of risk.

Certain diet 'types' or patterns have been shown to be associated with perinatal outcome (Mitchell, Robinson et al. 2004; Knudsen, Orozova-Bekkevold et al. 2008). A further Danish study also found that women who ate a 'Health Conscious' diet (high in vegetables, fruit and fish) had a reduced risk of delivering a SGA baby compared to women who ate a 'Western Style' diet (high in red and processed meat and high fat dairy) OR 0.74 (95%CI: 0.64 , 0.86) (Knudsen, Orozova-Bekkevold et al. 2008).

New Zealand

There have been no studies to date that have looked at the impact of nutritional status on risk of stillbirth in New Zealand. Studies have found, however, that women who had higher intakes of fish, carbohydrate rich foods and folate during pregnancy were at reduced risk of delivering a SGA baby (Mitchell, Robinson et al. 2004; Thompson, Wall et al. 2010). McCowan et al also found that women who had a low fresh fruit intake pre-pregnancy had an increased risk of delivering an SGA baby, and women who had a high green leafy vegetable intake prior to pregnancy were at reduced risk aOR 0.47 (95%CI: 0.28, 0.79) (McCowan, Roberts et al. 2010).

Summary

There remains limited information on the role of diet and nutritional status on risk of stillbirth. Maternal dietary habits and maternal nutritional status are influenced by socio-demographic factors and it may be that future research and resources will need to concentrate on how to ensure good nutrition in pregnancy in disadvantaged groups.

3.7.6 Physical Activity

There have been few studies that have examined the impact of differing forms of physical activity on birth outcomes; these mostly relate to preterm birth and small for gestational age (Pompeii, Savitz et al. 2005; Orr, James et al. 2006; Bonzini, Coggon et al. 2009; Takito, Benicio et al. 2009; Both, Overvest et al. 2010; McCowan, Roberts et al. 2010). A wide variety of study designs and measures of physical activity have been employed in these studies and therefore the relationship between physical activity in pregnancy and birth outcomes remains unclear (Chasan-Taber, Evenson et al. 2007). A recent review found that light to moderate physical activity in pregnancy was not associated with adverse pregnancy outcomes (Schlussel, Souza et al. 2008). However there is a lack of information regarding specific aspects of physical activity in pregnancy and risk of stillbirth.

The study by Both et al (2010) is one of the few studies that has included stillbirth as one of the birth outcome measures. Information on daily activity was collected prospectively by postal questionnaire from over 11,000 pregnant women in the United Kingdom. They found that physically demanding activities were not associated with adverse birth outcomes. In contrast, a sedentary lifestyle was associated with a lower birthweight.

Pompeii et al. (2005) assessed the relationship between specific work related aspects of physical exertion and risk of preterm birth and suboptimal fetal growth. This prospective cohort study involved 1,908 pregnant women in the United States; participants were asked about physical exertion at work during pregnancy. Specific areas of inquiry concerned repeated lifting and standing for long periods; data on night work and average hours worked were also obtained. Repeated lifting and standing for long periods were not found to be associated with adverse outcomes. However, night duty was found to be associated with an increased risk of preterm birth.

New Zealand

Although there have been no studies that have explored a relationship between physical activity in pregnancy and risk of stillbirth, McCowan and colleagues found that vigorous daily activity (defined as daily activity leading to heavy breathing or being out of breath) was associated with an almost threefold increase in delivering an SGA baby, aOR 2.9 (95% CI: 1.4, 6.2) (McCowan, Roberts et al. 2010).

Summary

Light to moderate exercise is not associated with adverse pregnancy outcomes. Vigorous exercise may be associated with a reduction in birthweight. As there has been limited research on a relationship between physical activity and stillbirth it remains unclear whether excessive exercise or specific aspects of physical activity are associated with stillbirth.

3.8 Psychosocial stress

Assessment of psychosocial stress in pregnancy is complex as the pregnancy itself can impact on levels of stress; overall levels of stress have been found to be high in pregnancy (Lobel, Cannella et al. 2008: Woods, Melville et al. 2010). Stress has also been shown to be associated with other social and behavioural factors related to pregnancy outcome, such as domestic violence and drug use (Bewley 2009; Woods, Melville et al. 2010).

Retrospective studies that explore an association between stress and birth outcomes (in particular stillbirth) could be susceptible to recall bias (Brandt and Nielsen 1992). However as stillbirth is a relatively rare outcome, there are currently few prospective studies that have assessed levels of stress during pregnancy, and have sufficient power to assess any difference in outcomes (Zhu, Hjollund et al. 2004; Wisborg, Barklin et al. 2008).

The Danish study conducted by Wisborg and colleagues is currently the only large prospective study that has examined the relationship between psychosocial stress and risk of late stillbirth (Wisborg, Barklin et al. 2008). This was part of the Aarhus Birth Cohort Study and included over 19,000 pregnancies. The researchers used the 12 item General Health Questionnaires (Schmitz, Kruse et al. 1999) to assess psychological stress; scores were generated from a sum of all the answers (each contributing a value between 0 and 3) and three categories of stress (low, intermediate and high) were applied. They found that a high level of stress (assessed at around 30 weeks of gestation) was associated with an 80% increased risk of stillbirth (Wisborg, Barklin et al. 2008). Even when women with other complications of pregnancy were excluded, this association remained. This study was, however, still relatively small (with only 66 stillbirths) and adjustment was not made for drug use or violence in pregnancy.

Zhu et al (2004) investigated the relationship between job stress and late stillbirth risk as part of the prospective Danish Birth Cohort study and found no association between perceived job stress and risk of stillbirth (Zhu, Hjollund et al. 2004). In a retrospective study on job stress and risk of adverse birth outcomes, Brandt and Nielsen also did not find a significant association between high levels of job stress and risk of stillbirth (Brandt and Nielsen 1992).

The evidence linking psychosocial stress with preterm birth and SGA is mixed with some demonstrating an association (Wadhwa, Sandman et al. 1993; Copper, Goldenberg et al. 1996; Hobel and Culhane 2003; Hobel 2004); in contrast other studies have not shown an association between stress in pregnancy and adverse birth outcomes (Perkin, Bland et al. 1993; Pryor, Thompson et al. 2003).

Anxiety has been shown to be associated with increased uterine artery resistance, however this study only had a sample size of 100 women and could not show whether or not this change in uterine artery resistance translated to an adverse effect on perinatal outcome (Teixeira, Fisk et al. 1999). A small study looking at fetal sleep states in women with different levels of stress or anxiety found that women with higher anxiety levels had babies who spent more time in quiet sleep and had fewer movements (Groome, Swiber et al. 1995). Again, due to the small sample size (18 women between 38 and 40 weeks gestation) there was no indication what significance this change in fetal behaviour might have in relation to perinatal outcome.

New Zealand

No such studies exploring a relationship between stress and stillbirth have as yet been conducted in New Zealand. The Auckland Birthweight Cohort (ABC) study explored the impact of stress in pregnancy and risk of small for gestational age (Pryor, Thompson et al. 2003), and did not find any association between stress and increased risk of SGA.

Summary

The research on psychosocial stress and risk of stillbirth is limited. It remains unclear whether a relationship exists between increased levels of stress in pregnancy and stillbirth.

3.9 Sleep

Approximately one third of an individual's life is spent asleep, or in bed, and yet there has been little research on the potential impact of sleep practices on the developing fetus. Previous studies have reported an association between sleep disordered breathing and pregnancy complications such as pre-eclampsia and preterm birth (Yinon, Lowenstein et al. 2006; Louis, Auckley et al. 2010), but exploration of a potential association with stillbirth has been limited to a single case report (Brain, Thornton et al. 2001).

Sleep disordered breathing in pregnancy

Sleep disordered breathing describes a range of abnormal breathing patterns from primary snoring to obstructive sleep apnea. The symptoms of sleep disordered breathing are generally characterised as habitual snoring, periods of apnea, and gasping and choking sensations during sleep. The majority of women experience some degree of sleep disturbance while pregnant, with increased sleepiness, more disturbed sleep and an increase in symptoms of sleep disordered breathing commonly reported (Santiago, Nolledo et al. 2001; Pien and Schwab 2004; Facco, Kramer et al. 2010). It has been shown, however, that the majority of sleepiness is related to pregnancy factors other than snoring (Izci, Martin et al. 2005). Self-reporting questionnaires have also been shown to have a low predictive value of obstructive sleep apnea as diagnosed by polysomnography (the 'gold standard') (Sahin, Koken et al. 2008; Olivarez, Maheshwari et al. 2010).

These changes in sleep patterns during pregnancy are likely to be influenced by the reproductive hormones of pregnancy and gestational weight gain (Pien and Schwab 2004; Young, Peppard et al. 2005). Obesity appears to play an important role not only in the occurrence of symptoms of sleep disordered breathing, but also in the metabolic changes seen in women with sleep apnea (Sharma, Kumpawat et al. 2007). Obese pregnant women have been shown to have a greater incidence of sleep disordered breathing and other sleep disturbances compared to normal weight women (Maasilta, Bachour et al. 2001; Vorona, Winn et al. 2005). The severity of sleep disordered breathing in non-pregnant individuals can also be affected by sleep position; obstructive sleep apnea in non-pregnant subjects has been shown to increase in the supine sleep position compared to the lateral position, particularly in those who have a mild form of the disease (Itasaka, Miyazaki et al. 2000; Mador, Kufel et al. 2005).

Sleep disordered breathing and adverse pregnancy outcomes

A number of studies have described an association between sleep disordered breathing and pre-eclampsia (Franklin, Ake Holmgren et al. 2000; Yinon, Lowenstein et al. 2006; Venkata and Venkateshiah 2009; Louis, Auckley et al. 2010). A relationship between sleep disordered breathing and an increase in preterm birth has also been identified, in particular in induced, rather than spontaneous, preterm birth (Louis, Auckley et al. 2010). A limited number of studies have looked at the effect of obstructive sleep apnea on fetal heart rate patterns, and the findings have been inconsistent (Sahin, Koken et al. 2008; Olivarez, Maheshwari et al. 2010). A small study by Sahin et al conducted simultaneous polysomnography and non stress tests on four women diagnosed with obstructive sleep apnea. They found that in three of the four cases, fetal heart rate decelerations accompanied maternal de-saturations. Olivarez et al., on the other hand, who conducted a similar, larger study (20 women who were diagnosed with obstructive sleep apnea), found no fetal tracing abnormalities during periods of apnea (Olivarez, Maheshwari et al. 2010).

There has only been one case report that has reported a relationship between sleep disordered breathing and stillbirth (Brain, Thornton et al. 2001). This case report described a 22 year old, moderately overweight pregnant woman with spina bifida. Following a miscarriage and then the stillbirth of a growth restricted baby at 26 weeks gestation, she was diagnosed with severe obstructive sleep apnea. During her subsequent pregnancy she was treated with nocturnal nasal continuous positive airways pressure (CPAP); sleep studies at 26 weeks showed no peripheral oxygen de-saturation and she delivered a live, normally grown baby at term (Brain, Thornton et al. 2001).

New Zealand

There have been no studies to date on sleep related practices and risk of stillbirth in New Zealand.

Summary

Studies investigating sleep disordered breathing and pregnancy outcomes are hampered by the low correlation between self reported symptoms of sleep disordered breathing and confirmation of the diagnosis with the use of polysomnography. Sleep disordered breathing appears to be associated with pre-eclampsia and induced preterm birth. It is

unclear whether it is associated with any other adverse pregnancy outcomes. Obesity is related to an increased incidence of sleep disturbances, in particular of obstructive sleep apnea.

There have been no studies that have explored a relationship between sleep disordered breathing and stillbirth risk.

There have been no studies that have explored a relationship between other sleep related practices and stillbirth risk.

3.10 Fetal growth

Optimal fetal growth is a good indicator of placental functionality and fetal wellbeing. Suboptimal fetal growth, which is generally assessed by the proxy of small for gestational age, has long been known to be associated with a marked increase in perinatal mortality and morbidity (Cnattingius, Haglund et al. 1998; Gardosi, Mul et al. 1998). Excessive fetal growth, or macrosomia, has also been associated with more modest increases in rates of stillbirth and neonatal morbidity (Oral, Cagdas et al. 2001; Boulet, Alexander et al. 2003; Zhang, Decker et al. 2008)

3.10.1 Small for gestational age

Population centiles

Small for gestational age (SGA) can be an indicator of suboptimal fetal growth. Traditionally, SGA babies have been classified as those whose birthweight falls below the 10th percentile for a given gestation on population based reference curves (Beeby, Bhutap et al. 1996; Gardosi, Mul et al. 1998). Absolute birthweight categories (such as <2500gms or <1500gms) do not take into account gestational age and can only be of use in crude analyses when gestational age is not known. Population based birthweight centiles account for gestational age and often infant sex, but not for individual variations in maternal characteristics and may misclassify a proportion of constitutionally small babies as SGA.

Customised centiles

In order to improve the identification of suboptimal fetal growth, as opposed to constitutionally small babies, Gardosi and others developed customised centiles that adjust for individual maternal characteristics (such as ethnicity, parity, height and weight) (Gardosi, Chang et al. 1992; McCowan, Stewart et al. 2004). A number of studies have compared the outcome of babies classified as SGA by population centiles and customised centiles (Clausson, Gardosi et al. 2001; McCowan, Harding et al. 2005; Ego, Subtil et al. 2006). When customised birthweight centiles have been applied to a cohort of births, a sub-group of babies who were SGA by population centiles only were reclassified as normally grown; these babies were shown to have low perinatal mortality and morbidity. Conversely a new group, born to bigger mothers, were identified as SGA by customised centiles (and not population centiles), and these babies have been shown to have elevated mortality and morbidity (Clausson, Gardosi et al. 2001; McCowan, Harding et al. 2005;

Ego, Subtil et al. 2006). Customised birthweight centiles are therefore thought by many to more accurately identify babies with growth restriction than population birthweight centiles.

The preferential use of individual customised birthweight centiles is not, however, universally accepted (Hutcheon, Zhang et al. 2011). It has recently been suggested that a generic reference, based on the mean birthweight of a local population as well as median maternal height and weight (a simplified customised centile), is just as predictive, and is much simpler to use than individualised references (Mikolajczyk, Zhang et al. 2011). This analysis used data from the 2004-08 WHO Global Survey on Maternal and Perinatal Health, a multinational facility based survey that included births from Africa, Latin America and Asia (Mikolajczyk, Zhang et al. 2011). Although many countries, and almost 300,000 births, were included in the analysis, the findings from the study are not easily transferable to a multi-ethnic society. The countries that were included were predominantly ethnically homogenous and therefore unlikely to have as wide a local variation in maternal characteristics as one might find in more ethnically diverse countries such as the United Kingdom, the United States or New Zealand.

SGA and stillbirth

There is now a large body of evidence that (even after exclusion of babies with congenital abnormalities) there is a strong association between SGA and increased risk of stillbirth (Cnattingius, Haglund et al. 1998; Clausson, Gardosi et al. 2001; Vashevnik, Walker et al. 2007; Ananth and Vintzileos 2009; Flenady, Koopmans et al. 2011). Clausson and others examined the risk of stillbirth and neonatal death for babies who were SGA (by both customised and population based standards) in more than 326,000 births from the Swedish Birth Register (Clausson, Gardosi et al. 2001). This study found that, compared to babies who were not SGA, babies that weighed less than the 10th centile by both measures had a fivefold increased risk of stillbirth, OR 5.1 (95% CI: 4.3, 5.9) (for those that were SGA by the customised standard only, the risk was also high OR 6.1 (95% CI: 5.0, 7.5). A meta-analysis conducted by Flenady and others showed that gestational size of less than the 10th percentile was associated with a fourfold increase in risk of stillbirth, aOR 3.9 (95% CI: 3.0, 5.1) (Flenady, Koopmans et al. 2011).

The timing of fetal death can be uncertain; the gestation at death may precede the gestation at diagnosis of death. Although post-mortem data has shown that the time of death is estimated to be within 72 hours of post-mortem in over 90% of cases (Gardosi, Mul et al. 1998), this may exaggerate the proportion of babies who are classified as SGA. In order to mediate this source of potential bias, many studies and reports are conservative in their estimation of gestation at fetal death (Gardosi, Mul et al. 1998; McCowan, George-Haddad et al. 2007; PMMRC 2011).

Identification of SGA in the antenatal period

In most settings, only 20-40% of SGA babies are identified before birth (Gardosi, Chang et al. 1992; McCowan, Roberts et al. 2010). It has been shown that identification of SGA can be improved by the use of customised growth charts (Gardosi, Chang et al. 1992; Gelbaya and Nardo 2005). In order to determine whether antenatal detection of SGA had a positive impact upon perinatal outcome, Lindqvist and Molin compared SGA babies that were identified prior to birth (n=681) with SGA babies not identified (n=573), SGA was defined as birthweight below 2 SD of a Swedish reference population (Lindqvist and Molin 2005). They found that SGA babies that were not identified antenatally had a fourfold increased risk of adverse outcome, including severe fetal distress, aOR 4.5 (95% CI: 2.2, 9.0) and perinatal mortality, aOR 4.2 (95% CI: 21, 8.5) (Lindqvist and Molin 2005).

3.10.2 Large for gestational age

Large for gestational age (LGA) is generally defined as birthweight above the 90th percentile for gestational age by population or customised birthweight references, although at times a birthweight of greater than 4000gms or 4500gms, is also used (Zhang, Decker et al. 2008). There has been an increase in the mean birthweight and proportion of LGA babies in many high income countries in recent years; this has been attributed to an increase in maternal height, BMI and diabetes (Kramer, Morin et al. 2002). Zhang and others found, in their study of over 5 million births, that babies who weighed 4500-4999gms at birth had an almost threefold increased risk of stillbirth after adjustment for maternal demographic and clinical risk factors, including diabetes, aOR 2.7 (95% CI: 2.2, 3.4) and that babies who weighed over 5000gms had a thirteen-fold risk, compared to a baby who weighed between 3500 and 4499 gms (Zhang, Decker et al. 2008). There is an association between high maternal BMI and both LGA and stillbirth (Kristensen, Vestergaard et al. 2005) and it may be that increased BMI may play a part in the increased

rate of stillbirths in LGA babies. The few studies that have explored stillbirth risk in LGA babies have been limited in their ability to adjust for BMI (Oral, Cagdas et al. 2001; Zhang, Decker et al. 2008).

New Zealand

McCowan and others, in a hospital based cohort study of 437 stillbirths (≥20 weeks' gestation), found that the mean birthweight of stillborn babies was significantly less than that of live born babies at each gestational age group ($p < 0.0001$) (McCowan, George-Haddad et al. 2007). Almost 50% of stillborn babies were found to be SGA by customised centiles and 34% were SGA using population based centiles (McCowan, George-Haddad et al. 2007).

Summary

The relationship between fetal growth and stillbirth appears to form a U shaped curve, with a strong association between suboptimal fetal growth and increased risk of stillbirth, and also an association between excessive growth and increased stillbirth risk.

3.11 Fetal activity

Maternal perception of fetal activity is perhaps the oldest screening tool for fetal wellbeing, and yet there is currently no consensus as to what constitutes normal fetal movements in late pregnancy There is considerable variance in the number of daily fetal movements felt by women, from as low as four a day up to hundreds of movements daily (Sadovsky and Polishuk 1977; Saastad, Ahlborg et al. 2008). It is also unclear whether there is a substantive change in perception of fetal movement as pregnancy progresses. Some studies have reported a maximum frequency of fetal movements between 29 and 38 weeks, with a small reduction at term (Sadovsky and Yaffe 1973; Pearson and Weaver 1976; Roodenburg, Wladimiroff et al. 1991), and yet other studies have shown no overall reduction in fetal movements with advancing gestation (Valentin, Mars et al. 1986; Connors, Natale et al. 1988). A detailed ultrasound study by Roberts and others investigating fetal activity in the third trimester reported a reduction in frequency of fetal movement as pregnancy advanced, although due to a concurrent increase in duration of movement, there was no overall reduction in total fetal activity (Roberts, Little et al. 1979).

Decreased fetal movements

Decreased fetal movements have long been associated with poor pregnancy outcomes and from 4-15% of women will contact their health care provider with some concern about decreased fetal movements (DFM) in the third trimester (Froen 2004). One of the first descriptions of decreased fetal movements preceding fetal death in the obstetric literature was by Sadovsky in 1973 (Sadovsky and Yaffe 1973). Since then many papers have reported an association between reduced fetal movements and adverse pregnancy outcomes; specifically: fetal growth restriction (Sinha, Sharma et al. 2007; Saastad, Ahlborg et al. 2008; O'Sullivan, Stephen et al. 2009); and stillbirth (Pearson and Weaver 1976; Leader, Baillie et al. 1981; Holm Tveit, Saastad et al. 2009; O'Sullivan, Stephen et al. 2009).

In reports from case series, Sadovsky and Pearson both described a decrease in fetal movements prior to death (Sadovsky and Yaffe 1973; Pearson and Weaver 1976). The association between decreased fetal movements and fetal growth restriction is clearly established, however there is a difficulty in clearly establishing the relationship between

decreased fetal movements and stillbirth, as it can be unclear whether the perception of decreased movements indicates a compromised fetus or a fetus that has already died. Due to the presence of amniotic fluid and the suspension of the fetus in that fluid, women can misinterpret that the baby is moving after it has already died.

O'Sullivan and others conducted a retrospective study into the relationship between perception of fetal movements and perinatal outcome (O'Sullivan, Stephen et al. 2009). Cases were women who presented to the Royal Blackburn Hospital with decreased fetal movements as their primary complaint and where the fetus was alive on initial presentation. In this study the rate of stillbirth was 15.1/1000 for women who had presented with decreased fetal movements, compared to 5.1/1000 for the total population at the Royal Blackburn Hospital (p=0.02). A larger Norwegian population based study also showed a significant association between maternal perception of decreased fetal movements and stillbirth (Tveit, Saastad et al. 2009); however the findings from this study are difficult to interpret as it is not clear in their report whether or not the baby was alive when the mother reported or presented with decreased fetal movements. This could potentially over estimate the association between decreased movements and stillbirth as it is not clear whether the decreased movements were an indication of impending death, or death itself.

Unusually vigorous movement

There has been minimal research into the significance of unusually vigorous fetal movements. It has been suggested, in a single report, that a sudden increase in fetal movement can be associated with acute fetal distress and poor outcome (Sadovsky and Polishuk 1977). Repeated episodes of unusually vigorous fetal movements, on the other hand, may be reassuring. In the only previous study that has reported on repeated episodes of excessive movements, no association was found with adverse outcomes (Rayburn 1982).

Fetal hiccups

Fetal hiccups are easily felt by pregnant women and have been identified on ultrasound as abrupt fetal movements occurring every two to three seconds and lasting for five to ten minutes (Zheng, Sampson et al. 1998). Although the physiological mechanism(s) underlying fetal hiccups remains unclear, they have been reported to occur throughout

pregnancy and are thought to be related either to the preparation for postnatal breathing, or the development of suckling or gasping patterns (Popescu, Popescu et al. 2007), and as such are considered a sign of a normally functioning fetus. The few studies that have investigated the effect of fetal hiccups on fetal heart rate patterns support the suggestion that fetal hiccups are a normal aspect of fetal behaviour, more commonly observed in the active fetal state (van Woerden, van Geijn et al. 1989; Pillai and James 1990; Goldkrand and Farkouh 1991; Witter, Dipietro et al. 2007). Fetal hiccups have also been associated with reactive non-stress tests (Goldkrand and Farkouh 1991). In a case series reported by Hems, it was suggested that periods of regular fetal jerking movements (which may be interpreted as hiccups) may be a sign of respiratory distress, or fetal 'gasping' (Hems 1973). There have been no more recent published studies, however, that have supported this hypothesis.

New Zealand

In 1986 Westgate and Jamieson conducted a retrospective study into the relationship between fetal movements and stillbirth (Westgate and Jamieson 1986). This retrospective study found that less than 4% of women who experienced an unexplained stillbirth had used fetal movement record cards. Although this study was limited in that it did not have denominator data on the overall proportion of women who used fetal movement record cards, there was a reduction in the overall perinatal mortality rate after the introduction of the record cards which suggested that maternal awareness of fetal movement may be associated with a reduced risk of stillbirth.

Summary

Decreased fetal movements have long been associated with poor perinatal outcomes, specifically fetal growth restriction and stillbirth. However, although an association is suggested, there is still a lack of robust research in this area and it remains unclear to what extent a maternal perception of reduced movements is associated with risk of stillbirth or an indication of fetal demise.

3.12 Antenatal care

The aim of antenatal care is to optimise the health of the mother and baby. There is however no high quality research that describes the optimal quantity or content of care (Dowswell, Carroli et al. 2010).

The following section will review existing research that has examined the relationship between aspects of antenatal care and risk of stillbirth. Two broad areas will be discussed, namely antenatal care utilisation and model of antenatal care provision.

3.12.1 Antenatal care utilisation

Indices for assessing adequacy of antenatal care utilisation

Utilisation of antenatal care has been examined in a number of ways, using either the gestational age at initiation of care or the subsequent number of visits attended. Most commonly they have been considered separately, but they have also been combined to describe an overall 'adequacy of care'. A number of indices exist that provide a framework for determining the adequacy of antenatal care utilisation (Kessner, Singer et al. 1973; Alexander and Cornely 1987; Kotelchuck 1994). An analysis of these indices has shown that they identify different aspects of care and are not interchangeable (Heaman, Newburn-Cook et al. 2008), therefore suggesting that they should be used with caution when exploring the impact of inadequate antenatal care utilisation on adverse pregnancy outcomes. One of the limitations of these indices is that they are generally associated with the definitions of expected care within the country or region in which they have been developed (Kotelchuck 1994); and therefore are not necessarily transferrable, as low utilisation of care in one country may be considered an acceptable standard in another.

No antenatal care

Lack of any antenatal care has repeatedly been shown to be associated with an increased risk of stillbirth, and other adverse pregnancy outcomes such as preterm birth and fetal growth restriction (Vintzileos, Ananth et al. 2002; Mohsin, Bauman et al. 2005; Raatikainen, Heiskanen et al. 2007; Tucker, Ogutu et al. 2009). However the magnitude of risk and whether or not it is directly causal remains unclear. Women who do not access antenatal care are more likely to be younger (Tucker, Ogutu et al. 2009), of lower socio-economic status (in particular have received less education), and be smokers and users of

illicit drugs (Maupin, Lyman et al. 2004). In some communities they are also more likely to be of ethnic or cultural minorities (Tucker, Ogutu et al. 2009). All these factors are likely to have an impact on the risk of stillbirth. As most population based studies are unable to adjust for all these factors it is therefore possible that a degree of confounding exists within the majority of the studies that have explored the relationship between antenatal care utilisation and risk of stillbirth.

Vintezilios et al. (2002) examined the impact of antenatal care on the stillbirth rate in the United States (Vintzileos, Ananth et al. 2002). This large population based study found that absence of antenatal care was associated with a more than threefold increase in rate of stillbirth greater than 24 weeks' gestation, OR 3.3 (95%CI: 3.1, 3.6). Women who did not receive antenatal care were also more likely to have other high risk conditions, such as anaemia, diabetes, chronic hypertension, pregnancy induced hypertension, fetal growth restriction and bleeding of unknown cause. It was found, however, that a difference in stillbirth rate was seen in the absence, as well as the presence, of these high risk conditions. This study was able to take account of a wide range of antenatal conditions and a number of potential socio-demographic confounders, but it was still not able to adjust for all potential confounders such as illicit drug use. Mohsin et al (2005) in their large population based study (n=433,379) from Australia also found that women who received no care during their pregnancy had a twofold increased risk of stillbirth, aOR 2.04 (95% CI 1.78, 2.34) (Mohsin, Bauman et al. 2005). Again, although a large number of confounders were accounted for, illicit drug use was not.

Initiation of care

There has been considerable variance in the literature as to the definition of 'late' booking, or late initiation of antenatal care. Some studies have considered initiation of care after the first trimester as 'late' (Getahun, Ananth et al. 2007), while others have classified late initiation of care as over 20 weeks' gestation (Mohsin, Bauman et al. 2005). Some have used more than one category and have considered the trimester in which antenatal care was initiated (Huang, Usher et al. 2000).

A large cross sectional study was conducted in the United States (n=626,883) which looked at a wide range of potential risk factors, and compared the stillbirth rate in women who booked in the first trimester to those who booked later, or who had no antenatal care

(Getahun, Ananth et al. 2007). This study found that there was a significant increase in risk of stillbirth in those women who did not initiate antenatal care until after the first trimester ($p<0.001$). However, in further analysis it was found that this only applied to White Americans who experienced an antepartum stillbirth (≥20 weeks' gestation), OR 1.3 (95% CI 1.1, 1.5), and not Black Americans OR 1.0 (95% CI 0.8, 1.2). Mohsin et al (2005) also found that women who booked later than 20 weeks' gestation had a slightly increased risk of stillbirth, aOR 1.14 (95% CI: 1.02. 1.28). Both these studies combined late initiation of care and no care in their analysis, thus potentially confusing any interpretation of the findings.

In contrast, Huang et al, who considered a wide range of risk factors for unexplained stillbirth (≥20 weeks' gestation) in Canada (Huang, Usher et al. 2000) found no association between trimester of initiation of care and risk of unexplained stillbirth.

Quantity of antenatal care visits

A systematic review into the schedule of antenatal care visits suggested that a reduction in the number of visits in high income countries (to an average of 8.2 from 12 visits) could be introduced without having a negative impact on perinatal mortality rates (Dowswell, Carroli et al. 2010). However, when a reduced schedule was applied to low to middle income countries (where visits were often reduced to five or less), there was an adverse impact on mortality; this is likely to reflect the accepted quantity of antenatal care in such countries (which is even less than that suggested in the reduced schedule in high income countries). In interpreting the findings from the published research, it is therefore important to be aware of the context within which the research has taken place.

Raatikainen et al (2007) examined the effect of low utilisation of antenatal care in Finland where care is free and easily accessible (Raatikainen, Heiskanen et al. 2007). Pregnancy outcomes of women who received no antenatal care (n=270), 1-5 visits (n=207) and 6-18 visits (n=23137) were compared. Both under-attenders (defined as those receiving 1-5 visits) and non-attenders were found to have an increased risk of stillbirth, OR 12.05 (95% CI: 5.95, 24.40) and OR 5.19 (95% CI: 2.04 to 13.22) respectively. As stated in the paper, antenatal care attendance in Finland is high, with 99.8% of pregnant women receiving some form of antenatal care. The average number of antenatal visits in Finland was stated to be 17, which is considerably greater than the number recommended by many

International/National Guidelines (Carroli, Villar et al. 2001; National Institute for Health and Clinical Excellence 2008). The Finnish population may therefore not be representative of other populations.

A limitation of these studies is that adjustment was not made for gestational age; stillborn babies are more likely to be preterm and therefore there is a shorter time within which to attend antenatal care. To compare all stillbirths with live (generally term) births is likely to overestimate any relationship between under-utilisation of antenatal care and increased risk of stillbirth. Researchers have taken various approaches in order to take this into account: Stephansson and others only considered antenatal attendance up until 24 weeks' gestation (Stephansson, Dickman et al. 2001); and Huang restricted the analysis to those greater than 37 weeks' gestation (Huang, Usher et al. 2000). Although these approaches ameliorate the limitation to some extent, they also make it difficult to compare the findings from the different studies.

In one of the few studies that have used a gestation adjusted index, Reime et al. suggested that when considering the whole population, utilisation of antenatal care was not associated with stillbirth risk (Reime, Lindwedel et al. 2009). Reime applied an adapted Adequacy of Prenatal Care Utilisation Index to a German population (Kotelchuck 1994) and found that it was only women of Mediterranean origin who received an inadequate amount of antenatal care, and who showed an increased risk of stillbirth compared to German women who had received adequate care. It may be that the combination of the factors that constitute adequacy of care (gestational age at initiation and number of visits, adjusted to the length of pregnancy) obscure the significance of either one of the elements. The disparity in effect between different ethnic groups, also found in Getahun's study, may suggest that there are characteristics of women who do not access the recommended schedule of antenatal care which are also associated with risk of stillbirth, and that these factors are possibly culturally or ethnically specific.

Quality of care

Utilisation of antenatal care can only assess quantity of care and not quality; quality is harder to assess. Froen's study into risk factors for unexplained stillbirth found that many factors, such as maternal age, obesity, are easily identifiable by basic antenatal care (Froen, Arnestad et al. 2001). Froen suggested that quality antenatal care, where these factors are

identified as risk factors, may be associated with improved outcomes. However Reddy and others argue that such pre-pregnancy risk factors are not individually of enough significance to increase antenatal surveillance (Reddy, Laughon et al. 2010) and therefore their early identification might have no beneficial influence on outcome.

The EuroNatal study explored the background to differences in perinatal mortality between countries and regions within Europe, in particular to identify any suboptimal care factors (Richardus, Graafmans et al. 2003). This study, which examined 1619 deaths, found that in almost half (46%) suboptimal care factors contributed in some way to the outcome. Lack of detection of severe intrauterine growth restriction was considered the most important professional care factor.

New Zealand

There has only been one study in New Zealand that has explored a relationship between antenatal care utilisation and adverse pregnancy outcomes. This study (which was part of the Pacific Islands Families study) found that less frequent attendance at antenatal care was associated with an increased risk of prematurity and small for gestational age babies (Gao, Paterson et al. 2006). There is no New Zealand research that has explored a relationship between antenatal care attendance and risk of stillbirth.

3.12.2 Model of care

A variety of different models of antenatal care provision exist both between and within individual countries, comprising of obstetric specialists, general practitioners and midwives. The relative effectiveness of these different models of care in relation to perinatal mortality and morbidity continues to be debated both in the maternity care literature and when determining the organisation of maternity care in different countries.

Bai and others (2008) examined the outcomes of almost 68,000 births in public hospitals in Sydney (Bai, Gyaneshwar et al. 2008). This study explored perinatal outcomes between different models of antenatal care; the authors report that there was no difference between perinatal mortality rates for the different models of care once adjustment was made for antenatal problems, maternal smoking and gestational age. A systematic review comparing case-loading midwifery and 'standard' care suggested that there was a similar, marginally significant, increase in stillbirth rates for case-loading midwifery care (OR 1.66, 95% CI

0.99, 2.59) compared to standard care (Waldenström and Turnbull 1998). It is not clear from these trials whether the deaths were associated with substandard care.

A recent systematic review of randomised trials was undertaken by Hatem (2009) to compare the outcome for mothers and babies between midwifery-led care and other models of care (Hatem, Sandall et al. 2009). This review included 11 studies involving 12,276 women of low and mixed risk of complications, nine of which reported on perinatal mortality. In contrast to the previous review, no difference in perinatal mortality (>24 weeks gestation) was found between those randomised to midwifery-led care compared to other models of care, OR 1.01 (95% CI: 0.67, 1.53).

New Zealand

The model of maternity care provision in New Zealand altered significantly in the early 1990s following the Nurses Amendment Act of 1990, which resulted in a change from a predominantly doctor-led to a midwifery-led model of care. There have been no studies to date that have explored whether there are any differences in perinatal mortality between the different models of care or types of care provider in New Zealand.

Summary

The current literature on the relationship between utilisation of antenatal care and risk of stillbirth is heterogeneous in methodology and is therefore difficult to interpret. The evidence on the increased risk of adverse outcomes, including stillbirth in women who receive no antenatal care, appears strong. However the magnitude of the association is not well established, due to the potential confounding influence of the characteristics of those women who do not access care in pregnancy, only some of which are accounted for in the literature. Any significance of the gestation at initiation of care has not been clearly shown, nor has the specific number of visits required in order for there to be a beneficial effect on rates of stillbirth. Current research suggests that safe maternity care can be provided in a variety of ways.

3.13 Summary of literature review

This chapter has provided a literature review of key factors that are related to the risk of stillbirth; this section provides a summary of these factors.

In this summary, the GRADE approach was used as a framework to assess the strength of evidence; this system classifies the quality of evidence in one of four grades (*Table 8*) (Guyatt, Oxman et al. 2008).

GRADE	DEFINITION
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Table 8: Definitions of strength of evidence (Guyatt, Oxman et al. 2008).

Table 9 presents a summary of key risk factors, their estimate of effect and the strength of evidence from currently available literature. Although the assessment made here is subjective, the grading is generally well accepted.

Risk factor	Estimate of effect	Strength of evidence	Comments
Maternal age ≥ 35	60-70% increase	High	Dose-gradient
Maternal age < 20	uncertain	Very low	
Minority/disadvantaged ethnicity	30-300% increase	Moderate-low	Differences between ethnic groups
Nulliparity	20-40% increase	Moderate	
Grandmultiparity	50-200% increase	Moderate	Dose-gradient
Previous fetal death	30-300% increase	Moderate	
Previous SGA	2-5 fold increase	Moderate	Risk increased if also preterm
Previous caesarean section	30-60%	Moderate	Increased association with unexplained stillbirth
Socio-economic disadvantage	60-200%	Moderate	
Pre-pregnancy weight • BMI: 25-29.9 • BMI: ≥ 30	 10-40% increase 50-70% increase	 High High	Dose-gradient
Weight gain in pregnancy	Uncertain	Very low	
Smoking	30-50% increase	High	
Alcohol	20-80% increase	Low	Variations n study design and population norms
Illicit drug use	60% +	Low	Depends on the drug, dose and related factors
Caffeine Diet in pregnancy	30-60% increase Uncertain	Low Very low	Likely to have a dose-gradient
Physical activity	Uncertain	Very low	
Psychosocial stress	Uncertain	Very low	
Sleep disordered breathing	Uncertain	Very low	
Small for gestational age	400% increase	High	
Maternal perception of decreased fetal movements	60-300%	Low-Moderate	Difficulties in interpretation due to inconsistent study designs
No antenatal care Inadequate antenatal care utilisation	2-3 fold increase Uncertain	Moderate Very low	 Depends on the definition of 'inadequate'
Model of care	No effect	Moderate	For low risk pregnancies

Table 9: Factors associated with risk of stillbirth; effect estimates and quality of evidence

Chapter 4

Methods and rationale

This chapter explains the methods and rationale of the study and was published as a paper in the Australian and New Zealand Journal of Obstetrics and Gynaecology. The editorial that accompanied the paper welcomed this novel approach to the exploration of late stillbirth (Dickinson 2011).

Title:

The Auckland Stillbirth study, a case control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale.

Journal:

Australian and New Zealand Journal of Obstetrics and Gynaecology
2011: Vol 51: pages 3-8

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Contribution

TS participated in the design and coordination of the study, carried out the data collection, conducted statistical analysis of the data and drafted the manuscript.

JT participated in the design of the study, assisted with statistical analysis and helped to draft the manuscript.

EM participated in the conception and design of the study and helped to draft the manuscript.

AE participated in the design of the study and helped to edit the manuscript.

JZ participated in the design of the study and helped to edit the manuscript.

LM participated in the conception and design of the study and helped to draft the manuscript.

4.1 Abstract

Background

In high-income countries, stillbirth rates have been static in recent decades. Unexplained stillbirths account for up to 50% of these deaths.

Methods

A case-control study was conducted in Auckland, New Zealand, from July 2006 to June 2009 to explore modifiable risk factors for late stillbirth (≥ 28weeks of gestation). Eligible participants were women who had a singleton late stillbirth without a congenital abnormality. Two controls with ongoing pregnancies were randomly selected at the same gestation as each case. Data were collected through face-to-face interviews and from clinical records.

Results

A total of 155/215 (72%) cases and 310/429 (72%) controls consented to take part in the study. Women who had a late stillbirth were more likely to be of Pacific ethnicity and of parity ≥ 4 (OR = 1.7, 95% CI: 1.1-2.6 and 2.7, 95% CI: 1.4-5.3, respectively). The median gestational age at diagnosis of fetal death was 261 days (IQR 239-279), and the median gestation at which the controls were interviewed was 264.5 days (IQR 240-274) P =0.48. 'Unexplained antepartum death' (n=61, 39.4%) and 'fetal growth restriction' (n= 29, 18.7 %) accounted for almost 60% of stillbirths. The post-mortem rate for all cases was 47% (73/155) and 43% (26/61) for those classified as 'unexplained antepartum death'.

Conclusion

This study of risk factors for stillbirth is novel in that it used gestation-matched controls with ongoing pregnancies. Its detailed investigation of maternal health and behaviour during pregnancy has the potential to lead to a better understanding of modifiable risk factors for late stillbirth.

4.2 Paper I

The Auckland Stillbirth study, a case control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale.

Introduction

Stillbirth remains a major public health problem in high-income countries where there has been little change in rates in recent decades. Almost 1% of births result in stillbirth, and stillbirths account for more than half of all perinatal deaths in wealthy countries (Laws, Abeywardana et al. 2007; Smith and Fretts 2007; PMMRC 2009). Unexplained stillbirth is the most common classification of cause of death, accounting for 27-75 % of all deaths, varying according to the classification system used (Smith and Fretts 2007; CEMACII 2009; PMMRC 2009), sub-optimal fetal growth accounts for a further 14-23% of stillbirths (Smith and Fretts 2007; PMMRC 2009). As pregnancy progresses, the relative risk of stillbirth increases, as does the proportion of stillbirths that is classified as unexplained (Yudkin, Wood et al. 1987; Huang, Usher et al. 2000; PMMRC 2009).

Internationally, a number of risk factors have been associated with stillbirth, including advanced maternal age (Fretts and Usher 1997; Salihu, Wilson et al. 2008), high pre-pregnancy body mass index (BMI) (Nohr, Beech et al. 2005), smoking (Salihu, Shumpert et al. 2004), fewer than four antenatal visits (Huang, Usher et al. 2000), maternal ethnicity (Salihu, Kinniburgh et al. 2004; Willinger, Ko et al. 2009) fetal growth restriction (Clausson, Gardosi et al. 2001; McCowan, George-Haddad et al. 2007) and low socio-economic status (Stephansson, Dickman et al. 2001), but understanding of the epidemiology remains limited. The majority of studies specifically investigating risk factors for stillbirth have been birth register based retrospective studies and have been able to explore only a limited number of variables (Huang, Usher et al. 2000; Salihu, Wilson et al. 2008; Willinger, Ko et al. 2009).

In order to reduce the burden of stillbirth, prospective studies are required to explore a broader range of potential risk factors. The main aim of The Auckland Stillbirth Study was to determine whether modifiable risk factors for late (≥28 weeks gestation) stillbirth could be identified. The study focussed on late stillbirth, as deaths in the last few months

of pregnancy occur in potentially salvageable babies. It is also the period during which the greatest proportion of stillbirths is classified as unexplained.

Materials and Methods

Study population

Data collection for The Auckland Stillbirth Study took place between 1 July 2006 and 30 June 2009 in the three District Health Boards that provide health care to the greater Auckland region: Waitemata, Auckland and Counties Manukau District Health Boards. Auckland, the largest city in New Zealand, has a population of over 1.4 million people (Statitics New Zealand 2009). The greater Auckland region accounts for over a third of the population of New Zealand and over 35% of all births (approximately 24,000) (PMMRC 2009). Auckland has a unique ethnic mix containing the largest population of Pacific peoples of any city in the world.

Ethical approval was gained for this study from the Northern X Regional Ethics Committee. New Zealand. **NTX/06/05/054**

Recruitment

Case selection

The study included all women booked to give birth in the region and who experienced a stillbirth at, or after 28 weeks gestation. Women with multiple pregnancies and those where the baby died due to a congenital abnormality were excluded from the study. Cases were identified by the clinician responsible for the woman's pregnancy, key staff members in the respective centres, and from hospital birth records which were checked on a weekly basis by the principal investigator (TS). Eligible subjects were introduced to the study by their midwife, doctor or social worker; they were given a brief description of the study and asked whether the researcher could contact them to discuss the study further. If they agreed to be contacted, the researcher then rang the woman and explained the study in greater detail and answered any questions. If the woman consented to participate, a time and place for the interview was arranged.

Control selection

Each case was matched with two randomly selected controls with an ongoing pregnancy. Up-to-date lists of all women registered to give birth within each District Health Board

('booking lists') were obtained fortnightly, and controls were randomly selected using a computer-generated list of random numbers produced prior to the commencement of the study. If a control declined to participate or was not able to be contacted, another control was randomly selected for recruitment. To accurately compare characteristics of the pregnancies of cases and controls, the controls were matched to the cases by gestation and Health Board where the birth was planned. The controls were therefore representative of the antenatal population at the same gestation at which the stillbirth occurred.

Participants were given a feedback form at the end of the interview, in which they were asked: "how did you feel about being involved in this study?" They were provided with a stamped addressed envelope so that feedback could be submitted anonymously. The feedback was read for overall understanding and themes were then identified using an inductive process (Bradley, Curry et al. 2007).

Data collection

Interviewer administered questionnaire

All the participants were interviewed by one of two trained interviewers. The interviewers were both midwives and interviewed the same ratio of cases and controls. The structured interviews lasted approximately one and a half hours and were conducted in the first few weeks following the stillbirth, or, for controls, at the equivalent gestation of pregnancy at which the stillbirth occurred. A questionnaire was administered, relating to the woman's health and behaviours during pregnancy, including: general health; medications; smoking, drug and caffeine intake; socio-economic factors such as education level and type of housing; physical activity; sleep patterns and sleep positions; work during pregnancy; fetal movements; validated depression and perceived stress scales were also administered (Sheldon, Kamarck et al. 1983; Arroll, Khin et al. 2003).

Clinical data collection

Clinical data were also collected at the time of the interview, directly from the woman and from her antenatal record. Further clinical data were extracted from the hospital records. Standard investigations into the cause of stillbirth, as per the Perinatal Society of Australia and New Zealand Clinical Practice Guideline for Perinatal Mortality Audit (PSANZ 2009), were offered to women who experienced a stillbirth, which is standard clinical practice in

the region. Data from these investigations were also collected. No additional clinical tests were performed on either the cases or the controls for the purposes of the study.

Ethical approval was gained to collect limited demographic data: maternal age, ethnicity and parity, on all eligible subjects. These are the only demographic data being reported in this methods paper. Maternal age was defined as the participant's age at time of stillbirth (or interview for the controls). Parity was the number of births (both live births and stillbirths) of at least 20 weeks' gestation that the woman had experienced at time of booking. Ethnicity was assigned using a system of prioritisation based on the standardised system of ethnicity data collection used by the New Zealand Ministry of Health (New Zealand Ministry of Health 2004). In this system, if more than one ethnicity is identified, they are prioritised into the following groups, in order: Maori, Pacific, Indian, Other Asian, Other and New Zealand European. For the purposes of this study, due to small numbers, all non-Maori, non-Pacific, non-European groups were combined and defined as 'other'.

Stillbirth classification

The Perinatal Society of Australia and New Zealand Perinatal Death Classification System (PSANZ-PDC) is used throughout New Zealand as a standardised tool to classify perinatal deaths (Chan, King et al. 2004). This hierarchical system aims to identify the obstetric origins that precede the sequence of events leading to the death and is based on modifications of the Aberdeen and Whitfield classifications (Baird, Walker et al. 1954; Whitfield, Smith et al. 1986). Stillbirth classification was performed at a local level in each participating District Health Board, after mortality review meetings had taken place. They were then audited at a National level to ensure consistency.

Statistical analysis

All statistical tests were performed using SAS (SAS Institute Inc., Cary NC USA). A chi-squared test was used to analyze categorical variables. For non- parametric variables, the Wilcoxon test was used. Odds ratios were estimated by logistic regression. Statistical significance was defined at the 5% level. The study was designed with 80% power and a significance level of 0.05 to enable detection of an odds ratio (OR) of 2, given prevalence for a risk factor of 20%, meaning we required a minimum of 137 cases and 274 controls. These numbers were exceeded during the recruitment period.

Results

Participants

During the recruitment period 215 women experienced a third trimester stillbirth and were eligible to participate in the study, 155 (72%) consented, 27 (13%) declined and 33 (15%) were not able to be contacted. Out of those who were unable to be contacted, 23 were not receiving postnatal care in the region and were not able to be contacted by the clinician responsible; four women agreed for the researcher to make contact, but then did not return calls or were not at home when visited; and in three cases, the clinician responsible for the care did not think it was appropriate to discuss the study with the woman.

A similar proportion of eligible controls, 72% (310/429), consented to participate, 15% (65) declined and 13% (54) were unable to be contacted. Of the 54 that were not able to be contacted, 41 either did not have a current contact number, or did not answer/return calls within the required time frame to be at an equivalent gestation to the case; 11 were not offered the opportunity to discuss the study as the clinician did not feel it was appropriate to ask them. In two potential controls, the clinicians responsible for their care were not able to be contacted (in order to start the consent process) within the required time frame.

The median gestation at diagnosis of fetal death (261 days, IQR 239-279), and the median gestation at which the controls were interviewed (264.5 days, IQR 242-274) did not differ $P = 0.48$. The median time interval between the stillbirth and interview was 25 days (IQR 18-39).

Amongst all eligible participants, women of parity ≥ 4 were more likely to have a stillbirth compared to women with parity 1-3 (OR 2.7 95% CI: 1.4-5.3) (*Table 10*). Women of Pacific ethnicity were also more likely to have a stillbirth compared with European women (OR 1.7 95%CI: 1.1-2.6). Maternal age did not differ between groups.

Characteristics of participants versus non-participants

There was a difference in the overall participation rates by parity and ethnicity. Women of parity ≥ 4 were the least likely to consent with a participation rate of 59% and primiparous women were the most likely to participate (76%). Within the different ethnic groups, European women were the most likely to participate (82%) and Maori women the least likely (58%). However, as can be seen in *Table 11*, there was no statistically significant

	All eligible cases n=215		All eligible controls n=429		OR	95%CI	P value
Parity							
0	98	(46%)	188	(44%)	1.2	(0.9-1.7)	
1-3	96	(45%)	223	(52%)	1.0	Ref	0.01
≥4	21	(10%)	18	(4%)	2.7	(1.4-5.3)	
Maternal age (years)							
<20	24	(11%)	47	(11%)	1.0	(0.6-1.7)	
20-34	143	(67%)	288	(67%)	1.0	Ref	1.00
≥35	48	(22%)	94	(22%)	1.0	(0.7-1.5)	
Ethnicity							
Maori	33	(15%)	60	(14%)	1.4	(0.9-2.4)	
Pacific	67	(31%)	102	(24%)	1.7	(1.1-2.6)	0.07
European	71	(33%)	185	(43%)	1.0	Ref	
Other	44	(21%)	82	(19%)	1.4	(0.9-2.2)	

Table 10: Demographic characteristics of eligible participants

	Cases consented/total n=155/215 % consented		Controls consented/total n=310/416 % consented		Relationship between participation rates of cases and controls
Parity					
0	75/98	(77%)	140/188	(74%)	$\chi^2 = 0.15$ $P = 0.70$
1-3	66/96	(69%)	161/223	(72%)	$\chi^2 = 0.39$ $P = 0.53$
≥4	14/21	(67%)	9/18	(50%)	$\chi^2 = 1.11$ $P = 0.29$
Maternal age (years)					
<20	17/24	(71%)	30/47	(64%)	$\chi^2 = 0.35$ $P = 0.56$
20-34	106/143	(74%)	208/288	(72%)	$\chi^2 = 0.18$ $P = 0.68$
≥35	32/48	(67%)	72/94	(77%)	$\chi^2 = 1.60$ $P = 0.21$
Ethnicity					
Maori	16/33	(48%)	38/60	(63%)	$\chi^2 = 1.93$ $P = 0.17$
Pacific	47/67	(70%)	66/102	(65%)	$\chi^2 = 0.54$ $P = 0.46$
European	60/71	(85%)	150/185	(82%)	$\chi^2 = 0.41$ $P = 0.52$
Other	32/44	(73%)	56/82	(68%)	$\chi^2 = 0.27$ $P = 0.61$

Table 11: The proportion of cases and controls that consented by demographic characteristic

difference in the proportion of cases and controls that consented, by demographic characteristics.

Classification of cause of death

The most common classification for all cases was 'unexplained antepartum death' with almost 40% of stillbirths having no explanation for cause of death (*Table 12*). The second

most common classification overall was that of 'fetal growth restriction' (18.7%). Hypoxic peripartum deaths accounted for almost 15 % of term stillbirths, and no preterm stillbirths. The distribution of classifications in this study was similar to that of New Zealand as a whole in 2007 (P =0.82). The overall rate of post-mortem was 47 % (n= 73) and 43 % (n=26) for unexplained stillbirths.

	Late stillbirth NZ 2007 [1] **n=204**		**All cases n=155**		**Preterm cases**[2] **n=68**		**Term cases**[3] **n=87**	
Perinatal Infection	9	(4%)	12	(8%)	4	(6%)	8	(10%)
Hypertension	8	(4%)	4	(3%)	4	(6%)	0	0
APH	18	(9%)	13	(8%)	4	(6%)	9	(11%)
Maternal Conditions	14	(7%)	7	(5%)	3	(4%)	4	(5%)
Specific Perinatal Conditions	25	(12%)	14	(9%)	5	(7%)	9	(11%)
Hypoxic peripartum	17	(8%)	13	(8%)	0	0	13	(15%)
Fetal growth restriction	32	(16%)	29	(19%)	20	(30%)	9	(10%)
Spontaneous preterm	3	(2%)	2	(1%)	2	(3%)	0	0
Unexplained antepartum	78	(38%)	61	(39%)	26	(38%)	35	(40%)

Table 12 Cause of death using Perinatal Society of Australia and New Zealand Perinatal Death Classification System (PSANZ-PDC) by gestation at delivery

Participants' feedback regarding study participation

Of the 155 women who had a stillbirth, 33 (21%), returned written feedback on their experience of participating in the study, and 73 (24%) of controls also returned feedback forms. No negative feedback was received. The main theme that emerged from the feedback from controls was that of 'helping others' as indicated by the following quote: "I'm pleased to have been invited to participate and hope that this study is able to help future parents avoid the unnecessary pain and sorrow of stillbirth"(control). For the cases, three main themes emerged: 'helping others', 'finding answers' and 'talking and sharing'. The following quotes are examples of comments from cases representing each theme: 'helping others, "Hopefully we can help others in the future with the information that we gave, and something good might come from the tragic loss of our beautiful girl"; 'finding answers', "I was very happy to be involved and help in any way. Because as a mother that

* Perinatal and Maternal Mortality in New Zealand 2007 [3] PMMRC (2009). Perinatal and Maternal Mortality in New Zealand 2007. Third report to the Minister of Health. Wellington, Ministry of Health. excluding congenital abnormalities, ≥ 28weeks gestation

[1] 28-36.6 weeks' gestation at time of stillbirth

[3] ≥ 37 weeks' gestation at time of stillbirth

has lost a baby I have so many questions and most of them unanswered"; talking and sharing', "It is good to share your story as opposed to just becoming another statistic". The approach of the interviewer and the need for compassion and understanding when conducting this kind of research were also mentioned.

Discussion

Few previous studies have interviewed women following stillbirth to investigate risk factors (Pastore, Hertz-Picciotto et al. 1999; Saade 2010). This is the first study to be reported in which women with ongoing pregnancies have been selected as controls. In previous case-control studies there have been two main approaches to control selection: random selection from all live births (Pastore, Hertz-Picciotto et al. 1999) and random selection of live births delivering at the same gestation as the stillbirth (Parker 2011). A limitation of the former approach is that the majority of live births occur at term, and therefore the controls are likely to have a greater average length of gestation compared to the cases. This approach does not take into account the importance of the timing of an exposure (Hertz-Picciotto, Pastore et al. 1996), or potential recall bias if questions are about specific time periods during the pregnancy. When controls are selected from all live births occurring at the same gestation as the stillbirth, a potential bias is introduced by including a disproportionate number of women who have a preterm birth in the control group. Risk factors for preterm birth such as smoking, hypertension and fetal growth restriction are also associated with stillbirth (Salihu and Wilson 2007; Barton and Sibai 2008; Gardosi and Francis 2009). This latter method of selecting controls could therefore potentially mask important risk factors. The current study overcomes the limitations of previous methods, as the median gestation of the cases and controls was similar, and the controls were representative of the overall antenatal population at the gestation at which the stillbirth occurred.

As has been found in other studies, women of high parity had an increased rate of stillbirth (Bai, Wong et al. 2002; Aliyu, Salihu et al. 2005; Akwuruoha, Kamanu et al. 2009). The increased rate of stillbirth amongst Pacific women compared to European is consistent with a previous report from New Zealand (Craig, Mantell et al. 2004) and reflects a similar pattern to that found with black and Asian women in the United Kingdom (Clarke, Clayton et al. 1988; CEMACH 2009) and black women in the United States (Wingate and Alexander 2006; Willinger, Ko et al. 2009) when compared to white women. Although

racial disparities in stillbirth risk are well documented, the reasons for these differences between ethnicities are still not well understood and contributing factors need to be explored further.

A potential limitation to this study is the possibility of recall bias as participants knew whether they were a case or a control. This was reduced by using a structured interview and by ensuring that the participants were not aware of the specific study hypotheses being investigated. The cases were also interviewed after the birth of their baby, whereas the controls were mostly interviewed while still pregnant. The median time interval between the stillbirth and interview was just over three weeks. Findings from similar studies about risk factors for sudden infant death syndrome have shown that a five week time interval did not influence the accuracy of the results, as women could remember in great detail the events leading up to and around the time of their baby's death (Drews, Kraus et al. 1990; Gibbons, Ponsonby et al. 1993).

In the design phase of this study, there was some concern expressed about the feasibility of recruiting controls into a study about stillbirth risk while the women were still pregnant and therefore potentially at risk of experiencing a stillbirth themselves. Wide consultation took place with bereavement support organisations and maternity service providers to discuss these concerns; the high recruitment rate amongst controls (72%) suggests that this concern was unfounded. The potential impact of interviewing recently bereaved mothers was also discussed. Although the responses received from participants may not be able to be generalised due to the low return rate, the fact that all the feedback received was positive can be reassuring to ethics committees and clinicians providing antenatal care, who may be concerned about the potential impact on women who are invited to take part in such research (Braunack-Mayer 2002). Other studies involving bereaved parents have indicated that although participants often agree to take part in research for altruistic reasons, they may also gain personal benefit from the research process themselves (Hynson, Aroni et al. 2006).

Conclusion

This paper describes the methods and rationale for The Auckland Stillbirth Study. Through detailed exploration of women's health and behaviours during pregnancy, this prospective

case control study has the potential to lead to a better understanding of modifiable risk factors for late stillbirth.

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Chapter 5

Socio-demographic factors

This chapter presents results on the relationship between certain socio-demographic factors (such as maternal obesity and ethnicity) and risk of late stillbirth in Auckland.

Title:

Relationship between obesity, ethnicity and risk of late stillbirth: a case control study

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Contribution

TS participated in the design and coordination of the study, carried out the data collection, conducted statistical analysis of the data and drafted the manuscript.

JT participated in the design of the study, assisted with statistical analysis and helped to draft the manuscript.

EM participated in the conception and design of the study and helped to draft the manuscript.

AE participated in the design of the study and helped to edit the manuscript.

JZ participated in the design of the study and helped to edit the manuscript.

LM participated in the conception and design of the study and helped to draft the manuscript

5.1 Abstract

Background

In high income countries there has been little improvement in stillbirth rates over the past two decades. Previous studies have indicated an ethnic disparity in the rate of stillbirths. This study aimed to determine whether maternal ethnicity is independently associated with late stillbirth in New Zealand.

Methods

Cases were women with a singleton, late stillbirth (≥28 weeks' gestation) without congenital abnormality, born between July 2006 and June 2009 in Auckland, New Zealand. Two controls with ongoing pregnancies were randomly selected at the same gestation at which the stillbirth occurred. Women were interviewed in the first few weeks following stillbirth, or at the equivalent gestation for controls. Detailed demographic data were recorded. The study was powered to detect an odds ratio of 2, with a power of 80% at the 5% level of significance, given a prevalence of the risk factor of 20%. A multivariable regression model was developed which adjusted for known risk factors for stillbirth, as well as significant risk factors identified in the current study, and adjusted odds ratios and 95% confidence intervals were calculated.

Results

155/215 (72%) cases and 310/429 (72%) controls consented. Pacific ethnicity overweight and obesity, grandmultiparity, not being married, not being in paid work, social deprivation, exposure to tobacco smoke and use of recreational drugs were associated with an increased risk of late stillbirth in univariable analysis. Maternal overweight and obesity, nulliparity, grandmultiparity, not being married and not being in paid work were independently associated with late stillbirth in multivariable analysis, whereas Pacific ethnicity was no longer significant (aOR 0.99; 95% CI: 0.51-1.91).

Conclusions

Pacific ethnicity was not found to be an independent risk factor for late stillbirth in this New Zealand study. The disparity in stillbirth rates between Pacific and European women can be attributed to confounding factors such as maternal obesity and high parity.

5.2 Paper II

Relationship between obesity, ethnicity and risk of late stillbirth: a case control study

Background

Stillbirth remains a common and devastating pregnancy complication. Approximately 8 in 1000 New Zealand births result in stillbirth (fetal death ≥ 20 weeks' gestation) and more than 1 in 300 result in late stillbirth (death ≥ 28 weeks' gestation) (PMMRC 2009). Unfortunately the decline in stillbirth rate in New Zealand and elsewhere that occurred in the 1980's and 1990's has not been sustained in the last decade (Craig, Stewart et al. 2004; NZHIS 2007; CEMACH 2009; PMMRC 2009).

Previous retrospective New Zealand studies have documented ethnic disparity in the rate of stillbirth, with Pacific women having an increased risk of stillbirth compared to European women (Ekeroma, Craig et al. 2004; McCowan, George-Haddad et al. 2007). Ethnic disparity in stillbirth risk has also been reported elsewhere. In the UK, both Black and Asian women have a disproportionate number of stillbirths compared to White women (Clarke, Clayton et al. 1988; Balchin, Whittaker et al. 2007; CEMACH 2009). In the United States, African American women have more than twice the risk of stillbirth compared to White women (Salihu, Kinniburgh et al. 2004; Willinger, Ko et al. 2009). The reasons for these reported ethnic disparities have not yet been determined.

International studies have reported several demographic risk factors associated with stillbirth, including; advanced maternal age (Fretts, Schmittdiel et al. 1995; Canterino, Ananth et al. 2004), obesity (Cedergren 2004; Nohr, Bech et al. 2005) smoking in pregnancy (Wisborg, Kesmodel et al. 2001), low socio-economic status (Stephansson, Dickman et al. 2001a) and extremes of parity (Raymond, Chattingius et al. 1994; Aliyu, Salihu et al. 2005). Many previous studies that have reported ethnic disparity in the risk of stillbirth were retrospective in design and had insufficient variables to enable appropriate adjustment for confounders (Clarke, Clayton et al. 1988; McCowan, George-Haddad et al. 2007; Willinger, Ko et al. 2009).

The main aim of the prospective Auckland Stillbirth Study was to identify modifiable risk factors for late stillbirth. We hypothesised that, after adjustment for demographic risk

factors, the risk of late stillbirth amongst Pacific women would not differ from that in European women and that obesity would be an independent risk factor for late stillbirth.

Methods

All women booked to give birth in the greater Auckland region and who experienced a stillbirth at or after 28 weeks' gestation between July 2006 and June 2009 were eligible to participate in the study. Late stillbirth was selected as the primary outcome as live born babies born at or after 28 weeks are likely to survive. Women with multiple pregnancies and those where the baby died due to a congenital abnormality were excluded. Each case was matched with two randomly selected controls with an ongoing pregnancy at the same gestation at which the stillbirth occurred. A description of the manner in which cases and controls were identified and recruited, and other detailed methods have been described previously (Stacey, Thompson et al. 2011). Data were obtained through interviewer administered questionnaires and from clinical data extraction.

Ethical approval was gained for this study from the Northern "X" Regional Ethics Committee.

Data collection

Interviews took place in the first few weeks following the stillbirth, or for controls, at the equivalent gestation of pregnancy at which the stillbirth occurred. Demographic data included maternal age, ethnicity and country of birth, body mass index, education level, social deprivation index, work status, marital status, parity, smoking and recreational drug use during pregnancy.

A single ethnicity was self assigned using a system of prioritisation based on the standardised system of ethnicity data collection used by the New Zealand Ministry of Health (Ministry of Health 2004). In this study, due to small numbers, all non-Māori, non-Pacific, non-European groups were combined and defined as 'other'.

Maternal Body Mass Index (BMI) was calculated from the earliest known weight taken in pregnancy and maternal height measured at interview. BMI was considered as a continuous, and also as a categorical, variable. BMI was classified according to two criteria: conventional World Health Organisation (WHO) (WHO 2000) and ethnic specific

(WHO Expert Consultation 2004). Only 2 (1.3%) cases and 6 (1.9%) controls were classified as underweight, and BMI was therefore categorised into 3 groups: <25 kg/m^2, 25-29.9 kg/m^2, and ≥ 30 kg/m^2 for WHO criteria. Appropriate cut off points for overweight and obesity differ between ethnic groups as the BMI and body fat ratios differ (Swinburn, Ley et al. 1999; Deurenberg 2002) and consequently ethnic specific categories have been developed for use in multi ethnic populations (Razak, Anand et al. 2007). For Asians, overweight was defined as ≥23 kg/m^2 and obesity as ≥27.5 kg/m^2 and for Pacific/Māori, overweight is ≥26 kg/m^2 and obesity >32 kg/m^2[21 22].Three ethnic specific BMI categories were therefore also created: normal/underweight, overweight and obese. As ethnic specific BMI categories are not universally accepted, the conventional WHO criteria were used in the multivariable analysis.

The level of social deprivation (Deprivation Index) was determined by the address at which the participant was living at the time of stillbirth/interview, based on the 2006 New Zealand Deprivation Index (NZDep2006) (Salmond, Crampton et al. 1998). Smoking status was assigned to one of three groups: smoking at any time during pregnancy (smoker), non smoker who lived with a smoker (passive only), and those that did not smoke in pregnancy and lived in a smoke free environment (smoke free).

Analysis

The study was powered to detect an odds ratio of 2, with a power of 80% at the 5% level of significance, given a prevalence of the risk factor of 20%. All statistical tests were performed using SAS 9.1 (SAS Institute Inc., Cary NC USA). Standard conditional regressions were used for matched case control studies using the 'proc logistic' procedure, with the 'strata' statement to control for matching. Continuous variables were compared using t-tests. Statistical significance in multivariable analysis was defined at the 5% level. Odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals were used to calculate risk in univariable and multivariable analysis respectively.

The main multivariable regression model included maternal variables known to be associated with increased risk of stillbirth, based on evidence from previous literature (maternal age, BMI, ethnicity, parity, smoking and socio-economic status). Other demographic variables from this study with a p-value of <0.10 were also included in the model.

Results

During the study period 215 eligible cases of late stillbirth were identified, 155 (72%) consented to take part in the study, as did 310/429 (72%) of the eligible controls. No significant difference was identified between the characteristics of those who consented and those who did not (Stacey, Thompson et al. 2011).

In univariable analysis, Pacific women were found to have an increased risk of late stillbirth compared to European women (OR 1.88 95% CI 1.13-3.13), whereas the risk for Māori women did not differ [*Table 13*]. There was no significant difference in the gestation at which the earliest pregnancy weight was measured (14.3 weeks (SD 7.0) for cases and 13.8 weeks (SD 7.1) for controls p–0.54). Using conventional WHO BMI groupings, both overweight and obese women were found to have an increased risk of stillbirth relative to normal/underweight women. A similar pattern, with slightly reduced odds ratios, was also found when ethnic specific BMI criteria were used.

Women who were; grandmultiparous (parity ≥4), not married, lived in the most deprived areas, or were not in paid work were also found to be at increased risk of late stillbirth. Both cigarette smokers and non smokers regularly exposed to environmental cigarette smoke had a similar degree of increased risk. Recreational drug use was associated with a greater than two-fold increase in risk. Marijuana was the most commonly used recreational drug in pregnancy in 9 (5.8%) cases and 11 (3.6%) controls, and the majority of marijuana smokers also smoked cigarettes; 82% of marijuana smoking cases and 100% of marijuana smoking controls also smoked cigarettes.

In this study, no significant relationship was found between risk of late stillbirth and maternal age, country of birth or school leaving age. Previous adverse pregnancy outcome was not found to be significantly associated with late stillbirth risk in this study.

After multiple regression analysis was performed, adjusting for potential confounders, maternal Pacific ethnicity was no longer found to be independently associated with late stillbirth (aOR 0.99 (95%CI: 0.51, 1.91), and Māori ethnicity was now found to be associated with a significantly reduced risk of late stillbirth (aOR 0.41 (95%CI: 0.17, 0.96) [*Table 14*].

	Cases n=155 (%)	Controls n=310 (%)	Univariable OR 95% CI
Maternal age			
<20	10(6.5)	24(7.7)	0.80 0.38-1.71
20-34	113 (72.9)	216 (69.7)	1.00 -
>35	32 (20.7)	70 (22.6)	0.86 0.53-1.41
Maternal ethnicity			
Māori	19(12.3)	46(14.8)	1.08 0.57-2.04
Pacific	48 (31.0)	67 (21.6)	1.88 1.13-3.13
European	55 (35.5)	139 (44.8)	1.00 -
Other	33 (21.3)	58 (18.7)	1.46 0.85-2.51
Country of birth			
New Zealand	83(53.6)	168(54.2)	1.00 -
Other	72 (46.5)	142 (45.8)	0.97 0.65-1.45
Marital status			
Married	84(54.2)	202 (65.2)	1.00 -
Not married	71 (45.8)	108 (34.8)	1.60 1.07-2.38
Deprivation Index			
1-4	91(58.7)	218(70.3)	1.00 -
5 (most deprived)	64 (41.3)	92 (29.7)	1.74 1.14-2.67
School leaving age			
<17 years	36 (23.2)	56 (18.1)	1.37 0.85-2.18
≥17	119 (76.8)	254 (81.9)	1.00 -
Employment in last month			
Paid work	41 (26.5)	118(38.1)	1.00 -
Not in paid work	114 (73.6)	192 (61.9)	1.75 1.13-2.70
Parity			
0	77(49.7)	144(46.5)	1.40 0.93-2.09
1-3	62 (40.0)	156 (50.9)	1.00 -
≥4	16 (10.3)	10 (3.2)	5.10 1.98-13.11
BMI			
< 25	55(35.5)	156(50.3)	1.00 -
25-29.9	39 (25.2)	67 (21.6)	1.69 1.03-2.78
≥ 30	61 (39.4)	87 (28.1)	2.08 1.30-3.33
Ethnic specific BMI groups			
Normal/underweight	57(36.8)	151(48.7)	1.00 -
Overweight	44 (28.4)	81 (26.1)	1.46 0.91-2.35
Obese	54 (34.8)	78 (25.2)	1.91 1.18-3.09
Smoking in pregnancy			
Smoke-free	80 (51.6)	201 (64.8)	1.00 0.99-2.83
Passive only	29 (18.7)	43 (13.9)	1.67 1.11-2.85
Smoker	46 (29.7)	66 (21.3)	1.78
Recreational drugs			
No drug use	142 (91.6)	298 (96.1)	1.00 -
Any drug use	13 (8.4)	12 (3.9)	2.35 1.02-5.42
Previous preterm birth			
Yes	11 (7.10)	15(4.8)	1.52 0.67-3.43
No	143 (92.3)	295 (95.2)	1.00 -
Previous small for gestational age	12 (7.7)	15	
Yes	143 (92.3)	295(4.8)	1.60 0.75-3.42
No		(95.2)	1.00
Previous stillbirth			
Yes	2(1.3)	3(1.0)	1.33 0.22-7.98
No	153 (98.7)	307 (99.0)	1.00

Table 13: Characteristics of women with late stillbirth compared with gestation matched controls

Maternal overweight and obesity remained significant, with obese women having a more than two-fold increase in risk compared to normal weight/underweight women (aOR 2.11; 95% CI 1.14-3.91). As obesity is known to be associated with pre-eclampsia and diabetes, we fitted an additional model including these two variables (prevalence 0.9% and 4.5% respectively). The findings of the original model were unchanged when adjustment was made for these additional variables.

	Adjusted OR*	(95% CI)
Maternal age		
<20	0.61	0.24-1.52
20-34	1.00	-
≥35	0.82	0.46-1.46
Maternal ethnicity		
Māori	0.41	0.17-0.96
Pacific	0.99	0.51-1.91
European	1.00	-
Other	1.69	0.92-3.11
Marital status		
Married	1.00	-
Not married	1.75	1.03-2.98
Deprivation Index		
1-4	1.00	-
5	1.20	0.72-2.00
Employment in last month		
Paid work	1.00	-
Not in paid work	1.66	1.00-2.77
Parity		
0	1.75	1.08-2.83
1-3	1.00	-
≥4	4.22	1.44-12.40
BMI		
< 25	1.00	-
25-29.9	1.75	1.00-3.05
≥ 30	2.11	1.14-3.91
Smoking		
Smoke-free	1.00	-
Passive only	1.36	0.74-2.47
Smoker	1.28	0.71-2.32
Recreational drugs		
No drug use	1.00	-
Any drug use	2.77	0.96-7.99

Table 14: Multivariable odds ratios for maternal characteristics associated with late stillbirth

**adjusted for all variables in the table*

Discussion

Auckland, the largest city in New Zealand, contains the greatest numbers of Pacific people of any city in the world (ARC 2006). The increased rate of late stillbirth amongst Pacific women compared to European found in univariable analysis is consistent with previous studies from New Zealand and with other international studies indicating ethnic disparity in stillbirth risk (Craig, Mantell et al. 2004; Wingate and Alexander 2006; CEMACH 2009; Willinger, Ko et al. 2009). This study was able to adjust for a number of potential demographic confounders such as obesity, parity and poverty. After this adjustment, Pacific ethnicity was no longer found to be independently associated with an increased risk of late stillbirth.

The results from this study also suggest that after adjusting for known confounding factors, Māori ethnicity was associated with a reduced risk of late stillbirth. This finding seems inconsistent with two other studies which reported that Māori women had a similar overall stillbirth risk to European women (Craig, Mantell et al. 2004; McCowan, George-Haddad et al. 2007), although these former studies were not able to adjust for BMI, smoking or drug use in pregnancy. There is also evidence that Māori women may have an increased risk of stillbirth prior to 28 weeks gestation, rather than late stillbirth (ADHB 2010). Our findings of a reduced rate of late stillbirth in Māori, when considered with other New Zealand data suggesting an increase in early stillbirth, are compatible with the previous studies which showed no overall increase in stillbirth risk for Māori compared with European (Craig, Mantell et al. 2004; McCowan, George-Haddad et al. 2007). However our data suggest that Māori women who do not have lifestyle risk factors may have a reduced risk of late stillbirth, and future well designed studies are needed to confirm or refute these findings.

Consistent with previous research, we found a twofold increase in late stillbirth risk in obese women (Stephansson, Dickman et al. 2001b; Cedergren 2004; Nohr, Bech et al. 2005; Salihu, Dunlop et al. 2007). Obesity is particularly prevalent amongst Pacific women in New Zealand, with almost 64% of all Pacific women being classified as obese (Ministry of Health 2008). Obesity is also more prevalent in African Americans compared to White women in the United States (Ramos and Caughey 2005). Few previous studies showing disparity in stillbirth risk between ethnic groups have been able to adjust for BMI (Willinger, Ko et al. 2009; Craig, Mantell et al. 2004). One study, by Salihu and others,

which has explored this relationship, reported that obesity compounded the stillbirth risk for African American women, as the increased risk of stillbirth for obese African American women was on average 50% greater than that for obese White women (Salihu, Dunlop et al. 2007).

A novel feature of this study is that we have investigated the risk of stillbirth using ethnic specific as well as conventional WHO BMI criteria. The relationship between obesity and stillbirth was similar regardless of which criteria were used.

The mechanism(s) by which obesity increases the risk of stillbirth is not clear and is likely multifactorial. Metabolic disorders such as diabetes and pre-eclampsia are associated with obesity (Leung, Leung et al. 2008), and are in turn associated with an increased risk of stillbirth (Smulian, Ananth et al. 2002); however in our study adjustment for these factors did not diminish the independent effect of obesity. Obese pregnant women have altered metabolic profiles compared with non obese women, including higher glucose levels (even when not meeting criteria for diabetes), altered lipids and a pro-inflammatory milieu (Sheehan and Jensen 2000). In high income countries, obesity is associated with lower socio-economic status, and women who do not have access to micronutrient rich food have been found to be more likely to be overweight or obese (Asfaw 2007). In this study, however, adjustment for socio-economic status did not reduce the effect of obesity on the risk of stillbirth. Further research is required to determine whether nutritional status has an impact on the risk of stillbirth (Yakoob, Menezes et al. 2009). Obese pregnant women have significantly more sleep-related disordered breathing than normal weight women (Maasilta, Bachour et al. 2001). Snoring has been associated with fetal growth restriction and pregnancy-induced hypertension (Franklin, Ake Holmgren et al. 2000), but there has been only one case study reported that suggested a link between obstructive sleep apnoea and stillbirth (Brain, Thornton et al. 2001). Obesity has also been associated with altered perception of fetal movements, with more overweight and obese women presenting with reduced fetal movements compared with women of normal weight (Holm Tveit, Saastad et al. 2009).

As has been found in other studies, both extremes of parity were shown to be associated with an increased risk of stillbirth (Bai, Wong et al. 2002; Aliyu, Salihu et al. 2005). In our study grandmultiparous women had the highest risk and Pacific women were more likely

to be grandmultiparous than women of other ethnicities. Advanced maternal age can impact upon the relationship between stillbirth and grandmultiparity, however in this study maternal age was included in the adjusted model and the relationship remained. The mechanisms that might underlay the relationship between high parity and stillbirth risk are not yet understood. A speculation by Aliyu and others is that "uterine exhaustion" is reached and the uterus becomes less effective in its nurturing of the fetus (Aliyu, Salihu et al. 2005). As previous pregnancy complications were not associated with increased risk of stillbirth in this study it is unlikely that the effect of high parity is medicated by adverse outcomes in previous pregnancies.

We found no association between maternal age and stillbirth; this may be due to the study being underpowered for such an association, as previous large population based studies have found associations between both young (Wilson, Alio et al. 2008; de Vienne, Creveuil et al. 2009) and advanced maternal age (Huang, Sauve et al. 2008; Salihu, Wilson et al. 2008) and stillbirth. Advanced maternal age has also been specifically associated with unexplained stillbirth (Huang, Usher et al. 2000; Froen, Arnestad et al. 2001), whereas in this study we included all causes of late stillbirth (after exclusion of fetal abnormalities and multiple pregnancies) which may dilute an association between advanced maternal age and unexplained stillbirth in particular. One other possible explanation for our differing findings may be that in two of the three District Health Boards where this study took place, women over 35 years are routinely offered increased antenatal testing in late pregnancy with a low threshold for early induction at term and beyond (Fretts, Elkin et al. 2004).

A causal relationship between maternal smoking and poor perinatal outcomes is well established (Salihu, Sharma et al. 2008). The association between smoking and late stillbirth was significant in univariable analysis but was not in the multivariable analysis, however the aOR is consistent with findings from other larger studies (Raymond, Cnattingius et al. 1994; Stephansson, Dickman et al. 2001a) and the lack of statistcial significance in the current study may be due to lack of power. Previous studies that have explored the relationship between passive smoking and stillbirth have also shown an increased risk for non-smokers exposed to environmental tobacco smoke (Kharrazi, DeLorenze et al. 2004; Subramoney, d'Espaignet et al. 2010).

This study was powered to detect an odds ratio of 2, with a power of 80% at the 5% level of significance for a risk factor with 20% prevalence, such as obesity or Pacific ethnicity. However it had insufficient power to determine the significance of risk factors with lower prevalence (such as recreational drug use), or that have a smaller strength of association with late stillbirth, such as smoking.

Conclusion

Pacific ethnicity was not found to be an independent risk factor for late stillbirth. The disparity in stillbirth risk experienced by Pacific women can therefore be attributed to other factors such as obesity and high parity. Further research is required to better understand the mechanisms by which factors such as obesity and high parity are associated with late stillbirth.

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Chapter 6

Maternal perception of fetal activity

This section presents results on the association between maternal perception of fetal activity and risk of late stillbirth.

Title:

Maternal perception of fetal activity and late stillbirth risk - findings from the Auckland stillbirth study.

Journal:

Birth-Issues in perinatal care (In press)

Authors

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Contribution

TS participated in the design and coordination of the study, carried out the data collection, conducted statistical analysis of the data and drafted the manuscript.

JT participated in the design of the study, assisted with statistical analysis and helped to draft the manuscript.

EM participated in the conception and design of the study and helped to draft the manuscript.

AE participated in the design of the study and helped to edit the manuscript.

JZ participated in the design of the study and helped to edit the manuscript.

LM participated in the conception and design of the study and helped to draft the manuscript

6.1 Abstract

Background

Maternal perception of decreased fetal movements has been associated with adverse pregnancy outcomes, including stillbirth. Little is known about other aspects of perceived fetal activity. The objective of this study was to explore the relationship between maternal perception of fetal activity and third trimester stillbirth risk.

Methods

Cases were women with a singleton, third trimester stillbirth (≥28 weeks' gestation) without congenital abnormality, born between July 2006 and June 2009 in Auckland, New Zealand. Two controls with ongoing pregnancies were randomly selected at the same gestation at which the stillbirth occurred. Detailed demographic and fetal movement data were collected via interview in the first few weeks following stillbirth, or at the equivalent gestation for controls.

Results

155/215 (72%) cases and 310/429 (72%) controls consented to take part in the study. Maternal perception of increased strength and frequency of fetal movements, fetal hiccups, and frequent vigorous fetal activity were all associated with a reduced risk of third trimester stillbirth. In contrast, perception of decreased strength of fetal movement was associated with a more than two fold increased risk of third trimester stillbirth aOR 2.37 (95 % confidence interval: 1.29 to 4.35). A single episode of vigorous fetal activity was associated with an almost seven fold increase in third trimester stillbirth risk aOR 6.81 (95 % confidence interval: 3.01 to 15.41).

Conclusions

Our study suggests that maternal perception of increasing fetal activity throughout the last three months of pregnancy is a sign of fetal wellbeing, whereas perception of reduced fetal movements is associated with increased risk of third trimester stillbirth.

6.2 Paper III

Maternal perception of fetal activity and late stillbirth risk - findings from the Auckland stillbirth study.

Background

Fetal activity is a reflection of a normally functioning central nervous system and regular fetal movements have long been considered an indicator of fetal wellbeing (Froen 2004). The first description of decreased fetal movements preceding fetal death was by Sadovsky in 1973 (Sadovsky and Yaffe 1973). Since that time many papers have reported an association between reduced fetal movements and adverse pregnancy outcomes, specifically; fetal growth restriction (Sinha, Sharma et al. 2007; O'Sullivan, Stephen et al. 2009), preterm birth (Holm Tveit, Saastad et al. 2009), and stillbirth (Rayburn 1982; Holm Tveit, Saastad et al. 2009). Some studies have suggested that maternal perception of fetal movements are too subjective, with only a minority of movements that are detected by a Doppler device being perceived by women (Johnson, Jordan et al. 1990). However a number of other studies have reported a good correlation between objective recordings and maternal perception of fetal movement, in particular when movements involve the fetal trunk and lower limbs (Sadovsky, Mahler et al. 1973; Rayburn 1980). Maternal perception of fetal movements has been shown to be affected by a number of factors including; body mass index, placental location, maternal position and psychological factors (Tuffnell, Cartmill et al. 1991; Cito, Luisi et al. 2005; Saastad, Ahlborg et al. 2008).

There is currently no consensus as to what constitutes normal fetal movements in late pregnancy, with considerable variance in the number of daily fetal movements felt by women (Sadovsky and Polishuk 1977; Saastad, Ahlborg et al. 2008). It is also unclear whether there is a substantive change in perception of fetal movement as pregnancy progresses. Some studies have reported a maximum frequency of fetal movements between 29 and 38 weeks, with a small reduction at term (Sadovsky and Yaffe 1973; Pearson and Weaver 1976; Roodenburg, Wladimiroff et al. 1991), and yet other studies have shown no overall reduction in fetal movements with advancing gestation (Roberts, Griffin et al. 1980; Valentin, Mars et al. 1986; Connors, Natale et al. 1988). Consequently there are contradictory sources of information available to women and health professionals as to the significance of a decrease in fetal movements in late pregnancy, with some

consumer sources and professional texts suggesting that it is normal for fetal movements to decrease at term (Rådestad 2010).

In addition, there has been no published research exploring other aspects of perceived fetal activity, such as sudden vigorous activity or fetal hiccups, and their relationship to stillbirth risk.

The primary aim of The Auckland Stillbirth Study was to identify potentially modifiable risk factors for third trimester (≥28 weeks) stillbirth. This paper explores the relationship between third trimester stillbirth risk and aspects of maternal perception of fetal activity, specifically; changes in strength and frequency of movement, unusually vigorous activity, and fetal hiccups. We hypothesised that women who experienced a third trimester stillbirth would perceive a decrease in the frequency and intensity of fetal movements compared to controls at the same gestation.

Methods

All women with a singleton pregnancy who experienced a stillbirth at or after 28 weeks' gestation between July 2006 and June 2009 in the greater Auckland region were eligible to participate in the study. Women with babies that died due to a congenital abnormality were excluded. Two randomly selected controls with an ongoing pregnancy were matched to each case by gestation at which the stillbirth occurred. Data were obtained through interviewer administered questionnaires and from clinical data extraction. Interviews took place in the first few weeks following the stillbirth, or for controls, at the equivalent gestation of pregnancy at which the stillbirth occurred. Further details of methods and participant characteristics have been described previously (Stacey, Thompson et al. 2011a; Stacey, Thompson et al. 2011b).

The study was approved by the Northern "X" Regional Ethics Committee.

No validated tools for the collection of data relating to maternal perception of fetal activity have been published. Questions were therefore developed for this study to explore a range of factors relating to maternal awareness of fetal activity. Patterns of fetal movement during the last two weeks (prior to fetal death or prior to interview for controls) were determined by asking participants to describe their baby's movements, in particular

whether there had been any change in frequency or strength. The response was written down during the interview. At completion of the study, these data were then coded separately by two researchers according to whether women perceived the strength and frequency of fetal movements to have 'increased', 'decreased', 'stayed the same' or 'unsure'. The researchers were blinded as to whether the response was from a case or control. Coding was then compared for consistency; there was a difference in coding in 17 responses. for these responses discussion was held with a third researcher and a consensus was agreed upon. The normal pattern of maternal perception of fetal movements in the third trimester of pregnancy is not well defined; therefore 'stayed the same' was used as the reference group in analysis.

In addition, presentation to a maternity assessment unit or to a maternity care provider, because of a concern about decreased fetal movements, was ascertained from participants' clinical records.

Participants were also asked: '*during the last two weeks (*prior to fetal death or interview*), did you notice any time that your baby was more vigorous than usual?*' and: '*during the last two weeks, did you feel your baby having hiccups (short jerking movements occurring at regular intervals, for a period of time)?*"

Demographic data and information on other potential confounding factors were also collected during the interview.

Analysis

All statistical analyses were performed using SAS version 9.1 (SAS_Institute_Inc 2004). Standard conditional regressions were used for matched case control studies using the 'proc logistic' procedure, with the 'strata' statement to control for matching. A multivariable regression model was developed to include maternal variables reported to be associated with increased risk of third trimester stillbirth or perception of fetal movements, based on previous literature (age, body mass index (BMI), ethnicity, parity, smoking and socio-economic status. The study was powered to detect an odds ratio (OR) of 2 with 80 percent power and significance level of 0.05, with a prevalence of the risk factor of 20 percent or more in the control population. Statistical significance in multivariable analysis

was defined at the 5 percent level. Odds ratios and adjusted odds ratios (aOR) with 95 percent confidence intervals (CI) were used to estimate risk.

Results

Of the 215 eligible stillbirths identified during the study period, 155 (72%) consented to participate, as did 72 percent (310/429) of the eligible controls. The median gestation at diagnosis of fetal death was 261 days, with 57 percent occurring at or after 37 weeks' gestation. Baseline characteristics of the study population have been described elsewhere (Stacey, Thompson et al. 2011a).

Overall 66 (42.6%) women who experienced a third trimester stillbirth presented to healthcare services with decreased fetal movements at some time in their pregnancy; in contrast to only 28 (9.0%) of controls. However, of those cases that presented with decreased movements only 15 (9.7% of all cases) presented prior to diagnosis of fetal death, of the remaining 51 cases fetal death was diagnosed at time of presentation.

Perceived fetal activity	Cases n=155 (%)	Controls n=310 (%)	Univariable OR 95% CI	Adjusted OR[4] 95% CI
Frequency FM[5]				
Increased	13 (8.4)	88 (28.4)	0.25 (0.13 to 0.50)	0.24 (0.12 to 0.50)
Same	76 (49.0)	135 (43.6)	ref	ref
Decreased	45 (29.0)	36 (11.6)	2.16 (1.24 to 3.77)	2.37 (1.29 to 4.35)
Unsure	21 (13.6)	51 (16.5)	0.65 (0.31 to 1.34)	0.76 (0.35 to 1.66)
Strength FM				
Increased	16 (10.3)	124 (40.0)	0.18 (0.09 to 0.34)	0.18 (0.09 to 0.36)
Same	76 (49.0)	112 (36.1)	ref	ref
Decreased	30 (19.4)	21 (6.8)	1.67 (0.88 to 3.15)	1.88 (0.93 to 3.79)
Unsure	33 (21.3)	53 (17.1)	1.05 (0.56 to 1.95)	1.03 (0.53 to 2.00)
Vigorous movement [6]				
None	97 (63.0)	202 (65.4)	ref	ref
Once	32 (20.8)	16 (5.2)	4.51 (2.23 to 9.10)	6.81 (3.01 to 15.41)
More than once	25 (16.2)	91 (29.5)	0.55 (0.33 to 0.93)	0.58 (0.33 to 1.03)
Hiccups [7]				
Yes	52 (33.6)	199 (64.4)	ref	ref
None	98 (63.2)	100 (32.4)	3.53 (2.31 to 5.40)	3.52 (2.18 to 5.68)
Unsure	5 (3.2)	10 (3.2)	2.04 (0.66 to 6.32)	2.23 (0.68 to 7.29)

Table 15 Maternal perception of fetal movements during the last two weeks of pregnancy

[4] Adjusted for maternal age, BMI, parity, ethnicity, social deprivation and smoking
[5] FM: Fetal movements
[6] Missing data: 1 case and 1 control
[7] Missing data: 1 control

During the last two weeks of pregnancy (prior to fetal death, or prior to interview for controls), an association was found between maternal perception of decreased frequency of fetal movements and third trimester stillbirth risk aOR 2.37 (95% CI 1.29 to 4.35) (*Table 15*). In addition, an overall increase in frequency or strength of fetal movement, compared to no change, was inversely associated with third trimester stillbirth risk, aOR 0.24 (95% CI 0.12 to 0.50) and aOR 0.18 (95% CI 0.09 to 0.36) respectively. Women who perceived unusually vigorous movements more than once also had a trend towards a reduced risk of third trimester stillbirth aOR 0.58 (95% CI 0.33 to 1.03). In contrast, women who perceived their baby to have had a single episode of more vigorous than usual movement were almost seven times more likely to experience a third trimester stillbirth. Women who did not perceive their baby to have had hiccups during the last two weeks had a more than threefold increased risk of third trimester stillbirth aOR 3.52 (95% CI 2.18 to 5.68) compared to those women who did notice their baby having hiccups.

Perceived fetal activity	**Preterm <37 weeks gestation**			**Term ≥ 37 weeks gestation**		
	Cases n=66	Controls n=132	aOR 95%CI	Cases n=89	Controls n=178	aOR 95%CI
Frequency FM - last 2 weeks	n %	n %		n %	n %	
Increased	5 (7.6)	45 (34.1)	0.10 (0.03, 0.37)	8 (9.0)	43 (24.2)	0.31 (0.11, 0.83)
Same	33 (50.0)	59 (44.7)	ref	43 (48.3)	76 (42.7)	ref
Decreased	20 (30.3)	6 (4.6)	8.00 (2.14, 29.91)	25 (28.1)	30 (16.9)	1.52 (0.73, 3.19)
Unsure	8 (12.1)	22 (16.7)	0.36 (0.08, 1.55)	13 (14.6)	29 (16.3)	0.85 (0.30, 2.41)
Strength FM - last 2 weeks						
Increased	3 (4.6)	60 (45.5)	0.04 (0.01, 0.21)	13 (14.6)	64 (36.0)	0.35 (0.16, 0.78)
Same	34 (51.5)	40 (31.8)	ref	42 (47.2)	70 (39.3)	ref
Decreased	16 (24.2)	4 (3.0)	3.73 (0.82, 17.03)	14 (15.7)	17 (9.6)	1.56 (0.65, 3.78)
Unsure	13 (19.7)	26 (19.7)	0.43 (0.14, 1.31)	20 (22.5)	27 (15.2)	1.78 (0.68, 4.71)

Table 16 Maternal perception of fetal movements during the last two weeks of pregnancy stratified by gestation

As the evidence is unclear regarding what is considered a normal pattern of fetal movements at term, interaction analysis was performed between perception of fetal activity and gestational age (preterm; 28 to 36 weeks and 6 days gestation and term; equal to or greater than 37 weeks' gestation). No interaction was found for fetal hiccups or episodes of unusually vigorous movements and gestational age, but an interaction was seen

for perception of strength of fetal movement (p=0.03) and a marginally significant interaction for perception of frequency of fetal movements (p=0.07). Further analysis was therefore performed for strength and frequency of movement, stratified by gestational age *(Table 16)*.

An inverse relationship between increased frequency and strength of fetal movements was found in both gestational periods, with the strongest association in the preterm period. In preterm stillbirths (28 to 36 weeks and 6 days gestation), a perception of decreased frequency of fetal movement, compared to fetal movements remaining the same, was strongly associated with an increased risk of third trimester stillbirth aOR 8.00 (95% CI 2.14 to 29.91), whereas such an association was not seen at term. No statistically significant association was seen between decreased strength of fetal movement and stillbirth risk in either gestational period.

Discussion

Maternal perception of an overall increase in fetal activity appears to be reassuring at any gestational age after 28 weeks' gestation. We report that a maternal perception of increased fetal movements over the last two weeks, compared to no change in perception of fetal movements, was associated with a significantly reduced risk of third trimester stillbirth. Our findings do not imply that there should be concern if women do not feel an increase in strength and frequency of fetal movements in the third trimester as it was most common amongst controls for the perception of the frequency of movements to stay the same (43%) and over a third felt that the strength of movements stayed the same. Furthermore there is no evidence to support the use of antenatal testing for women who do not feel an increase in fetal movements in the last three months of pregnancy.

As has been described elsewhere, maternal perception of decreased frequency of fetal movement was found to be associated with an increased risk of third trimester stillbirth (Mangesi and Hofmeyr 2007; Sinha, Sharma et al. 2007; Tveit, Saastad et al. 2010). There is currently no clear evidence to suggest that any objective limit of reduced fetal movements (such as number of kicks within a given time frame) is of greater value at predicting poor outcome than a more subjective overall maternal perception of reduction in movement (Heazell and Froen 2008), however recent studies have shown that an increased

maternal awareness of fetal activity may improve fetal outcome (Grant, Elbourne et al. 1989; Tveit, Saastad et al. 2009).

Prior to term, women who had a perception of decreased frequency of fetal movements had a more than 8-fold increased risk of third trimester stillbirth whereas this association was not evident at term. Almost 17 percent of term controls perceived a reduction in frequency of fetal movements in the last two weeks (compared to less than 5 percent prior to term). A large study investigating fetal activity in the third trimester also reported a reduction in frequency of fetal movement as pregnancy advanced, although due to a concurrent increase in duration of movement, there was no overall reduction in total fetal activity (Roberts, Griffin et al. 1980). Our findings do not negate the importance of maternal awareness of fetal activity, Tveit and others have shown that providing information to women to increase their awareness of fetal movements, and implementing consistent guidelines for the management of decreased fetal movements, may be associated with a reduction in stillbirths (Tveit, Saastad et al. 2009).

Unusually vigorous movement

There has been minimal research into the significance of unusually vigorous fetal movements. It has been suggested, in a single report, that a sudden increase in fetal movement can be associated with acute fetal distress and poor outcome (Sadovsky and Polishuk 1977); there have been no studies to confirm or refute this speculation. We report an association between third trimester stillbirth risk and maternal perception of a single episode of unusually vigorous movement. Our data suggest that a single episode of unusually vigorous movement is associated with a greater than six fold increased risk of third trimester stillbirth.

Repeated episodes of unusually vigorous fetal movements, on the other hand, may be reassuring. In the one previous study that has reported on repeated excessive movements, no association was found with adverse outcomes (Rayburn 1982). The clinical significance of the association between unusually vigorous movements and third trimester stillbirth risk is difficult to gauge, however, as it is only in retrospect that the frequency of unusually vigorous movements can be determined.

Fetal hiccups

A novel finding of this study was the protective association between maternal perception of fetal hiccups and third trimester stillbirth risk. This is the first study to have investigated such a relationship. Fetal hiccups are easily felt by pregnant women and have been identified on ultrasound as abrupt episodes of fetal movements occurring regularly every 2 to 3 seconds (Zheng, Sampson et al. 1998). Although the physiological mechanisms underlying fetal hiccups remains unclear, they have been reported to occur throughout pregnancy and are thought to be related either to the preparation for postnatal breathing, or the development of suckling or gasping patterns (Popescu, Popescu et al. 2007), and as such are considered a sign of a normally functioning fetus. The few studies that have investigated the effect of fetal hiccups on fetal heart rate patterns support the suggestion that fetal hiccups are a normal aspect of fetal behaviour, more commonly observed in the active fetal state (van Woerden, van Geijn et al. 1989; Pillai and James 1990; Goldkrand and Farkouh 1991; Witter, Dipietro et al. 2007). Fetal hiccups have also been associated with reactive non-stress tests (Goldkrand and Farkouh 1991). Further studies are still needed however, to determine the physiological significance of fetal hiccups and their association with fetal wellbeing.

Strengths and limitations

This is the first study that has explored a relationship between a broad range of maternally perceived fetal activity and stillbirth risk. Assessment of fetal activity by maternal perception is however subject to a number of maternal physical and psychological factors (Tuffnell, Cartmill et al. 1991; Cito, Luisi et al. 2005; Saastad, Ahlborg et al. 2008). This study was able to control for some of these factors (such as maternal body weight), but not others, such as placental position. A limitation of this study is the potential for recall bias as women who experienced a stillbirth may place different significance on the perception of their baby's movements prior to death compared to those that have a live ongoing pregnancy. This is particularly relevant to the perception of decreased movements which have long been associated in the general population with poor outcome. Sadovsky and others have described a reduction in fetal movements prior to death (Sadovsky and Yaffe 1973), however, decreased fetal movements may also be a sign of actual fetal death rather than impending fetal demise. Recall bias is less likely to be a factor in relation to unusually vigorous fetal activity and fetal hiccups, as they have not previously been described in relation to stillbirth risk

Conclusion

Our study suggests that a maternal perception of increasing fetal activity (in both frequency and strength) throughout the last three months of pregnancy is a sign of fetal wellbeing. The findings also confirm the association between maternal perception of decreased fetal movement and risk of third trimester stillbirth. This is of particular significance between 28 and 36 weeks gestation, and this suggests that raising maternal awareness of fetal movements may be of benefit from as early as 28 weeks gestation. The novel finding of a strong association between maternal perception of fetal hiccups and a reduced risk of third trimester stillbirth is of interest; further research is required to confirm or refute this finding and to explore the physiological significance of fetal hiccups.

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Chapter 7

Antenatal care factors

This section presents results on the relationship between antenatal care utilisation and identification of small for gestataional age and risk of late stillbirth.

Title:

Antenatal care, identification of suboptimal fetal growth and risk of late stillbirth: findings from the Auckland Stillbirth Study.

Journal:

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Contribution

TS participated in the design and coordination of the study, carried out the data collection, conducted statistical analysis of the data and drafted the manuscript.

JT participated in the design of the study, assisted with statistical analysis and helped to draft the manuscript.

EM participated in the conception and design of the study and helped to draft the manuscript.

JZ participated in the design of the study and helped to edit the manuscript.

AE participated in the design of the study and helped to edit the manuscript.

LM participated in the conception and design of the study and helped to draft the manuscript

7.1 Abstract

Background

Stillbirth remains a major public health problem in Australia and New Zealand. The role that antenatal care plays in the prevention of stillbirth in high income countries is unclear.

Methods

Cases were women with a singleton, late stillbirth without congenital abnormality, booked to deliver in the Auckland region and born between July 2006 and June 2009. Two controls with ongoing pregnancies were randomly selected at the same gestation at which the stillbirth occurred. Data were collected through interview administered questionnaires and from antenatal records. Small for gestational age (SGA) was defined as birthweight <10th customised centile. A multivariable regression model adjusted for known risk factors for stillbirth, and adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated.

Results

155/215 (72%) cases and 310/429 (72%) controls consented to take part in the study. Accessing less than 50% of recommended antenatal visits was associated with a more than twofold increase in late stillbirth (aOR 2.68, 95%CI 1.04 to 6.90) compared to accessing the recommended number of visits. SGA babies that had not been identified as SGA prior to birth were significantly more at risk of being stillborn (aOR 9.46; 95% CI 1.98 to 45.13) compared to SGA babies that were identified as such in the antenatal period.

Conclusions

This study reinforces the importance of regular antenatal care attendance. Identification of SGA may be one way by which antenatal care reduces stillbirth.

7.2 Paper IV

Antenatal care, identification of suboptimal fetal growth and risk of late stillbirth: findings from the Auckland Stillbirth Study.

Background

Stillbirth remains a common and devastating complication of pregnancy. More than 7 in 1000 births in Australia and New Zealand result in a stillbirth (fetal death ≥ 20 weeks gestation) with more than 1 in 300 resulting in late stillbirth (death ≥ 28 weeks gestation) (Cousens et al., 2011; Laws, Li, & Sullivan, 2010: PMMRC, 2010). During the 20th century there was a significant reduction in the rate of stillbirths in high income countries, in considerable part due to improvements in antenatal care (Goldenberg, Kirby, & Culhane, 2004; Vallgarda, 2010). Unfortunately the stillbirth rate has decreased little in the last two decades (CEMACH, 2009; Cousens et al., 2011; Craig, Stewart, & Mitchell, 2004; NZHIS, 2007).

Although antenatal care attendance is associated with improved perinatal and maternal outcomes, the actual number of antenatal visits required to make a difference to perinatal mortality is unclear (Dowswell et al., 2010). No previous studies have explored the relationship between antenatal care utilisation and risk of late stillbirth in New Zealand. The model of maternity care provision in New Zealand altered significantly in the early 1990's following the Nurses Amendment Act of 1990, which resulted in a change from a predominantly doctor led to a midwifery led model of care. There have, however, been no studies which have explored the relationship between type of maternity care provider or model of care and late stillbirth risk in New Zealand.

It is unclear what specific aspects of antenatal care might be associated with reduced risk of stillbirth. A relationship has long been established between suboptimal fetal growth and risk of stillbirth (Cnattingius, Haglund, & Kramer, 1998; McCowan, George-Haddad, Stacey, Thompson, et al 2007). A small number of publications have also reported that the large majority of stillborn SGA infants are not recognised before birth, but these studies have not had comparative rates of SGA recognition antenatally in a control population of liveborn infants (Gardosi, Kady, MacGeown, et al, 2005; PMMRC, 2010)

The primary aim of the Auckland Stillbirth Study was to identify modifiable risk factors for late stillbirth. The specific aim of this analysis was to assess the relationship between antenatal care and late stillbirth risk.

Methods

All women booked to give birth in the greater Auckland region and who experienced a late stillbirth (≥28 weeks' gestation) between July 2006 and June 2009 were eligible to participate in the study. Women with multiple pregnancies and those where the baby died due to a congenital abnormality were excluded. Each case was matched with two randomly selected controls with an ongoing pregnancy from the same hospital area, and at the same gestation at which the stillbirth occurred; this allowed for an accurate comparison of the characteristics of pregnancy for cases and controls. In order to ensure appropriate control selection only women who were booked for antenatal care were included in this study.

A description of the manner in which cases and controls were identified and recruited, and other details of the methods of this study have been described previously (Stacey et al., 2011a). Data were obtained through interviewer administered questionnaires which took place soon after the stillbirth (median 25 days, interquartile range 18-39 days) or at the equivalent gestation to the stillbirth for the controls. Clinical data were collected from antenatal records.

In New Zealand, as part of the publically funded maternity care system, a Lead Maternity Care provider is chosen by the woman to take responsibility for coordinating her care throughout the pregnancy and postpartum period. The Lead Maternity Carer was categorised primarily as midwife-led or doctor-led. In order to explore the impact of different models of care, further categorisation was made, specifically; self employed midwife, hospital employed (caseloading midwife, community antenatal clinic or medical/high risk clinic), private obstetrician, and General Practitioner (GP)/shared care (GP only or shared care between the GP and community antenatal clinic). The Lead Maternity Carer was classified as that at the time of booking (initial contact with the antenatal care provider).

Gestation at the booking visit with the Lead Maternity Carer, and number of antenatal visits, were ascertained from the participants' antenatal records. There is currently no

universally accepted antenatal care utilisation index that is recommended for assessing the adequacy of care. A number of indices exist (Alexander & Cornely, 1987; Kotelchuck, 1994b), however each one adopts a different approach to the definition of adequate utilisation, based in part on local expectations of care utilisation, and they are not interchangeable (Heaman, Newburn-Cook, et al 2008). Gestation at initiation of care, the number of visits attended (gestation adjusted), and an adapted antenatal care utilisation index are therefore reported in this study.

The Perinatal and Maternal Mortality Review Committee (New Zealand) (PMMRC, 2009), and the National Institute for Health and Clinical Excellence (NICE 2003) (UK) recommend that booking with a health professional should take place prior to 10 weeks' gestation, this was therefore used as the 'gold standard' or reference category for booking gestation. In order to assess the impact of later initiation of care, a further category of booking by 20 weeks' gestation was also defined.

The number of recommended antenatal visits at each gestational age was based on the schedule proposed by the National Institute for Health and Clinical Excellence (NICE 2003), and has been generally adopted in New Zealand. The recommendation is that, by term, in an uncomplicated pregnancy, there should be 10 antenatal visits for nulliparous women and 7 for multiparous women. The NICE Clinical guideline for Antenatal Care (NICE 2003) specifies at which gestation visits are recommended. The proportion of visits attended were divided into three categories; <50% of recommended visits, intermediate (more than 50% but less than 100%) and 100% or more of the recommended number of visits.

An overall adequacy of antenatal care access was also applied using an adapted version of the Adequacy of Prenatal Care Utilization Index (Kotelchuck, 1994b) as described by Reime and others (Reime et al., 2009). Two categories were defined; 'adequate', where care was initiated in the first trimester and at least 50% of the recommended visits were attended and 'inadequate' where care was initiated after the first trimester, and/or less than 50% of the recommended visits were attended.

Customised birthweight centiles were calculated (McCowan, Stewart, et al., 2004) for all babies. SGA was defined as birthweight <10^{th} customised centile, adjusted for maternal

characteristics (ethnicity, parity, height and weight) as well as infant sex and gestation at delivery (Clausson et al 2001). Duration of pregnancy was calculated in days, based on certain date of last menstrual period, or early ultrasound. Data were collected on date of diagnosis of fetal death as well as date of birth. With stillbirths, the gestation at death may precede the gestation at diagnosis of death; post-mortem data has shown that the time of death is estimated to be within 72 hours of post-mortem in over 90% of cases (Gardosi, Mul, et al., 1998). In a study assessing the role of small for gestational age in antepartum stillbirths, Gardosi and others used a two day correction from death to delivery by reducing the gestational age of each case by two days prior to applying the gestational age specific customised centile (Gardosi et al., 1998). In this study, as we had data on the date of diagnosis of death, we used a similar two day correction, but from death to diagnosis, thus ensuring an even more conservative estimate of gestational age for stillbirths. Clinical identification of suspected small for gestational age prior to birth (cases) or prior to interview (controls) was ascertained from the antenatal records (where ultrasound was ordered specifically to assess fetal growth due to suspected small for gestational age). The method of ascertainment was the same for cases and controls.

Ethical approval was gained for this study from the Northern "X" Regional Ethics Committee.

Analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, 2004). Standard conditional regressions were used for matched case control studies using the 'proc logistic' procedure, with the 'strata' statement to control for matching. The study was powered to detect an odds ratio (OR) of 2 with 80 percent power and significance level of 5%, with a prevalence of the risk factor of 20 percent or more in the control population. A multivariable regression model was developed to include maternal variables reported to be associated with increased risk of late stillbirth, based on previous literature (age, Body Mass Index (BMI) (<25, 25-29.9, ≥30 kg/m^2), ethnicity, parity (0, 1-3, ≥4), smoking (smoker/non-smoker), and socio-economic status (most deprived/other, based on the New Zealand Deprivation status (Salmond et al 2007)). Statistical significance in multivariable analysis was defined at the 5 percent level. Odds ratios (OR) and adjusted odds ratios (aOR) with 95 percent confidence intervals (CI) were used to estimate risk.

Results

155/215 (72.1%) cases and 310/429 (72.3%) controls consented to take part in the study. The characteristics of the women who agreed to take part and those that declined were not significantly different (Stacey et al., 2011b). Eighty nine (57.4%) stillbirths occurred at term (≥ 37 weeks' gestation) and 39.4% of all stillbirths were classified as unexplained. No significant difference was found between past adverse perinatal outcome and medical history of cases and controls (including; prior fetal loss, SGA, caesarean section, pre-gestational diabetes and essential hypertension), although it should be noted that the study was underpowered for most of these problems.

Gestational age at booking with a maternity care provider was not found to be associated with risk of late stillbirth (*Table 17*). In contrast, adequacy of the number of antenatal visits was associated with risk of late stillbirth. After adjustment for known confounders, compared to women who received the recommended number of antenatal visits, women who received less than 50% of visits were found to have an almost threefold increased risk of late stillbirth (aOR 2.68, 95% CI 1.04, 6.90).

Antenatal care	Cases n %	Control n %s	OR (95% CI)	aOR* (95% CI)
Gestation at Booking with Lead Maternity Carer**				
≤ 10 weeks	43 (27.7)	84 (27.1)	1.00 -	1.00 -
10-20 weeks	82 (52.9)	178 (57.4)	0.94 (0.61 to 1.45)	0.78 (0.46 to 1.30)
>20 weeks	30 (19.4)	45 (14.5)	1.39 (0.76 to 2.53)	0.63 (0.28 to 1.39)
Number of antenatal visits#				
100% of recommended visits	116 (74.8)	267 (86.1)	1.00 -	1.00 -
Intermediate	18 (11.6)	22 (7.1)	1.81 (0.94 to 3.48)	1.40 (0.68 to 2.88)
< 50% of recommended visits	19 (12.3)	14 (4.5)	3.73 (1.64 to 8.45)	2.68 (1.04 to 6.90)
Adequacy of antenatal care Index##				
Adequate	83 (54.3)	182 (59.7)	1.00 -	
Inadequate	70 (45.7)	123 (40.3)	1.21 (0.83 to 1.78)	0.78 (0.50 to 1.23)

Table 17 Antenatal care utilisation and risk of late stillbirth

** Adjusted for maternal age, BMI, ethnicity, smoking, parity, social deprivation, past medical and obstetric history*

*** 3 controls missing*

 # 7 Controls missing

Adequate care: care initiated in the first trimester and atleast 50% of recommended visits attended

Although there was no significant association found between risk of late stillbirth and intermediate antenatal care attendance (that is less than the recommended number of visits, but more than 50% of visits) a trend analysis showed a significant relationship between

reduced antenatal care attendance and risk of late stillbirth (p=0.0005). The modified index of overall adequacy of care, which incorporated both gestation at initiation of care and number of visits attended, showed no relationship with risk of late stillbirth.

137 (88.4%) cases and 274 (88.4%) controls booked with a midwife as Lead Maternity Carer, the majority being self-employed midwives (*Table 18*). No association was found between type or model of Lead Maternity Carer and risk of late stillbirth.

36.8% (57/155) cases were SGA at birth compared to 7.1% (22/310) controls; babies that were SGA at birth had a significantly increased risk of stillbirth compared to babies that were not (aOR 9.67; 95% CI 4.68 to 19.96). Of the babies that weighed less than the 10th customised centile at birth, 12.2%(7/57) of those that were stillborn were suspected to be SGA prior to birth/interview compared with 31.8% (7/22) of the SGA infants in the control mothers, p=0.04. Those infants that were not identified as being SGA prior to birth/interview were nine times more likely to be stillborn compared to those that were (aOR 9.46; 95% CI 1.98 to 45.13) (*Table 19*).

Antenatal Care Provider	Cases		Controls		OR (95% CI)		aOR* (95% CI)	
	n	%	n	%	OR	95% CI	aOR	95% CI
Lead Maternity Carer - type								
Doctor	18	11.6	36	11.6	1.00	-	1.00	-
Midwife	137	88.4	274	88.4	1.00	(0.53 to 1.90)	1.17	(0.52 to 2.64)
Lead Maternity Carer – model								
Self employed midwife	82	52.9	185	59.7	1.00	-	1.00	-
Hospital	47	30.3	73	23.6	1.47	(0.92 to 2.36)	1.14	(0.65 to 2.02)
Private obstetrician	10	6.5	26	8.4	0.85	(0.37 to 1.97)	0.90	(0.35 to 2.30)
GP/Shared care	16	10.3	26	8.4	1.43	(0.69 to 2.97)	0.83	(0.34 to 2.04)

Table 18 Type and model of antenatal care provider and risk of late stillbirth

* Adjusted for maternal age, BMI, ethnicity, smoking, parity, social deprivation

Discussion

This is the first study to examine an association between antenatal care utilisation and risk of late stillbirth in New Zealand. We found that inadequate antenatal care attendance, but not gestation at initiation of care, was associated with late stillbirth risk. Type or model of maternity care provider was not found to be associated with risk of late stillbirth.

Customised birthweight centile	Cases		Controls		OR (95% CI)		aOR* (95% CI)	
	n	%	n	%	OR	95% CI	aOR	95% CI
≥10th centile	98	63.2	288	92.9	0.44	0.15 to 1.29	0.45	0.14 to 1.48
<10th suspected prior to birth/interview	7	4.5	7	2.3	1.00	-	1.00	-
<10th not suspected prior to birth/interview	50	32.3	15	4.8	9.57	2.20 to 41.55	9.46	1.98 to 45.13

Table 19 Identification of small for gestational age and risk of late stillbirth

* Adjusted for maternal age, BMI, ethnicity, smoking, parity, social deprivation

The optimal gestation at which antenatal care should begin is not well established; the Ministry of Health in New Zealand recommend that antenatal care be commenced by 10 weeks' gestation (PMMRC, 2009). In this study, however we found no association between gestational age at booking and late stillbirth risk. Although an association has previously been described, the findings have been inconsistent and difficult to interpret. Some studies that found a significant relationship between risk of stillbirth and late initiation of care, combined late initiation of care with no care, thus making it difficult to determine whether it was the lack of overall care, or the gestation at initiation of care that was of significance (Getahun, Ananth, & Kinzler, 2007; Tucker, Ogutu, Yoong, Nauta, & Fakokunde, 2009). Other studies have also found no association between gestational age at onset of care and risk of stillbirth (Huang et al., 2000). Further research is required to clarify these relationships.

There is no high quality evidence as to what should be the optimal schedule of antenatal visits for low-risk women. It has been shown that a relatively reduced schedule of visits in high income countries (reducing from 13 to 14 visits during pregnancy to an average 8 to 9 visits) had no significant impact on perinatal mortality (Dowswell et al., 2010). However inadequate antenatal care utilisation has been associated with an increased risk of poor perinatal outcomes, including an increase in risk of stillbirth (Cruz-Anguiano et al., 2004; De Lange et al., 2008; Gao, Paterson, Carter, & Percival, 2006; Huang et al., 2000; Kotelchuck, 1994a; Raatikainen, Heiskanen, & Heinonen, 2007). Our study supports the finding that it is the substantial under utilisation of care (rather than a relative reduction in the number of visits) that is associated with increased mortality. This finding was independent of other factors associated with reduced utilisation of care such as social deprivation and high parity. Previous studies may have overestimated the strength of this

association as many have not adjusted for gestational age (Cruz-Anguiano et al., 2004; De Lange et al., 2008); stillbirth is associated with preterm birth, and therefore comparing antenatal utilisation with live births, predominantly born at term, will exaggerate any association. In this study we not only matched for gestational age but also determined adequacy of care throughout the third trimester.

The lack of association seen between overall adequacy of care as defined by an adapted Adequacy of Prenatal Care Utilization index is likely due to the lack of association of booking gestation and late stillbirth risk in our population.

In New Zealand the Lead Maternity Carer is responsible for the provision and coordination of maternity care. This study found that there was no significant difference in risk of late stillbirth between midwife-led or doctor-led care, or different models of care. The univariable risk of stillbirth was remarkably similar, however we cannot exclude that this may be due to lack of power due to the relatively small numbers involved, in particular in doctor-led care. Our data are consistent with previous studies that have found that there was no significant difference in perinatal mortality with midwife-led care compared to other models of maternity care (Bai, Gyaneshwar, & Bauman, 2008; Hatem, Sandall, Devane, Soltani, & Gates, 2009).

Suboptimal fetal growth has long been associated with increased risk of stillbirth (Cnattingius et al., 1998; McCowan et al., 2007), particularly when SGA is defined using customised rather than population based birthweight centiles (Clausson, Gardosi, Francis, & Cnattingius, 2001). Unfortunately in routine antenatal care the majority of SGA babies are not currently indentified antenatally (Gardosi, Chang, Kalyan, Sahota, & Symonds, 1992). In this study SGA infants were more likely to be identified before birth in control mothers compared with those mothers with stillborn infants. This is consistent with a previous study that found that antenatal identification of SGA reduced the risk of adverse outcomes (including the risk of stillbirth) (Lindqvist & Molin 2005). Antenatal identification of suspected SGA in this study was ascertained up until the time of birth for cases, and up until the time of interview for controls; it is therefore possible that more live-born babies that were SGA at birth, would additionally have been identified as SGA antenatally (between the time of interview and birth) but not classified as such in this study. This means that, if anything, we may have underestimated the association between

lack of identification of suboptimal fetal growth and risk of stillbirth. Women with stillborn infants in this study were more likely to be obese than control women (Stacey et al., 2011a) and this may have contributed to the reduced rate of antenatal detection of SGA, however when adjustment was made for potential confounders (including maternal body mass index), there was minimal change in the magnitude of association between lack of antenatal detection of SGA and stillbirth risk.

It has previously been found that utilisation of customised antenatal growth charts can improve the rate of antenatal detection of SGA (Gardosi et al., 1992; Gelbaya & Nardo, 2005) and this tool has been recommended for use in routine antenatal care in New Zealand (PMMRC, 2010). However, if women do not regularly attend antenatal care then it is much harder to perform adequate clinical assessment of fetal growth. It is likely that the effect of antenatal care on reduced stillbirth risk is multifaceted and that identification of suboptimal fetal growth is just one factor, and that further aspects of risk screening and management also play an important role. As Froen argues, many risk factors for antepartum stillbirth can be identified by basic antenatal care (Froen et al., 2001). Further studies which explore the impact of specific antenatal practices on stillbirth risk may help our understanding of what other elements of antenatal care are of importance.

Previous research has shown that being unbooked and receiving no antenatal care is associated with a number of adverse outcomes, in particular preterm birth, low birthweight babies (Tucker et al., 2009), and perinatal mortality (Raatikainen et al., 2007). However, in order to ensure that there was appropriate control selection; women who were not registered to give birth within the region and also those who received no antenatal care were excluded from this study and therefore we were not able to explore the impact of total lack of antenatal care on the risk of stillbirth in this study.

Conclusion

This study reinforces the importance of regular antenatal care attendance for reducing the risk of late stillbirth. Antenatal identification of SGA infants may be one of the ways by which regular antenatal care reduces the risk of stillbirth. Further studies which explore the impact of other antenatal practices on stillbirth risk may help our understanding of what specific elements within antenatal care are of most importance.

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Chapter 8

Maternal sleep practices

This chapter present results relating to maternal sleep practices and the risk of late stillbirth.

Title:

Association between maternal sleep position and risk of late stillbirth: a case control study

Journal:

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Authors

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Contribution

TS participated in the design and coordination of the study, carried out the data collection, conducted statistical analysis of the data and drafted the manuscript.

JT participated in the design of the study, assisted with statistical analysis and helped to draft the manuscript.

EM participated in the conception and design of the study and helped to draft the manuscript.

JZ participated in the design of the study and helped to edit the manuscript.

AE participated in the design of the study and helped to edit the manuscript.

LM participated in the conception and design of the study and helped to draft the manuscript

8.1 Abstract

Objectives To determine whether snoring, sleep position and other maternal sleep practices are associated with late stillbirth risk.

Design Prospective population-based case control study.

Setting Auckland, New Zealand

Participants Cases: 155 women with a singleton late stillbirth (at or greater than 28 weeks' gestation) without congenital abnormality, born between July 2006 and June 2009 and booked to deliver in Auckland. Controls: 310 women with single ongoing pregnancies and gestation matched to that at which the stillbirth occurred. Multivariable logistic regression adjusted for known confounding factors.

Main outcome measure Maternal snoring, daytime sleepiness (measured with the Epworth sleepiness scale), and sleep position at the time of going to sleep and on waking (left side, right side, back and other).

Results: The prevalence of late stillbirth in this study was 3.09/1000 births. No relationship was found between snoring or day time sleepiness and risk of late stillbirth. However, women who slept on their back or on their right side on the last night (prior to stillbirth or interview) were more likely to experience a late stillbirth compared to women who slept on their left side (adjusted odds ratio for back sleeping 2.54 (95% CI: 1.04, 6.18); and for right sleeping 1.74 (95% CI: 0.98, 3.01)). The absolute risk of late stillbirth for women who went to sleep on their left was 1.96/1000 and 3.93/1000 for women who did not go to sleep on their left. Women who got up to the toilet once or less on the last night were more likely to experience a late stillbirth compared to women who got up more frequently (aOR 2.28; (95% CI: 1.40, 3.71). Women who regularly slept during the day, in the last month, were also more likely to experience a late stillbirth compared to those who did not (aOR 2.03 (95% CI 1.26, 3.27).

Conclusions This is the first study to report maternal sleep related factors as risk factors for stillbirth and these findings require urgent confirmation in further studies.

8.2 Paper V

Association between maternal sleep position and risk of late stillbirth: a case control study

Background

The death of a baby before birth is a tragedy for the family and wider community. In high income countries more than one in two hundred births result in a stillbirth (Reddy, Laughon et al. 2010; Cousens, Blencowe et al. 2011). Stillbirth therefore remains an important public health issue, with little change in its rate over the last two decades (CMACE 2011; Cousens, Blencowe et al. 2011). Many studies have examined risk factors for stillbirth, but they have often been population based retrospective studies (Salihu, Wilson et al. 2008; Gray, Bonellie et al. 2009; Willinger, Ko et al. 2009) that have been unable to explore a broad range of potential risk factors, in particular those relating to maternal lifestyle and personal habits.

Around a third of a person's life is spent asleep, but there has been little research on the potential impact of sleep practices on the developing fetus. Previous studies have reported an association between sleep disordered breathing and pregnancy complications such as pre-eclampsia and preterm birth (Louis, Auckley et al. 2010), but exploration of a potential association with stillbirth has been limited to a single case report(Brain, Thornton et al. 2001). We and others have described a dose dependent relationship between maternal obesity and stillbirth risk (Nohr, Bech et al. 2005; Salihu, Dunlop et al. 2007; Stacey, Thompson et al. 2011a) but the mechanisms underlying this association are not understood. Obesity is also associated with sleep disordered breathing (Maasilta, Bachour et al. 2001). It is therefore possible that sleep disordered breathing is one of the mechanisms underlying the association between obesity and stillbirth risk.

Maternal supine position is associated with sleep disordered breathing (Mador, Kufel et al. 2005) and in late pregnancy, has also been associated with reduced maternal cardiac output (Kinsella and Lohmann 1994), however the impact of maternal position during sleep and risk of stillbirth is not known. There have been no reports of other sleep related practices and risk of stillbirth.

The broad aim of the Auckland Stillbirth Study was to identify potentially modifiable risk factors for late stillbirth (≥28 weeks' gestation). We explored a range of factors relating to women's health and behaviour during pregnancy, including general health, socio-economic factors, diet, exercise and maternal sleep practices (Stacey, Thompson et al. 2011b). We hypothesised that sleep disordered breathing and maternal supine sleep position would be associated with increased risk of late stillbirth. We also investigated the relationship between risk of late stillbirth and other sleep related practices, specifically; regular daytime sleep, duration of sleep, and getting up during the night.

Methods

Women who gave birth to a stillborn baby at or after 28 completed weeks of gestation in the Auckland region between July 2006 and June 2009 were invited to participate in the Auckland Stillbirth Study (Stacey, Thompson et al. 2011b). Stillbirth was defined as the birth of a baby that died in utero, either during the antenatal or intrapartum period. Cases were ascertained weekly from key clinicians in the respective centres and from hospital birth records checked on a regular basis (by TS). A national system for perinatal data collection commenced in New Zealand (PMMRC 2009) on the same date as recruitment began; cases were compared with this registry to ensure complete ascertainment.

Women were excluded if their baby had died from a congenital abnormality, was from a multiple pregnancy, or if they had not been booked to deliver their baby within the Auckland region (which consists of three district health boards). Two controls were randomly selected from the pregnancy registration list of the District Health Board in which the stillbirth occurred, with the same exclusion criteria as the cases. Controls were matched to cases by gestation, thus ensuring that the controls were representative of the antenatal population at the same gestation at which the stillbirth occurred.

Data were obtained through interviewer administered questionnaires in the first few weeks following stillbirth. For the controls, interviews occurred at the equivalent gestation of pregnancy as that of the matched case. Participants were not aware of any of the specific research questions related to risk factors for stillbirth. As there are no validated tools for screening for sleep disordered breathing in pregnancy, snoring and daytime sleepiness were used as proxy indicators for sleep disordered breathing (Izci, Martin et al. 2005). Participants were asked whether they regularly snored prior to pregnancy or during

pregnancy. The Epworth Sleepiness Scale was used to determine the general level of daytime sleepiness (Johns 1991).

Specific questions were asked about maternal sleep position both at the time of going to sleep and on waking. Sleep position was classified as left side, right side, back and other ('other' included front, sitting up, both sides, and unsure/don't remember). The time periods for which data were collected were: prior to the pregnancy; in the last month of the pregnancy; in the last week; and the last night. The last night was the night before when the woman thought that her baby had died, or for the controls, the night before the interview.

Participants were also asked whether they regularly slept during the daytime in the last month. Further questions were asked about the usual duration of sleep at night during the last month and frequency of getting up to the toilet. The reference duration of sleep was defined as 6-8 hours at night (Youngstedt and Kripke 2004; Chen, Wang et al. 2006) and sleep duration was therefore categorised as: < 6 hours; 6 to 8 hours; and > 8 hours. Data were collected on frequency of waking in the night and getting up to the toilet at night. A strong correlation was seen between these two variables and therefore only getting up to the toilet at night is presented here.

Demographic data and information on other potential confounding factors were collected during the interview, specifically; maternal age, ethnicity, parity, smoking status, booking body mass index and social deprivation level. Ethnicity was self assigned and a single ethnicity was applied using a system of prioritisation as described by the New Zealand Ministry of Health (Ministry of Health 2004). Smoking status was defined as having smoked at any time during the pregnancy. Maternal body mass index was calculated from the earliest known weight taken in pregnancy and maternal height, measured at interview. Social deprivation level was derived from the address at which the participant lived, based on the 2006 New Zealand census data, with category 1 being the least deprived and category 5 the most deprived (Salmond, Crampton et al. 2007). Detailed information about methodology has previously been reported (Stacey, Thompson et al. 2011b).

Analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc 2004). We used standard conditional regressions matched case control studies using the 'proc logistic' procedure, with the 'strata' statement to control for matching. We compared continuous variables with student's *t* test and used the Pearson correlation coefficient to assess the correlation between variables. There were no missing data for the variables included in this paper. A multivariable regression model was developed to include maternal variables reported to be associated with increased risk of stillbirth, based on previous literature (age, body mass index, ethnicity, parity, smoking and socio-economic status). The study was powered to detect an odds ratio (OR) of 2 with 80% power and significance level of 5%, with a prevalence of the risk factor of 20% or more in the control population. Statistical significance in multivariable analysis was defined at the 5% level. Global Chi-square statistics were used to assess the significance of variables in the models and individual level odds ratios were estimated for each category in comparison to a reference category, defined as the category hypothesised to have the lowest risk.

Results

During the study period 215 eligible women experienced a late stillbirth, giving a prevalence of late stillbirth of 3.09/1000 births. Of these 215 women 155 (72%) consented to participate, as did 72% (310/429) of the eligible controls and there were no significant differences in ethnicity, age or parity between those who consented and those who declined (Stacey, Thompson et al. 2011b). The overall post mortem rate was 47% (73/155). The most common classification for late stillbirth (based on the Perinatal Society of Australia and New Zealand Perinatal Death Classification System (PSANZ 2009)) was 'unexplained antepartum death' (Stacey, Thompson et al. 2011b). Women with late stillbirth were more likely to be obese, socioeconomically deprived, to smoke and be of high parity compared with controls (*Table 20*). Detailed analysis of these factors has been published previously (Stacey, Thompson et al. 2011a).

No association was seen between risk of late stillbirth and self reported snoring, either before or during pregnancy; 69/155 (44.5%) women who experienced stillbirth and 130/310 (41.9%) of controls reported snoring during pregnancy, adjusted odds ratio 1.12 (95% confidence interval 0.75 to 1.67).There was also no difference found between levels

of daytime sleepiness; with a mean (standard deviation) Epworth Sleepiness Scale score of 5.9 (4.1) for cases and 5.6 (3.8) for controls (p=0.51).

	Cases n=155 (%)	Controls n=310 (%)	p value
Maternal age			χ^2=0.56 p=0.75
<20	10 (6.5)	24 (7.7)	
20-34	113 (72.9)	216 (69.7)	
≥35	32 (20.7)	70 (22.6)	
Maternal ethnicity			χ^2=6.67 p=0.08
Māori	19 (12.3)	46 (14.8)	
Pacific	48 (31.0)	67 (21.6)	
European	55 (35.5)	139 (44.8)	
Other	33 (21.3)	58 (18.7)	
Parity			χ^2=11.88 p=0.003
0	77 (49.7)	144 (46.5)	
1-3	62 (40.0)	156 (50.9)	
≥4	16 (10.3)	10 (3.2)	
Social deprivation level			χ^2=6.25 p=0.01
1-4	91 (58.7)	218 (70.3)	
5 (most deprived)	64 (41.3)	92 (29.7)	
Maternal body mass index (at booking)			χ^2=9.72 p=0.008
<25	55 (35.5)	156 (50.3)	
25-29.9	39 (25.2)	67 (21.6)	
≥30	61 (39.4)	87 (28.1)	
Smoked in pregnancy			χ^2 3.98 p 0.05
Yes	46 (29.7)	66 (21.3)	
No	109 (70.3)	244 (78.7)	

Table 20: Characteristics of study population

In univariable analysis, a significant association was found between late stillbirth risk and maternal sleep position (both on going to sleep and waking up) on the last night (*Table 21*). Maternal position on going to sleep in the last month was also associated with late stillbirth risk (p=0.05), although none of the individual odds ratios reached statistical significance in comparison to the reference category. No relationship was seen between maternal sleep position prior to pregnancy and late stillbirth risk.

The study was not able to ascertain changes in sleep position during the night, so two data points were collected, position on going to sleep and position on waking up. These two positions were found to be highly correlated (Pearson correlation coefficient r=0.72 p <0.001). The association between risk of late stillbirth and non left sleeping position was only evident in those who neither went to sleep on the left, nor woke on the left (*Table 22*). As maternal position on going to sleep is more modifiable than waking position, position on going to sleep was used in multivariable analysis.

	Cases n=155 (%)	Controls n=310 (%)	Univariable OR (95% CI)
Go to sleep position - prior to pregnancy			χ^2=0.45 p=0.93
Left side	28 (18.1)	50 (16.1)	1.00
Right side	24 (15.5)	45 (14.5)	0.97 (0.49 to 1.91)
Back	16 (10.3)	35 (11.3)	0.82 (0.38 to 1.75)
Other	87 (56.1)	180 (58.1)	0.88 (0.53 to 1.46)
Go to sleep position - last month			χ^2=7.70 p=0.05
Left side	49 (31.6)	109 (35.2)	1.00
Right side	49 (31.6)	72 (23.2)	1.51 (0.92 to 2.47)
Back	12 (7.7)	13 (4.2)	2.01 (0.87 to 4.65)
Other	45 (29.0)	116 (37.4)	0.88 (0.55 to 1.42)
Go to sleep position - last week			χ^2=7.19 p=0.07
Left side	49 (31.6)	111 (35.8)	1.00
Right side	51 (32.9)	73 (23.6)	1.56 (0.95 to 2.55)
Back	10 (6.45)	12 (3.9)	1.83 (0.76 to 4.45)
Other	45 (29.0)	114 (36.8)	0.93 (0.57 to 1.50)
Go to sleep position - last night			χ^2=12.52 p=0.006
Left side	42 (27.1)	132 (42.6)	1.00
Right side	49 (31.6)	84 (27.1)	1.88 (1.14 to 3.10)
Back	15 (9.7)	15 (4.8)	3.28 (1.46 to 7.34)
Other	49 (31.6)	79 (25.5)	2.00 (1.20 to 3.33)
Wake up position - prior to pregnancy			χ^2=1.86 p=0.60
Left side	27 (17.4)	44 (14.2)	1.00
Right side	24 (15.5)	42 (13.6)	0.92 (0.47 to 1.84)
Back	21 (13.6)	38 (12.3)	0.92 (0.45 to 1.88)
Other	83 (53.6)	186 (60.0)	0.73 (0.42 to 1.25)
Wake up position - last month			χ^2=4.78 p=0.19
Left side	41 (26.5)	86 (27.7)	1.00
Right side	43 (27.7)	65 (21.0)	1.40 (0.82 to 2.40)
Back	21 (13.6)	33 (10.7)	1.36 (0.70 to 2.67)
Other	50 (32.3)	126 (40.7)	0.84 (0.51 to 1.37)
Wake up position - last week			χ^2=4.77 p=0.19
Left side	39 (25.2)	88 (28.4)	1.00
Right side	44 (28.4)	64 (29.7)	1.56 (0.90 to 2.69)
Back	22 (14.2)	37 (11.9)	1.36 (0.70 to 2.64)
Other	50 (32.3)	121 (39.0)	0.95 (0.57 to 1.58)
Wake up position - last night			χ^2=10.08 p=0.018
Left side	31 (20.0)	106 (34.2)	1.00
Right side	45 (29.0)	72 (23.2)	2.26 (1.28 to 3.97)
Back	23 (14.8)	37 (11.9)	2.32 (1.18 to 4.56)
Other	56 (36.1)	95 (30.7)	2.11 (1.24 to 3.57)

Table 21: Maternal sleep position and risk of late stillbirth

In univariable analysis, a significant relationship was seen between sleeping regularly in the daytime and late stillbirth risk (*Table 23*), as was longer than average night time sleeping duration.

Maternal position		Cases	Controls	Univariable
Going to sleep	Waking up	n=155 (%)	n=155 (%)	OR 95% CI
Left	Left	29 (18.7)	95 (30.7)	1.00
Left	Other	13 (8.4)	37 (11.9)	1.15 (0.54 to 2.45)
Other	Left	2 (1.3)	11 (3.6)	0.60 (0.13 to 2.84)
Other	Other	111 (71.6)	167 (53.9)	2.28 (1.35 to 3.52)

***Table 22*: Changes in sleep position on the last night and risk of late stillbirth**

Getting up to the toilet infrequently (once or less) during the night was also significantly associated with late stillbirth risk in the last month, the last week and the last night of pregnancy; there was no association between frequency of getting up to the toilet during the night prior to pregnancy and late stillbirth risk.

	Cases	Controls	Univariable
	n=155 (%)	n=310 (%)	OR 95% CI
Regular sleep in the daytime (last month)			χ^2=7.08 p=0.006
No	77 (49.7)	194 (62.6)	1.00
Yes	78 (50.3)	116 (37.4)	1.78 (1.18 to 2.68)
Hours of night-time sleep (last month)			χ^2=7.79 p=0.02
< 6 hours	30 (19.4)	46 (14.8)	1.72 (0.98 to 3.01)
6-8 hours	82 (52.9)	205 (66.1)	1.00
> 8 hours	43 (27.7)	59 (19.0)	1.83 (1.14 to 2.94)
Getting up to toilet at night - prior to pregnancy			χ^2=0 p=1.00
More than once	6 (3.9)	12 (3.9)	1.00
Once or less	149 (96.1)	298 (96.1)	1.00 (0.37 to 2.74)
Getting up to toilet at night - last month			χ^2=3.37 p=0.07
More than once	89 (57.4)	205 (66.1)	1.00
Once or less	66 (42.6)	105 (33.9)	1.44 (0.97 to 2.14)
Getting up to toilet at night - last week			χ^2=5.84 p=0.02
More than once	90 (58.1)	215 (69.4)	1.00
Once or less	65 (41.9)	95 (30.7)	1.62 (1.09 to 2.41)
Getting up to toilet at night - last night			χ^2=4.80 p=0.03
More than once	86 (55.5)	207 (66.8)	1.00
Once or less	69 (44.5)	103 (33.2)	1.55 (1.04 to 2.30)

***Table 23*: Other sleep related practices and risk of late stillbirth**

After adjustment was made for a range of potential confounders, not going to sleep on the left side on the last night remained independently associated with risk of late stillbirth (*Table 24*), with sleeping on the back having the greatest risk. Compared with women who went to sleep on the left side, women who went to sleep in any other position had a twofold increased risk of late stillbirth, aOR 2.03 (95% CI: 1.24, 3.29). The absolute risk of late stillbirth in this population was 3.09/1000 (95% CI 2.70, 3.53/1000); extrapolating our results to this population would give a risk of late stillbirth for women who went to sleep on the left of 1.96/1000, (95% CI: 1.50 to 2.51 /1000) and a risk of 3.93/1000 (95% CI: 3.35 to 4.59/1000) for women who did not go to sleep on their left.

	Adjusted* OR (95% CI)
Maternal sleep position - last night	χ^2=7.77 p=0.005
Left side	1.00
Right side	1.74 (0.98 to 3.01)
Back	2.54 (1.04 to 6.18)
Other	2.32 (1.28 to 4.19)
Regular sleep in the daytime - last month	χ^2=9.23 p=0.002
No	1.00
Yes	2.04 (1.26 to 3.30)
Hours of night-time sleep - last month	χ^2=6.13 p=0.05
<6 hours	1.89 (0.98 to 3.65)
6-8 hours	1.00
> 8 hours	1.71 (0.99 to 2.95)
Getting up to toilet - last night	χ^2=9.99 p=0.002
More than once	1.00
Once or less	2.42 (1.46 to 4.00)

Table 24: Maternal sleep position, regular sleep in daytime, length of sleep and getting up to toilet at night,: multivariable analysis

**Adjusted for age, ethnicity, overweight/obesity, parity, social deprivation level, smoking and all the variables in the table.*

The relationship between regular daytime sleeping and getting up to the toilet infrequently during the last night and risk of late stillbirth persisted in the multivariate analysis (*Table 24*). After adjustment for potential confounders the length of night-time sleep was also significantly associated with risk of late stillbirth (p=0.05).

Discussion

In this case control study, we did not find an association between snoring or daytime sleepiness and late stillbirth risk. However we report a novel association between late stillbirth risk and non-left sided maternal sleep position and also with other sleep related practices.

There is no validated questionnaire for sleep disordered breathing in pregnancy. Indeed the Berlin questionnaire which is one of the best validated questionnaires for obstructive sleep apnoea has been shown to perform poorly in pregnancy (Olivarez, Maheshwari et al. 2010). We therefore used self reported snoring and daytime sleepiness as markers for sleep disordered breathing (Izci, Martin et al. 2005; Venkata and Venkateshiah 2009). However, snoring is common in pregnancy and is mostly not associated with sleep apnoea (Izci, Vennelle et al. 2006). Tiredness and reduced daytime functioning are experienced more frequently by pregnant women, not just amongst those that have sleep disordered breathing, and this may make it harder to assess the true prevalence of sleep disordered breathing within the population (Izci, Vennelle et al. 2006; Venkata and Venkateshiah 2009). Further studies are warranted to more clearly distinguish between common symptoms of pregnancy and true sleep disordered breathing.

We report that women who slept on their left side on the last night had a reduced risk of late stillbirth compared to women who slept in any other position. The risk associated with non-left sided sleep position was independent of other known risk factors for late stillbirth, such as obesity. The association between maternal sleep position and late stillbirth risk was strongest on the last night; however a trend towards significance was also seen in the earlier time periods in pregnancy.

As the absolute risk of late stillbirth for an individual pregnant woman in a high income country is relatively low (3.09/1000 in our study population), for women who did not sleep on the left side, the increased risk would still be small in absolute terms (about 3.93/100), although this finding could be important at a population level if confirmed in other studies.

As far as we are aware, there are no previous studies that have described such an association. However, there have been a number of studies that have explored the impact

of maternal position in late pregnancy on cardiac output and fetal oxygen saturation (Milsom and Forssman 1984; Carbonne, Benachi et al. 1996; Kuo, Chen et al. 1997; Jeffreys, Stepanchak et al. 2006). Because of the anatomical position of the inferior vena cava and the aorta, the enlarged uterus can exert greater pressure on these vessels when the mother is in a supine or right lateral position compared to the left lateral position, thus inhibiting venous return and decreasing uterine blood flow (Milsom and Forssman 1984). Milsom and Forssman found that there was a gradient of effect of maternal body position on cardiac output, with the greatest reduction in cardiac output in the supine followed by the right lateral position when compared to the left lateral position (Milsom and Forssman 1984). Another study which investigated the effect of supine and right and left lateral positions also found a similar gradient of effect between these maternal positions in labour and fetal oxygen saturation (Carbonne, Benachi et al. 1996). Further studies have compared maternal and physiological parameters in supine and left sided positions and have also shown adverse effects in the supine position compared with the left-sided position, such as decreased uterine blood flow (Jeffreys, Stepanchak et al. 2006) and reduced pulsatility index in the fetal middle cerebral artery (Khatib, Haberman et al. 2011).

Although daytime sleepiness was not found to be associated with late stillbirth risk, sleeping regularly in the daytime was associated. This may seem to be contradictory; but there is not a direct correlation between the two variables. Women who are able to go to sleep in the day may feel less sleepy overall. These findings may also reflect what happens during daytime sleep; for instance, women who sleep during the day may spend additional time in a non-optimal position. Data were not collected on daytime sleep position and therefore this speculation could not be tested.

An association between length of sleep and risk of late stillbirth has not previously been described. Quantity of sleep, both too little (Spiegel, Leproult et al. 1999) and too much (Youngstedt and Kripke 2004), is associated with poor health outcomes unrelated to pregnancy.

Getting up to the toilet more frequently at night was also found to be associated with an independent reduction in risk of late stillbirth. Again there have been no previous studies that have explored this association.

Strengths and limitations of study

This is the first case control study of risk factors for stillbirth which selected controls from the pregnant population, matched by gestation. This method of control selection allowed for a comparison of maternal lifestyle practices between cases and controls at a similar gestation in pregnancy. This is also the first study that has explored the potential relationship between a range of maternal sleep habits in pregnancy and late stillbirth risk.

We were not able to validate maternal sleep position in the current study but participants frequently had reference points to remember their sleep position such as: "I always faced away from the door", "I slept facing my husband" and other similar comments. Case control studies are potentially subject to differential misclassification or recall bias. Misclassification reduces the ability to detect a difference between the cases and controls. Recall bias was reduced as far as possible in this study by using a structured interview and by ensuring that participants were not aware of the study hypotheses being tested. Sleep position and getting up in the night have not previously been related to stillbirth, so it is unlikely that recall bias had a significant impact on our findings. There is also the possibility of bias due to the time length between stillbirth and interview, which was 25 days on average, compared with controls, who were asked about sleep practices on the previous night. However, findings from studies about risk factors for sudden infant death syndrome have shown that women could remember in great detail the events leading up to and around the time of their baby's death (Drews, Kraus et al. 1990; Gibbons, Ponsonby et al. 1993).

It was not always possible to be certain as to the exact timing of fetal death, and therefore there is potential that in some cases the 'last night' was not the final night before fetal death, or the night during which the baby died. However, we also saw a relationship between going to sleep position in the last month and late stillbirth risk, which is consistent with the association seen on the last night.

The recruitment rate for this study was 72% for both cases and controls. Although this is a reasonable rate of recruitment for such a study (Austin, Hill et al. 1994) and there were no significant differences in age, parity or ethnicity between those who did and those who did not consent (Stacey, Thompson et al. 2011b), there is still a possibility of selection bias in the current study population. It is also possible that there is some other, as yet unidentified.

confounding factor(s) that is associated with both the position that women choose to sleep in at night and late stillbirth risk.

This is the first time that an association has been described between maternal sleep practices and late stillbirth risk and the findings need to be treated with caution. Further studies, ideally with prospectively collected sleep data, are urgently needed to confirm or refute our findings.

Conclusions

Our study has identified a potentially modifiable risk factor for late stillbirth; women who did not sleep on their left side on the last night had a twofold increased risk of late stillbirth compared to those who slept in other positions. This is a new observation, and confirmatory studies are needed before public health recommendations can be made. However, if our findings are confirmed, promoting optimal sleep position in late pregnancy may have the potential to reduce the incidence of late stillbirth.

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Chapter 9

Discussion

9.1 Overview of discussion

This chapter will provide a conclusion to the thesis. It will be a reminder of the context of this research, examine the strengths and weaknesses of the study and provide thoughts for the future.

The first section will briefly revisit the context of stillbirth in New Zealand: how the rate has changed over the years, and how the rate in New Zealand compares to that in other high-income countries. The causes of stillbirth will then be reconsidered: which stillbirths are preventable and what aspects of risk are modifiable.

The following section will critically appraise the methods used in this study and consider its strengths and limitations. The final section will review the main findings and discuss direction for future research.

9.2 Stillbirth in New Zealand

Every year around 400 New Zealand babies (that have reached at least 20 weeks' gestation) die before birth (PMMRC 2011). This stillbirth rate of approximately one baby for every 150 births has not improved for more than 10 years (PMMRC 2011). In addition, more than half of these babies die at or after 28 weeks gestation, a gestation at which the babies would have a high chance of intact survival if live-born. New Zealand is not alone in experiencing this prevalent public health problem; as the New Zealand perinatal mortality rate is similar to that of the United Kingdom and Australia (AIHW National Perinatal Statistics Unit 2009; CMACE 2011). In 2009 in the United Kingdom there were 5.2 stillbirths at or after 24 weeks' gestation for every 1000 births, compared to 5.3 per 1000 in New Zealand (using the same definition), again with minimal change in rate since 2000 (CMACE 2011; PMMRC 2011).

In much of the world stillbirths are invisible, the deaths themselves are not recorded and they do not feature on policy or programme agendas (Lawn, Blencowe et al. 2011). The

accurate recording or 'counting' of stillbirths is the essential first step on the journey to their reduction. Through the establishment of the Perinatal and Maternal Mortality Review Committee (PMMRC), New Zealand has now developed a robust system for quantifying perinatal mortality (PMMRC 2007). The PMMRC conducts a systematic and thorough ascertainment of cases, and is also developing the capacity to investigate contributory factors and potentially avoidable deaths (PMMRC 2011). The data collection and reporting established by the PMMRC has been positively critiqued and is being used as a template for developing a similar system in Australia (personal communication, ANZSA 2011).

National datasets provide a platform for the quantification and auditing of perinatal mortality. In New Zealand the lack of denominator data is clearly limiting as there is no systematic collection of baseline national perinatal epidemiological data; without this it is difficult to interpret from the national reports the true implications of certain socio-demographic characteristics of women experiencing stillbirth. National surveys are also limited in the range of variables that can be practically collected. The Auckland Stillbirth Study was the first study in New Zealand to be able to collect a wide range of variables relating to stillbirth and provide comparison data with a control group. This study has therefore been able to identify and analyse a range of risk factors for stillbirth not previously identified and provides the 'next step' on the journey to the reduction in the rate of stillbirths in New Zealand.

9.3 Preventability of stillbirth

It may be suggested that the reason there has been no substantive change in the rate of stillbirth in high-income countries in the last decade is that there is no further room for improvement: it is not possible to prevent all deaths. However there is a variation in the rate of stillbirth, even amongst high income countries and some countries have continued to see a reduction in rates of death, in particular in rates of late stillbirth (Flenady, Middleton et al. 2011). Norway, for instance, has seen a 50% reduction in rates of late stillbirth in the last 20 years, and now has a rate of 2.2 deaths per 1000 births (in comparison to the United Kingdom and New Zealand which have a rate of 3.5 late stillbirths for every 1000 births) (Cousens, Blencowe et al. 2011). This variation in rates and trends may in part be due to differing inclusion criteria and reporting of stillbirths, but is also likely to reflect a combination of personal habits, population characteristics and

quality of care, which suggests that there is still room for further reduction in stillbirth rates in many countries. In the recent report published by the PMMRC almost 14% of perinatal deaths were considered potentially avoidable (PMMRC 2011).

Stillbirths that occur after 28 weeks' gestation (or where the baby weighs over 1000gms) can be seen, in theory, as potentially preventable as the baby has a high chance of survival if born alive (Smith and Fretts 2007). Clearly, however, some deaths are more 'preventable' than others. In low-income countries where many births take place without medical or midwifery assistance a high proportion of deaths occur during the intrapartum period; in high-income countries where few births take place unattended, high rates of intrapartum hypoxic peripartum death can be seen to indicate deficiencies in care (Fretts 2005). The death of a baby with a significant congenital abnormality, on the other hand, may be less preventable. Even risk of congenital abnormality may be influenced by socio-demographic factors; living in a deprived area has been found to be associated with an increased risk of some non-chromosomal anomalies (Vrijheid, Dolk et al. 2000). Smoking and lack of periconceptual folate intake are both associated with increased risks of congenital anomaly (Green 2002; Leonardi-Bee, Britton et al. 2011).

Unexplained stillbirth continues to be the most common classification of late stillbirth in high income countries (Smith and Fretts 2007; PMMRC 2011). It is probable that at least some of these stillbirths are preventable, however until we understand what causes the death and what factors are associated with an increased risk of death, it is not possible to make an improvement in rates of unexplained death. From 1980 to 1999 in New Zealand, intrapartum stillbirth declined by 73% and deaths from antepartum asphyxia declined by 50%; in contrast 'unspecified fetal death' (unexplained stillbirth) increased (Craig, Stewart et al. 2004).

9.4 Study methods appraised

Case-control studies are one of the most frequently used methods for epidemiological inquiry (Breslow and Day 1980). They are commonly used in the exploration of diseases or outcomes that are relatively uncommon. This observational study design allows for an economical inclusion of enough cases and corresponding controls to make the analysis meaningful. The non-randomised, retrospective nature of case-control studies, however,

limits the strength of their conclusions; they can show association, but not causality. In order to mitigate the limitations to this type of study careful attention needs to be paid to potential sources of bias in the study design, and to the role of confounding and interaction in the analysis.

The Auckland Stillbirth Study employed a case-control method as this is the most appropriate way in which to explore new risk factors for late stillbirth (a relatively uncommon outcome); a cohort study with such a broad reach would need to include tens of thousands of participants and would be expensive and time consuming.

9.4.1 Study strengths

Control selection

The simplest form of control selection is the random sampling of subjects from the study population, independent of the characteristics of the cases (Wacholder, Silverman et al. 1992). This has been the most commonly adopted method in case control studies that have explored risk factors for stillbirth, where controls have been randomly selected from all live births (Stephansson, Dickman et al. 2001; Matijasevich, Barros et al. 2006; Warland, McCutcheon et al. 2009). This approach, however, does not take into account the fact that a high proportion of stillbirths occur preterm, resulting in a substantial difference in the mean gestational age between the cases and controls. This method of control selection does not therefore account for the importance of the timing of the exposure (Hertz-Picciotto, Pastore et al. 1996).

In order to account for this, other studies have matched live-born controls to the gestational age of the case (Parker 2011; Facchinetti, Alberico et al. 2011). Although this allows for the exploration of gestation specific exposures, it introduces a bias to the analysis. Women who give birth to a preterm baby are not representative of the total pregnant population; prematurity is pathological. Small for gestational age, for instance, is strongly associated with both stillbirth and prematurity (McCowan, George-Haddad et al. 2007; Gardosi and Francis 2009). In order to mediate this potential bias, Parker and others used a method of oversampling of preterm births, to answer specific hypothesis and used a weighting system in analysis to provide a representative sample of the total population.

In order to overcome these limitations, the controls for the Auckland Stillbirth Study were randomly selected from the pregnant population and matched to the case by gestation. The median gestational age of cases and controls did not differ, and controls were representative of the whole antenatal population at the same gestation at which the stillbirth occurred. This novel approach to control selection allowed for detailed questions to be asked about aspects of the pregnancy that might be gestation specific and ensured that recall would not be affected by any intervening period of pregnancy.

Study inclusion and exclusion criteria

The inclusion of only singleton pregnancies without congenital abnormality allowed for a more focussed assessment of modifiable risk factors for late stillbirth. Congenital abnormality is clearly strongly associated with mortality; multiple pregnancies are also associated with a greater risk of perinatal mortality due, in part, to different aetiologies than singleton pregnancies (Chattingius and Stephansson 2002; Salihu, Kinniburgh et al. 2004).

Although the exclusion of women who were not booked to receive maternity care in the region did not allow for the exploration of risk associated with not registering for maternity care, it did ensure that the controls were selected from the appropriate population base; it would not have been possible to include women who were not booked for maternity care in the region in the study base from which controls were selected.

Sample size

The study was designed with 80% power and a significance level of 0.05 to be able to detect an Odds Ratio of 2, given the prevalence for a risk factor of 20%. For this a minimum of 137 cases and 274 controls were required; the actual numbers recruited for this study exceeded this (155 cases/310 controls).

Community support and participant satisfaction

The case study population comprised bereaved mothers who were experiencing perhaps the most tragic event of their life. It was essential, therefore, to ensure that the process of engaging in this research project did not compound their grief. To this end, extensive community and stakeholder consultation took place prior to and during the study period.

The following groups and individuals were consulted:

* Stillbirth and newborn death society (SANDS), Auckland
* Midwifery staff/lead maternity carers
* Managers of maternity departments in hospitals
* Māori midwifery advisor
* Bereavement care services
* Social workers working in the area of perinatal loss
* Māori midwifery team

Ongoing consultation and updates regarding the process of the study took place during the study period on a one to one basis and through newsletters, in-service education and at clinic and unit meetings. There was considerable support for this study, from health professionals and those involved in the care of bereaved parents. Feedback from participants was also positive (see Chapter 4) and demonstrates that it is not only appropriate to conduct such studies with newly bereaved parents, but it is both needed and welcomed by the community.

9.4.2 Overall study limitations

Recall bias

As with any retrospective study, there was the potential for recall bias in this study; participants for the study were recruited prospectively, however the collection of exposures was retrospective. Recall bias was reduced by the use of a structured interview and by ensuring that the participants were not aware of specific study hypotheses that were being investigated. The controls were pregnant at the time of interview, whereas the cases had already given birth. The cases therefore had to recall aspects of their pregnancy from approximately 2-4 weeks previously (the median time between stillbirth and interview was 25 days), whereas with the controls, the recall period was shorter. This may be ameliorated by the fact that the events surrounding the death of a baby (including the pregnancy itself) are often indelibly remembered for the mother, whereas for the controls one week can blur into another. Similar studies that explored risk factors for sudden infant death syndrome found that a five week interval between the death of the infant and the interview did not influence the accuracy of the results (Drews, Kraus et al. 1990; Gibbons, Ponsonby et al. 1993). It would not have been appropriate to interview the women in the days just

following their bereavement and the grief process itself may have impacted upon recall so close to the death.

Sample size

Although the sample size recruited was slightly greater than the initial estimate, it still did not allow for the exploration of certain factors that were either less prevalent in the study population than 20% (such as illicit drug use), or that were not as strongly associated with late stillbirth (with an OR of less than two) (such as smoking). The sample size was also insufficient to enable the analysis of the interaction between variables, such as sleep position and other sleep related practices.

Recruitment

The overall rate of recruitment for this study was over 72% and there was no significant difference between key characteristics of cases and controls. There was a difference, however, in the rate of recruitment by ethnicity; overall 82% of European women consented to take part in the study compared to 58% of Māori women. Māori women who had experienced a stillbirth were the group least likely to consent to take part in the study (48%). This variation in rate of recruitment may have led to a degree of selection bias.

Post-mortem rate

Perinatal autopsy or post-mortem has been shown to provide valuable information on cause of stillbirth (Saller, Lesser et al. 1995; Faye-Petersen, Guinn et al. 1999). Studies have shown that a post-mortem can provide additional information or change the diagnosis in 22% to 76% of cases (Gordijn, Erwich et al. 2002) and therefore post-mortem remains the gold standard for investigation of perinatal death (Lyon 2004; Silver and Heuser 2010). Seeking consent for post-mortem can be difficult and there are many personal and cultural reasons that influence an individual's decision to consent to a postmortem on their baby (McHaffie, Fowlie et al. 2001; Rankin, Wright et al. 2002). Rankin and others found that 14% of those women who had refused a post-mortem regretted their decision, compared to 7% of those who had consented to a post-mortem (Rankin, Wright et al. 2002).

In New Zealand in 2009 only 41% of stillbirths underwent a full post-mortem examination (PMMRC 2011). This study did not have the resources to provide additional investigations following stillbirth and was reliant on local clinicians to gain consent for post-mortem. A slightly higher proportion of all stillbirths (47%) in the study underwent post-mortem.

Fifty seven percent of 'unexplained antepartum deaths' did not have a post-mortem, and might therefore be more appropriately described as unexplored deaths rather than unexplained (Measey, Charles et al. 2007).

9.5 Review of findings and implications

The Auckland Stillbirth Study aimed to identify and quantify risk factors for late stillbirth in Auckland. It also aimed to identify novel, modifiable risk factors with the goal of eventually reducing the incidence of late stillbirth in New Zealand. The following section provides a summary of key findings and their implications:

9.5.1 Socio-demographic factors

Maternal age

This study found no association between maternal age and late stillbirth risk. There is, however a large body of evidence that suggests that there is a J shaped relationship between maternal age and risk of late stillbirth, with the association becoming stronger with advancing age over 40 (Astolfi, De Pasquale et al. 2005; Wilson, Alio et al. 2008). It is unclear why no association was found in this study; one speculation is that the screening of women over 35 years at term for additional risk factors, and low threshold for induction of labour in two of the three DHBs studied, may have mitigated the risk (Fretts, Elkin et al. 2004). Teenage mothers have also been shown to be at increased risk of stillbirth in national and international reports (CMACE 2011; PMMRC 2011), although it is likely that confounding factors such as smoking and socio-economic status have a significant impact on these findings.

Research implications

The association between advanced maternal age and stillbirth risk is now well established from the international literature, especially at term and beyond; future studies should investigate the effect of specific screening and pregnancy management regimens on risk of stillbirth in older mothers.

Maternal Body Mass Index

Women who had an early pregnancy BMI of 30 kg/m^2 or greater were found to have twice the risk of late stillbirth compared to women who had a BMI of less than 25 kg/m^2.

Women who were overweight (BMI 25 kg/m^2 to 29.9 kg/m^2) also had an increased risk of stillbirth compared to women who had a BMI of less than 25 kg/m^2, although to a lesser degree (70% increased risk). These findings are consistent with previous studies which show a similar dose-related association between high maternal BMI and increased risk of stillbirth (Stephansson, Dickman et al. 2001; Salihu, Dunlop et al. 2007). There is a high prevalence of obesity throughout high-income countries, and the rate continues to rise (James, Rigby et al. 2004). Maternal overweight and obesity is one of the most important potentially modifiable risk factors for late stillbirth.

Research implications

Although it is clear that maternal BMI has a significant impact on perinatal outcomes, the mechanism(s) by which obesity increases the risk of stillbirth remains uncertain. More research is needed to determine the causal mechanism(s) relating to obesity and perinatal outcome and to what interventions, before and during pregnancy, are most effective in supporting women to reach optimal weight for a healthy pregnancy (Krishnamoorthy, Schram et al. 2006). Further study into the role of weight gain in pregnancy and risk of stillbirth is also required.

Maternal ethnicity

On univariable analysis there was a disparity in late stillbirth risk by maternal ethnicity; Pacific ethnicity was found to be associated with an 80% increased risk of late stillbirth compared to European ethnicity, which is consistent with other reports from New Zealand (PMMRC 2011). However, once adjustment had been made for known confounding factors, in particular maternal BMI, parity, marital status and living in a deprived area, this association was no longer seen. The disparity in stillbirth risk experienced by Pacific women can therefore be attributed to other factors such as obesity and high parity. This is an important finding in guiding the development of preventative strategies for reducing stillbirth in this community as it enables the identification of subgroups of women who are at greater risk.

After adjustment for known confounding factors, Māori women were found to have a reduced risk of late stillbirth compared to European women (aOR 0.37 95% CI: 0.16, 0.90). In contrast, national New Zealand data has shown that Māori women have a significantly increased risk of stillbirth compared to European women (PMMRC 2010;

PMMRC 2011). These national data include all stillbirths from 20 weeks' gestation and adjustment is not made for confounding factors such as smoking and living in a deprived area. Māori women have the highest rate of smoking in New Zealand; in 2007, 45% of Māori women smoked in pregnancy, compared to 14% of European women (Dixon, Aimer et al. 2009). There is also evidence that Māori women are more at risk of 'early' stillbirth (prior to 28 weeks gestation) than of late stillbirth (ADHB 2010), and that there is therefore a different distribution of risk by gestational age. Finally, as only 48% of Māori women who had a stillbirth and were eligible to take part in the study consented to participate, it may be that there was a degree of selection bias.

Research implications

This is the first study in New Zealand which has been able to examine in detail the reasons for the ethnic disparity in rates of stillbirth. Further research is required to determine the most effective way of reducing the prevalence of obesity, high parity and smoking in these communities and how to provide the most appropriate and accessible maternity care to close the gap in outcome between different ethnic groups in New Zealand.

Parity

Women having their first baby were found to have an almost 80% increased risk of late stillbirth. This finding is consistent with the existing literature and as primiparity accounts for around 44% of births in New Zealand (NZHIS 2007), it constitutes a significant contribution to the overall rate of stillbirth. Primiparity is not 'preventable' or 'modifiable', but an awareness of the associated risk may encourage vigilance in the care of women having their first baby.

Grandmultiparous women were found to have a four-fold increased risk of late stillbirth in this study. Again this finding supports the current body of literature, which suggests that increasing parity over four is associated with an increased risk of stillbirth in a dose dependant gradient (Bai, Wong et al. 2002; Aliyu, Salihu et al. 2005).

Research implications:

Grandmultiparity was associated with one of the greatest magnitudes of effect in this study and yet the mechanism(s) by which grandmultiparity increases the risk of stillbirth have not been identified. Greater understanding of the causal pathway(s) would assist in the

development of clinical guidelines for the antenatal management of women with high parity.

Socio-economic status

There were no consistent findings in this study regarding an association between socio-economic status and risk of stillbirth. Years of education was not shown to be significantly associated with risk, living in an area of deprivation *was* related to an increase in risk of stillbirth at a univariable level, but not once adjustment had been made for related factors such as obesity and smoking. Employment in the last month and marital status (both possible proxy variables for socio-economic status) were both found to be associated with an approximately 70% increased risk of stillbirth, even after adjustment for confounding factors. These findings reflect the current variations in the existing literature (Guildea, Fone et al. 2001; Goy, Dodds et al. 2008). Assessing socio-economic disadvantage and its affect on perinatal outcome is complex; it is likely that there are many contributing factors, including health risk behaviours, environmental exposures and health care issues.

Research implications

The social gradient of health has been well described (Marmot 2003) and the higher rates of stillbirth in deprived areas (PMMRC 2011) are a continued cause for concern. In order to reduce the inequalities in these areas there needs to be an understanding of the contributory factors in specific communities and a willingness to work collaboratively within communities and between agencies to address the issues identified.

Smoking

An association between smoking and late stillbirth risk was significant in univariable analysis but was not found to be so in the multivariable analysis. A causal relationship between maternal smoking and poor perinatal outcomes, including stillbirth, is well established (Salihu, Sharma et al. 2008). The lack of association in this study should be treated with caution, as it may be that the study did not have enough power to detect a significant but smaller magnitude of effect and an aOR of 1.54 and 95% confidence interval (CI) of 0.88-2.87 may be consistent with findings from other larger studies which found that women who smoked between one and nine cigarettes a day had a 40% increased risk of stillbirth compared to women who did not smoke; OR of 1.4 (95% CI; 1.1, 1.9) (Stephansson, Dickman et al. 2001). Other investigators have also found that the

association between smoking and risk of stillbirth was more marked at preterm gestations and decreased nearer term (Raymond, Cnattingius et al. 1994).

Research implications:

Smoking in pregnancy remains one of the most significant modifiable risk factors for poor perinatal outcome. New Zealand has one of the lowest overall rates of smoking in the OECD, however there are significant disparities in the rates of smoking between different ethnic groups; 48% of Māori women smoke, compared to 21% of European women and 5% of Asian women (Ministry of Social Development 2010). Future research needs to determine more effective cessation programmes in order to reduce the high rates of smoking prevalence amongst Māori women (Glover and Kira 2011).

9.5.2 Fetal activity

Perception of decreased fetal movements

This study confirmed the association between maternal perception of reduced fetal activity and risk of stillbirth (Rayburn 1982; Tveit, Saastad et al. 2010). It also confirmed that it was not normal for women to perceive a reduction in fetal movement at term. Maternal perception of fetal activity has long been used as an indicator for fetal wellbeing, and reduced perception of movement is considered an indicator of fetal compromise (Froen 2004).

Research implications

The formal methods for counting or quantifying reduced fetal movements that have currently been evaluated have shown a low sensitivity for poor perinatal outcome (Froen, Heazell et al. 2008). Further study is required to determine which aspects of fetal activity are most strongly associated with good and bad outcomes. There is also still a lack of evidence as to the optimal assessment and management of women who present with a perception of reduced fetal movements (Heazell, Sumathi et al. 2005; Froen, Heazell et al. 2008).

Perceptions of other fetal activity

A single episode of unusually vigorous movement was found to be associated with a greater than six fold increased risk of late stillbirth. The only previous report on such an

observation speculated that a sudden increase in fetal movement may be an indicator of fetal distress (Sadovsky and Polishuk 1977).

Women who did not perceive their baby to have had hiccups during the last two weeks also had a more than threefold increased risk of late stillbirth. It is unclear why this might be, although they have been reported to occur throughout pregnany and to be associated with normal fetal behaviour (Goldkrand and Farkouh 1991; Witter, Dipietro et al. 2007). In a letter to the American Journal of Obstetrics and Gynecology Collins suggests the contrary view and that fetal hiccups may be a sign of fetal distress (Collins 1991), however there has been no previous robust research that has explored an association between fetal hiccups and poor perinatal outcome.

Research implications:

The physiological significance of fetal hiccups has not been established. It would be interesting to have a greater physiological understanding of this common fetal activity. To date, there has been very little investigation into maternal perception of fetal activity (other than an overall assessment of reduced activity). It has been suggested that increasing women's awareness of their babies' activity in utero improves perinatal outcome (Tveit, Saastad et al. 2009); more research is required to determine the significance of maternal perception of a range of fetal activity.

9.5.3 Antenatal care factors

Utilisation of care and SGA identification

This study confirmed the importance of regular antenatal care attendance to reduce the risk of stillbirth (Raatikainen, Heiskanen et al. 2007). It found that inadequate antenatal care utilisation (less than 50% of recommended visits) was associated with an almost threefold increased risk of late stillbirth. Previous studies have shown that lack of antenatal attendance is associated with certain maternal characteristics such as; young maternal age, multiparity, less education and use of illicit drugs (Maupin, Lyman et al. 2004). When considering the provision, availability and accessibility of antenatal care, high risk women in particular need to be targeted.

Further investigation of the possible reasons for the association between reduced antenatal care attendance and poor perinatal outcome showed that women whose babies were SGA

at birth, but not identified as such antenatally, were nine times more likely to experience a late stillbirth than those whose babies were identified as being SGA prior to birth. Studies have shown that a significant proportion of SGA babies are not identified as such antentally (Gardosi, Chang et al. 1992), but that utilisation of customised antenatal growth charts can improve the rate of antenatal detection (Gelbaya and Nardo 2005). In order to improve antenatal detection of fetal growth restriction and improve perinatal outcomes, women must receive regular care and clinicians need to be alert to the optimal method for the detection of SGA.

Research implications:

Further research is required to determine the optimal number and schedule of antenatal care visits. There is also the need for further exploration of which specific aspects of antenatal care utilisation have an impact on the prevention of stillbirth.

Model of care

No significant difference was found between type of maternity care provider or model of care and risk of stillbirth in this study. This finding needs to be treated with some caution as it may be that the study did not have the power to explore such a difference; only 11% of participants had a doctor as their Lead Maternity Carer. Other studies, however, have suggested that there is the scope for maternity care to be delivered safely by a range of models (Hatem, Sandall et al. 2009).

Research implications:

There was a significant change in the organisation of maternity care in New Zealand in the early 1990s, and yet there has not been a full examination of the implications of this change. An in depth analysis of the efficacy and safety of the different models of maternity care provision would be beneficial but would require a national perinatal database which is not currently available in New Zealand.

9.5.4 Maternal sleep practices

Sleep disordered breathing

Snoring and daytime sleepiness (used as proxy markers for sleep disordered breathing) were not found to be associated with an increased risk of late stillbirth. This may, in part, be due to a limitation in the data collection. Polysomnography is the gold standard for

identifying sleep disordered breathing (Olivarez, Maheshwari et al. 2010) however due to constraints on time, expense and study design, it was not possible to conduct polysomnography on participants in this study. Although there are a number of validated sleep surveys (Facco, Kramer et al. 2010) (including the Epworth Sleepiness Scale used in this study), none of these tools have as yet been validated to assess sleep disordered breathing in pregnancy. Indeed the Berlin questionnaire which is one of the best validated questionnaires for obstructive sleep apnoea has been shown to perform poorly in pregnancy (Olivarez, Maheshwari et al. 2010). No previous studies (except for a single case report) have explored a relationship between sleep disordered breathing and risk of late stillbirth.

Research implications:

Further studies that use a range of sleep surveys and perform polysomnography on a subset of participants need to be conducted in order to develop a deeper understanding of the role of sleep disordered breathing in pregnancy and its implications for outcomes in the mother and baby.

Maternal sleep position and other sleep related practices

The potentially most significant finding in our study was that of the relationship between maternal sleep position and the risk of late stillbirth. This study found that women who did not go to sleep on their left side on the last night before fetal death (or interview) had a doubled risk of late stillbirth compared to women who went to sleep on their left side. In addition the study found that women who had got up to the toilet once or less on the last night, compared to those who got up more often, were also at higher risk of stillbirth, as were those who regularly slept during the day in the last month, compared to those who did not.

This is the first time that an association between maternal sleep practices and risk of stillbirth has been described. As discussed in the published paper on these findings (see Chapter 8), although maternal body position has not previously been associated with poor perinatal outcomes, there is evidence that it has an impact on maternal and fetal physiological parameters (Milsom and Forssman 1984; Carbonne, Benachi et al. 1996; Ryo, Unno et al. 2004; Jeffreys, Stepanchak et al. 2006; Khatib, Haberman et al. 2011), such as maternal cardiac output and fetal oxygen saturation (Milsom and Forssman 1984;

Carbonne, Benachi et al. 1996). Specifically it has been shown that maternal cardiac output in pregnant women late in pregnancy is greater in the left lateral position compared to the right lateral and even further reduced in the supine position (Milsom and Forssman 1984). This is speculated to be due to the anatomy of the lower abdomen (*Figure 4*) and the potential compression of the aorta and inferior vena cava caused by the weight of the uterus and growing fetus when the woman is in either the supine position or in the right lateral position.

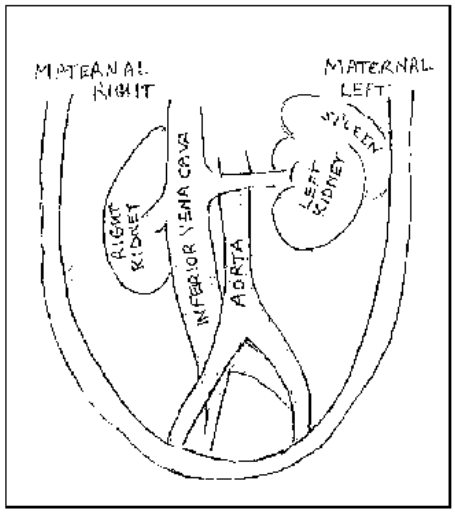

Figure 4 Main blood vessels of lower abdomen

It has also been shown that maternal cardiac output is correlated with changes in fetal heart rate pattern, with a significantly increased number of accelerations and short term variations in fetal heart rate in the left lateral position compared to the supine position (Tamas, Szilagyi et al. 2007), and that maternal body position has an impact on uterine blood flow and fetal oxygen saturation (Milsom and Forssman 1984; Khatib, Haberman et al. 2011). Although this observational study cannot determine causality, there is therefore a plausible physiological explanation for these findings that needs further investigation.

One concern regarding the validity of these findings was the ability to confirm the accuracy of the responses regarding maternal sleep position. Although there was no objective corroboration to the answers, participants used reference points such as: "*I always faced away from the door*", "*I liked to sleep facing the wall*", "*we had to change which side of the bed we slept because the other side became more comfortable*" to clarify their answers. If women could not recall or were unsure, they were classified as "other' and the rate of 'other' did not differ between cases and controls.

It has been suggested that this finding regarding maternal non-left sleep position and risk of late stillbirth could have been caused by bias; the cases were interviewed, on average, 25 days after the stillbirth and that left sided sleeping position could be a surrogate for access to educational information (Chappell and Smith 2011). This seems unlikely however, as in New Zealand there has been no previous association reported between maternal sleeping position and stillbirth, or any other poor perinatal outcome.

Another suggestion was that there was reverse causality, which is that the 'outcome' (fetal death) came before the 'risk' (Chappell and Smith 2011). This may be possible in relation to getting up to the toilet at night less frequently on the last night; if the baby had already died it may explain why the mother was less disturbed by fetal activity during that night. However getting up to the toilet in the last week of pregnancy was also significantly associated with late stillbirth risk (OR 1.62 (95% CI: 1.09, 2.41). Reverse causality is very unlikely to be associated with maternal sleeping position, as there appears no reason for the choice of position on going to sleep to be related to prior fetal death.

A further suggestion is that confounding by fetal growth restriction influenced the results of maternal sleep practices (Froen, Cacciatore et al. 2011). Froen and others argue in their rapid response to the paper published in the BMJ that a smaller uterus might result in a reduction in the normal progression in pregnancy towards the preference for a lateral sleeping position, less bladder compression, hence not having to get up to the toilet as frequently, and which would be associated with better and longer sleep duration. We conducted an additional analysis which adjusts for whether the infant was SGA at birth (*Table 25*); Model 1 shows the original analysis and Model 2 also adjusts for SGA. The point estimates and level of significance change very little.

The prevalence of non left sided sleep position in our study was 57.3% and the aOR for non-left sided sleep was 2.03; this means that the population attributable risk for non-left sided sleep was 37%. If there is a causative pathway between maternal sleep position and late stillbirth, over a third of late stillbirths may be attributable to maternal sleep position.

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Maternal sleep position - last night	χ^2=7.77 p=0.005	
Left side	1.00	1.00
Right side	1.74 (0.98 to 3.01)	1.88 (1.00 to 3.54)
Back	2.54 (1.04 to 6.18)	2.39 (0.87 to 6.53)
Other	2.32 (1.28 to 4.19)	2.25 (1.15 to 4.38)
Regular sleep in the daytime - last month	χ^2=9.23 p=0.002	
No	1.00	1.00
Yes	2.04 (1.26 to 3.30)	1.74 (1.03 to 2.96)
Hours of night-time sleep - last month	χ^2=6.13 p=0.05	
<6 hours	1.89 (0.98 to 3.65)	2.29 (1.07 to 4.87)
6-8 hours	1.00	1.00
> 8 hours	1.71 (0.99 to 2.95)	1.80 (0.97 to 3.33)
Getting up to toilet - last night	χ^2=9.99 p=0.002	
More than once	1.00	1.00
Once or less	2.42 (1.46 to 4.00)	2.39 (1.38 to 4.16)

Table 25: Association between maternal sleep practices and late stillbirth risk, Model 1 adjusts for maternal age, BMI, ethnicity, parity, smoking, social deprivation, Model 2 as 1 but also adjusts for SGA (<10th customised centile)

Research implications

These findings have important research implications, which if confirmed in future studies, could potentially impact significantly on the incidence of stillbirth, but they should currently be seen as hypothesis generating. Further studies need to be conducted as soon as possible to see if these findings are reproducible. Larger population-based case control studies are required to confirm (or refute) these findings. They need to have sufficient size to be able to determine whether:

- The effect of maternal sleep position on the risk of late stillbirth is mediated by other factors, such as fetal size or maternal body mass index.
- There is an interaction between sleep position and prolonged sleep; that is whether there is a relationship between sleep position, prolonged sleep and risk of stillbirth that is not purely additive.

- There a gestational gradient; are these sleep related factors of greater significance at different gestational ages?

A larger study is planned and is awaiting funding decisions.

Physiological studies are also required to validate the questionnaire data on maternal sleep position and to explore the impact of maternal body position (both while awake and during sleep) on fetal wellbeing. This would likely involve focussed studies, with fewer participants, and would include the use of polysomnography, maternal cardiac assessment and measures of fetal wellbeing such as fetal heart rate monitoring, Doppler studies etc. Planning is also underway for these studies.

9.6 Conclusion

This study has enhanced our understanding of the role of many known risk factors for late stillbirth, and given us greater insight into the New Zealand context. It has also identified novel and potentially modifiable risk factors for late stillbirth; confirmation of these findings is urgently required. Maternal sleep position may contribute to up to 37% of late stillbirths, and this risk is potentially modifiable. A change in maternal sleep position could have as big effect on stillbirth rates as "Back to Sleep" did on rates of sudden infant death syndrome. Stillbirth research needs to be made a priority for us to make a real impact on the current unacceptable high rate of death of unborn babies. Let us hope that the recent Lancet series highlighting the problem of stillbirth indicates that the tide is beginning to turn and that stillbirth will soon be seen as the important public health issue that it is.

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Appendix A Participant Information and consent

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

We would like to express our sincerest sympathy at the loss of your baby

TASS

The Auckland Stillbirth Study

This study seeks to gain a greater understanding of stillbirth

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We invite you to take part in this study.

Background to TASS

For every 1000 babies born in New Zealand, about 8 are stillborn. The rate has not decreased in the last 10 years either in New Zealand or overseas. There is still limited understanding of why many of these babies are dying before birth.
This study will examine standard medical factors related to stillbirth, and it will also examine the role of previously uninvestigated environmental and lifestyle factors.
Once we have a better understanding of late pregnancy stillbirth we can develop further ways to reduce the incidence of this tragic event.

The study

TASS is taking place over three years across the Auckland Region. A research midwife will contact women who have recently experienced a stillbirth (when they were 28 week's or more pregnant) to discuss the possibility of being part of the study.
A random sample of women who have an ongoing pregnancy will also be approached to act as a comparison group.

What does this study involve?

There are two main parts to TASS: a review of clinical records, and an in-depth interview.
The interview will cover a range of subjects such as sleeping habits in pregnancy, diet and exercise, as well as other lifestyle and environmental factors.
The interview will be carried out at a time and place that suits you (within the next 3 weeks). We estimate the interview will take about one to one and a half hours.

Your participation in the study

Your participation in this study is totally your choice. If you decide to be part of the study, you are free to withdraw your consent at any later time, without giving a reason.

Your care will not be altered in any way whether you do or do not decide to be part of this research.

Confidentiality

No information that could personally identify you will be used in any report from this study. A unique identification number will be assigned to your study records rather than your name, and the records will be stored in a locked filing cabinet.

Please feel free to contact the researchers if you have any questions about this study, or you would like further information.

Results of the study will be published in medical journals and discussed at local forums and a copy of the report will be sent to participants on request

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and you case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you might still not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is the result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.
If you have any questions about ACC, connect your nearest ACC office, or the investigator.

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a
Health and Disability Advocate,
telephone 0800 555 050

Consent Form
The Auckland Stillbirth Study

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

Obstetrics and Gynaecology Department
The University of Auckland
Private Bag 92019
Auckland
New Zealand.

Telephone: 64 9 3737599 ex 89192

Email: l.stacey@auckland.ac.nz

Name:_____

Date of birth:_____

Request for an interpreter

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Samoan	Ou te mana'o e ia i ai se fa'amatala upu.	Ioe	Leai
Tongan	'Oku fiema'u ha fakatonulea.	Io	Ikai
Mandarin	Wo xiang qing yi wei fan yi.	Yao	BoYao
Fijian	Au gadreva me dua e vakadewa vei au	Io	Sega
Tokelaun	Ko au fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai

I have read and understood the information sheet dated May 2006 (version 4) for volunteers in The Auckland Stillbirth Study designed to identify potential risk factors for stillbirth.

I have had the opportunity to discuss this study; I am satisfied with the answers provided.

I have the opportunity to use whanau support or a friend to help me ask questions and understand the study.

I understand that taking part in this study is my choice and that I may withdraw from the study at any time and this will not affect my continuing health care.

I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

I have had time to consider whether to take part. I know whom to contact if I have any problems or further questions.

I understand that participation in The Auckland Stillbirth Study will require the researchers to collect information from my clinical records and to interview me about aspects of my lifestyle and environment.

I, _____hereby consent to take part in this study.

Signature:_____Date_____

Project explained by:_____(Researcher)

Signature:_____Date_____

I wish to receive a copy of the results YES/NO Address to send to:

Appendix B
The Auckland Stillbirth Study: Maternal Interview Questionnaire

	The Auckland Stillbirth Study	*(A)*
Study number: _ _ _ _	Maternal interview	Date: __/__/____

I would like to ask you some questions about your general health

(Taken at interview) Height in cms: Weight in kgs:

1. General Health

1.1 In general, how do you rate your health compared to other pregnant women that you know?

1 Better than others
2 About the same
3 Worse than others
4 Don't know

1.2a Did you have any of these common illnesses during your pregnancy[8]?

	Anytime during your pregnancy	In the last month	In the last week
High fever			
(Was it confirmed by a thermometer?)			
Runny nose/sore throat/swollen glands			
Cough with Phlegm			
Diarrhoea and/or vomiting			
Rash			
Urinary tract infection (for which you sought advice)			
Vaginal discharge (for which you sought advice)			

8 **Options**
1 Yes 2 No 3 Can't remember

1.2b When did you first see a health practioner about your pregnancy?

1.2c What type of health practioner did you see first?

1.2d How often did you see your GP during the pregnancy? □□

1.3 During this pregnancy did you experienced abdominal pain? _
1–Yes 2–No

1.3a If yes: gestation(s):□□,□□,□□

1.4 If yes: was it severe enough for you to call or to mention it to your Lead

14a Maternity Carer/GP?□
1=Yes 2=No

1.5 Did you visit a maternity department during your pregnancy (other than when in labour)? *1=Yes 2=No*

What gestation(s)

1.5a What was the reason?

1.5b Did you go to an Accident and Emergency Centre, or after hours medical centre during your pregnancy prior to coming for delivery?□
1=Yes 2=No

1.6 If yes:

Where	*When (Gestation)*	*Reason*

1.7 Did you stay in hospital overnight during your pregnancy?
1=Yes 2=No

1.8 If yes:

Where	*When (Gestation)*	*Reason*

1.9 Were you unwell in any way in the last 2 weeks (of the pregnancy)?
1=Yes 2=No

1.9a If yes please describe: (text)_____

1.10 Have your[9]...

	During your pregnancy	In last month	In the last week
...gums bled while brushing?	⊔	_	⌟
...teeth been sore when chewing?	⊓	¯	⌝
...gums been swollen?	⌶		⌶

I would now like to ask you a couple of questions about your family history

2. Family's obstetric/medical history

2.1 Have you, or your father , mother, brother or sister ever been diagnosed with a blood clotting disorder (or genetic tendency for blood clots/thrombophilia)?

	Yes[10]	*No*	*Don't know*
Self			
Mother			
Father			
Brother			
Sister			

2.2 Has your mother or sister(s) experienced any of the following[11]?

	Miscarriage	Stillbirth	Neonatal death	Child with disability
Mother				
Sister 1				
Sister 2				
Sister 3				

2.4 Do you know your birthweight?
1=Yes *2=No*

2.5 If yes, what was it _____

9 Options
1 Yes 2 No 3 Can't remember

10 **Blood clotting disorders**
01 Deep vein thrombosis 02 Pulmonary embolism 03 Stroke 04 Bleeding diathesis or clotting deficiency 05 Genetic 99 Other

11 Number

2.6 **Were you born prematurely?**
1=Yes 2=No 3=Don't know

2.7 **If yes, how preterm were you? (gestation)** ☐☐

3. Medications

3.1 During your pregnancy did you take any medications prescribed to you by your doctor/midwife?

Name	*Reason*	*Gestation*

3.2 During your pregnancy did you take any non prescription medications or treatments?

Name[12]	*Reason*	*Gestation*

4. Traditional/natural therapies

4.1 **Did you see any natural therapist or traditional healer during your pregnancy?**
1=Yes 2=No

4.2 **If yes, which**

	Anytime in pregnancy	*Last month*	*Last week*
Acupuncture			
Aromatherapy			
Chiropractor			
Herbalist			

12 **Medication in pregnancy**
01=Antacids 02=Antihistamines 03=Anti inflammatory 04=Aspirin 05=Cough mixture 06=Evening primrose oil 07=Fish oils 08=Herbal remedies (specify) 09=Homeopathic medications (specify) 10=Nose spray 11=Paracetamol 00=none 99=Other

	Anytime in pregnancy	*Last month*	*Last week*
Homeopath			
Hypnotherapy			
Massage: relaxation			
Massage: traditional			
Naturopath			
Osteopath			
Traditional/spiritual healer			
Other traditional therapies please state			

Comments:

5. Diet

5.1 How often eat did you eat fish? (any kind of fish, tinned, smoked, fresh, raw)?

	In the first 3 months of the pregnancy	*Last month*	*Last week*
4-7 times a week			
1-3x a week			
Less than once a week			
Less than once a month			
Hardly ever			

5.2 How often did you eat green leafy vegetables (these are vegetables high in folate such as spinach, broccoli, boc choy, cabbage, lettuce, watercress)?

	In the first 3 months of the pregnancy	*Last month*	*Last week*
4-7 times a week			
1-3x a week			
Less than once a week			
Less than once a month			
Hardly ever			

5.3 How many pieces of fruit did you eat a day?

	In the first 3 months of the pregnancy	*Last month*	*Last week*
>3			
1-2			
<1			
Hardly ever			

5.4 How often did you eat the following foods[13]?

	In the first 3 months of pregnancy	*Last month*	*Last week[14]*
Burger (such as McDonalds, Burger King, Wendy's etc)	☐☐	☐☐	☐☐
Fried chicken (such as KFC)	☐☐	☐☐	☐☐
Pizza	☐☐	☐☐	☐☐
Fish and Chips	☐☐	☐☐	☐☐

5.5 Did you have morning sickness this pregnancy?
1–Yes *2–No*

5.6 If yes, did you have
1. Nausea only
2. Nausea with spitting
3. Nausea and vomiting

5.7 How many weeks altogether did you vomit at least once a day?

5.8 Did you seek medical advice for your morning sickness?
1=Yes *2=No*

5.9 If yes, who?
1. Midwife
2. GP
3. Obstetrician
4. Acupuncturist
5. Traditional healer
6. Other _____

13 **How often**
01=More than 2x week 02=1-2 times a week 03=<1 a week 04=<1 a month 05=hardly ever

14 **How often**
01=More than 2x week 02=1-2 times a week 03=not in last week

5.10 Were you admitted to hospital due to your vomiting?
1=Yes 2=No

5.11 Did you lose weight at any time during your pregnancy?
1=Yes 2=No

5.11a If yes, how much did you lose?

5.12 Did you try to lose weight or restrict your diet (in relation to your weight) at any time in your pregnancy?
1=Yes 2=No

If yes why...(text explanation)

5.13 Did you take any dietary supplements during your pregnancy
1. Iron – Oral
2. Folate Lo Dose
3. Folate Ili Dose
4. Pregnancy Multivit
5. Other
6. None

5.14 Did you take folate supplement in the 3 months before getting pregnant?
1=Yes 2=No

I would now like to ask you some questions about your personal habits

6 Personal habits

6.1 Do you currently smoke?
1. Yes 2. No

6.2a If yes, how many/day Number: _____

b, How many at the beginning of your pregnancy? _____

6.3 Have you used nicotine patches or gum in pregnancy?
1=Yes 2=No

6.4 If yes, details please detail: _____

6.5 If you are currently not smoking, have you...
1. Stopped in pregnancy
2. Stopped before pregnancy
3. Never smoked

6.5a If you stopped in the pregnancy: at what gestation? ☐☐

6.6 Were you referred to Smokechange (or equivalent)
1=Yes *2=No*

6.7 Does anyone who lives in your house smoke?
1=Yes *2=No*
6.7a If yes, number of people: .....

6.8 On average, how many (if any) of the following drinks did you have each week?

	In the first 3 months of your pregnancy	In the last month	In the last week
a. Can/small bottle of beer			
b. Glass of wine			
c. Serve of spirits			
d. Can/bottle of ready to drink (RTD)			
e. Glass of port or Sherry			
f. Other alcoholic drink			

6.9 What were the most glasses/cans of alcoholic drink that you had on any one occasion during your pregnancy and what were the types of drink?
Number:_____ Type(s) _____

6.10 On average, how many (if any) of the following drinks did you have each day?

	In the first 3 months of your pregnancy	In the last month	In the last week
a. Cup of tea			
b. Cup of coffee			
c. Can of coke, Pepsi, Mountain Dew			
d. Can of Energy drinks such as, V, Red Bull			
e Chocolate drink such as cocoa			

6.11 At any stage in your pregnancy did you use any of the following drugs:

	In the first 3 months of your pregnancy	In the last month	In the last week
1 cannabis			
2 Herbal highs			
3 amphetamine/P			
4 ecstasy			
5 hallucinogen			
6 cocaine			
7 heroin			
8 Petrol/paint/glue etc			
9 Methadone			
10 other			

6.12 If yes, please give details (ie how often):

In the following section I will ask you about your sleeping habits.

7. Sleep

7.1 What position did you usually *go to sleep* in[15]:

Before you were pregnant: ☐
The last four weeks: ☐
The last week of your pregnancy: ☐
The night before your baby died/last night: ☐

7.2 What position did you usually *wake up* in:

Before you were pregnant: ☐
The last four weeks: ☐
The last week of your pregnancy: ☐
The night before your baby died/last night: ☐

15 **Sleep position**
1=On my left side mostly 2=On my right side mostly 3=Both sides just as much 4=On my back mostly 5=On my front mostly 6=Just as much on my side as my front and back 7=Sitting up/propped up 8 =I don't remember/don't know

7.3 How often did you usually wake up during the night [16]?

Before you were pregnant: ⌟
The last four weeks: ⌟
The last week of your pregnancy: ⌞
The night before your baby died/last night: ⌐

7.4 During the night how often do you have to get up to use the toilet[17]?

Before you were pregnant: ⌟
The last four weeks: ⌟
The last week of your pregnancy: ⌞
The night before your baby died/last night: ⌐

7.5 Before you were pregnant did you have any of the following sleep problems?

a Snoring ☐
b Pauses in breathing while sleeping ☐
c Choking, gasping or suffocating attacks ⌐
d Restlessness during sleep with frequent tossing and turning in the bed ⌐
e Regular jerking of arms or legs while sleeping ☐
f Nighttime indigestion/heartburn ☐
g Coughing in sleep ☐
h Wheezing ☐
i My nose was partially or completely blocked ⌞⌞
j Waking feeling unrefreshed or still tired ⌐
k Dry mouth on waking ☐
l Headache immediately after waking ☐
m Soaking sweats ☐

7.6 Since you have been pregnant have you have had any of the following sleep problems?

a Snoring ☐
b Pauses in breathing while sleeping ☐
c Choking, gasping or suffocating attacks ☐
d Restlessness during sleep with frequent tossing and turning in the bed ☐
e Regular jerking of arms or legs while sleeping ☐
f Nighttime indigestion/heartburn ⌐
g Coughing in sleep ☐
h Wheezing ☐
i My nose was partially or completely blocked ☐
j Waking feeling unrefreshed or still tired ☐
k Dry mouth on waking ☐
l Headache immediately after waking ⌐
m Soaking sweats ☐
n Discomfort/tummy cramps/back ache ☐
o Leg cramps ☐
p Waking because of baby kicking ☐

---

16 **Wake up**
1=Rarely 2=Once 3=More than once 4=Frequently (each night) 5=I don't remember/don't know

17 **Going to toilet**
1=Rarely 2=Once 3=More than once 4=Frequently (each night) 5=I don't remember/don't know

7.7 During the past month, how would you rate your overall sleep quality?

1. Very good
2. Fairly good
3. Fairly bad
4. Very bad

7.8 During the past month, how many hours of actual sleep did you usually get at night? □□

7.9 Do you regularly sleep during the daytime? *1= Yes 2= No*

7.10 If so, for how long?(mins)□□□

7.11 During your pregnancy, how likely were you to dose off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you[18].

a	Sitting and reading	□
b	Watching TV	□
c	Sitting, inactive in a public place (ie theatre or meeting)	□
d	As a passenger in a car for an hour without a break	□
e	Lying down to rest in the afternoon when circumstances permit	□
f	Sitting talking to someone	□
g	Sitting quietly after lunch without alcohol	□
h	In a car, while stopped for a few minutes in the traffic	□

9. Relationship and fertility

I would like to ask you some questions about your relationship, and about you becoming pregnant...

9.1 What is your marital status?□

1=single
2=married
3=defacto

9.2 How old is the father of your baby? □□ *in years / Don't know* □

9.3 How would you describe his ethnicity (you can circle up to 3).

00=Unknown
01=Maori
02=New Zealand European
03=Chinese
04=Cook Islander
05=Fijian

18 1=would never doze 2=slight chance of dozing 3=moderate chance of dozing 4=high chance of dozing

06=Indian
07–Niuean
08=Samoan
09=Tongan
10=Other Asian _____
11=Other European _____
12=Other Pacific Island _____
99–Other _____

9.4 Is this your first pregnancy with this partner

1–Yes 2–no

9.5 Is your relationship ongoing
1=Yes 2=no 3. On/off 4. declined to answer

9.6 How long have you had a relationship with this partner?
1. In years _____ 2. declined to answer

9.7 Were you trying to get pregnant when you became pregnant this time?
1=Yes 2=no 3. declined to answer

9.8 If yes, how many months did it take to become pregnant? _____

9.9 Did you have treatment to get pregnant with this baby?

1–Yes 2–no

9.10 If yes, what was the treatment?
1.NA unassisted
2.artificial insemination
3.ovulation induction
4.IVF
5.GIFT
6.ICSI intracytoplasmic sperm injection

9.11 Do you have a history of polycystic ovarian syndrome?
1. No
2. Yes confirmed by USS
3.Yes by bloods
4.Yes USS/bloods
5.Unsure

9.12 If yes, did you receive any treatment?

1–Yes 2–No

9.13 If yes, please state _____

14.1 Thinking back, just before you became pregnant, which of the following best describe how you were feeling at that time?

a=I wanted this pregnancy at an earlier time, as well as at that time
b=I wanted to become pregnant at that time
c=I did not want to become pregnant at that time, but wanted a child sometime in the future
d=I did not want to become pregnant at that time, or at any time in the future.

14.2 Which of the following statements best describes your partner during the 3 months before you became pregnant?

a=He wanted me to get pregnant
b=He partly wanted me to get pregnant and partly wanted me not to get pregnant
c=He didn't care one way or the other whether I got pregnant
d=He did not especially want me to get pregnant
e=He wanted very much for me not to get pregnant

I would now like to ask some questions about your living and work situation

10. Social and demographic and work information

10 How do you describe your ethnicity:

01=Maori
02=New Zealand European
03=Chinese
04=Cook Islander
05=Fijian
06=Indian
07=Niuean
08=Samoan
09=Tongan
10=Other Asian _____
11=Other European _____
12=Other Pacific Island _____
99=Other _____

10.1 What best describes the place that you live in?

1.Own house/flat mortgage free
2. Own house/flat mortgage
3.private rental
4.govt/council rental
5.hostel/boarding house
6. garage
7. caravan
8.Other _____

10.2 How many people do you usually live with ?

1. Children <16 _____
2. Adults _____

10.2a How many bedrooms do you have?

10.3 What age did you leave school? □¯

Did you complete secondary school? *1=Yes* *2=no*

10.4 Did you go on to university education? *1=Yes* *2=no*

10.5 If yes:
1=Graduated
2=still attending/attending until got pregnant
3=dropped out prior to pregnancy

10.6 If no, did you attend any other education after school (such as trade or professional courses)? *1=Yes* *2=no*

10.7 If yes,
1=Graduated
2=still attending/attending until got pregnant
3=dropped out prior to pregnancy

10.8 What was your job situation prior to this pregnancy?
1.Full time work
2.Part time work
3.Student
4.Home maker
5.Unemployed
6.Sickness beneficiary
7. Other, please state_____

10.9 What was your job situation in the last month?
1.Full time work
2. Part time work
3.student
4.home maker
5.unemployed
6. sickness beneficiary
7. Other, please state_____

10.10 If you were in work, what was it?

10.17 What was your partner's job situation in the last month?
1=Full time work
2=Part time work
3=student
4=home maker
5=unemployed
6.=sickness beneficiary
7= Other, please state_____
8=NA

10.18 If he/she was in work, what was it?

10.13 If you do/did paid work, what time of day (or night) do/did you usually work?

	Before pregnancy?	Last month of pregnancy?	Last week of pregnancy?
Day			
Evening			
Night			
Mixed			
NA			

10.14 If you stopped work in your pregnancy, how many weeks pregnant were you?

1. N/A (still working)
2. N/A (didn't do paid work in pregnancy).
3. _____

10.15 If you do/did paid work, do/did you feel that you have too many tasks at your work? *1=Yes 2=No 3=NA*

10.16 If you do/did paid work, do/did you feel that you have the opportunity to influence your tasks and working conditions? *1=Yes 2=No 3=NA*

10.12 What <u>best</u> describes your main activities during the day? (Tick one box)

	Before pregnancy?	Last month of pregnancy?	Last week of your pregnancy?
Administrative/sitting activities			
Sitting and some walking Standing			
Standing and walking			
Standing and walking plus intermittent strenuous exercise Regular strenuous exercise			

10.11 In an average week how long did you spend watching TV each day? (hrs)

11. Sport and exercise

11.1 Since you have become pregnant has your level of physical exercise:

☐ 1. Stayed the same 2.Become less 3Become more

11.2 How often have you engaged in vigorous exercise in last month (exercise which made you breathe harder or puff or pant such as tennis, jogging, aerobics, heavy gardening, rollerblading, skiing, rowing, rowing/cycling machine)?

1. Never
2. One a week
3. 2-3 times a week
4. 4-6 times a week
5. Daily
6. More than once a day

11.2 a If yes, on average how long did the exercise last for (in minutes)?

11.3 How often have you engaged in less vigorous exercise for recreation, sport or health-fitness purposes in the last month which did not make you breathe harder or puff and pant?

1. Never
2. One a week
3. 2-3 times a week
4. 4-6 times a week
5. Daily
6. More than once a day

11.3 a If yes, on average how long did the exercise last for (in minutes)?

11.4 How often did you have sexual intercourse in the last four weeks of your pregnancy?

1. More than daily
2. Daily
3. 2-6 times a week
4. Weekly
5. Less than weekly
6. Never
7. NA
8. Declined to answer

11.5 If yes, did you experience any tightenings or pain following intercourse in the last four weeks?

1=Yes *2=No*

11.6 If yes, did you experience any bleeding following intercourse in the last four weeks ?

1=Yes *2=No*

12. Depression and Stress

12.6 I would now like to ask you about some events that might have happened to you over the last 12 months. Have you…

1) had something significant lost or stolen
2) moved house
3) you, your partner, close friend or relative been put in prison
4) Experienced money worries
5) failed an important test of some sort
6) you or your partner given a lower paid/lower status position at work
7) You or your partner lost a job (sacked)
8) You or your partner had a business that failed
9) you or your partner looked for work for more than one month
10) death of a partner
11) death of a close relative
12) death of a close friend
13) separated from partner for more than one month
14) separated from close friend for more than one month
15) broke off engagement or steady relationship
16) usual family member left home permanently
17) major problems in your relationship with your partner
18) any other stressful event (please specify)……

How did you feel about these events?

Was the time prior to getting pregnant, and during this pregnancy particularly stressful for you?

12.1 During your pregnancy were you often bothered by feeling down, depressed, or hopeless?
1=Yes 2=No

12.2 During your pregnancy were you often bothered by little interest or pleasure in doing things?
1=Yes 2=No

12.3 Have you ever sought medical advice for depression or anxiety?
1=Yes 2=No

12.4 If yes, was it during your pregnancy?
1=Yes 2=No 3=NA

12.5 If yes, What treatment did you receive?
1. No treatment
2. Counselling
3. Referral to Maternal mental Health
4. Medication
5. Hospital admission

12.7 The following questions are about your feelings and thoughts during the last month of your pregnancy.
Here are the different answers you can have for each question:
how often in the last month of your pregnancy have you...

a...been upset because of something that happened unexpectedly?
b...felt you were unable to control the important things in your life?
c...felt nervous and stressed?
d...felt confident about your ability to handle your personal problems?
e...felt that things were going your way?
f...found you could not cope with all the things you had to do?
g...been able to control small hassles in your life?
h...felt that you were on top of things?
i...been angered because of things that happened that were outside your control?
j...felt difficulties were piling so high that you could not overcome them?

13. Support

13.1 During the last six months how helpful have you found the following groups of people[19] ?

a) Your parents
b) Your partners parents
c) Your relatives/whanau/family
d) Your partner's relatives
e) Your partner
f) Your friends
g) Your partner's friends
h) Your own children
i) People you work with
j) School, day-care centre, Kohanga Reo
k) Parent of other support groups
l) Social groups or clubs
m) Church
n) Family doctor or practice nurse
o) Plunket or Karitane nurse
p) Midwife
q) Professional agencies (e.g. Social welfare)
r) Other professional helpers (e.g. Teachers)

- ***Tell me more about your support: what support was most useful, what area of support did you feel was missing?***

---

19 19 **How helpful**
1=Not available 2=Not used 3=Not at all helpful 4=Sometimes helpful 5=Generally helpful 6=Very helpful 7=Extremely helpful 8=NA

14. Fetal movements

I would like to ask you some questions about your baby's movements while you were pregnant

14.1 Were you at any time alarmed or suspicious about your baby being less active than usual during pregnancy? *1=Yes 2=no*

14.2 If yes: *1= once 2=sometimes 3=often*

14.3 If yes, did you seek medical advice? *1=Yes 2=no*

14.4 If yes, how long did you notice reduced movements before you sought advice[20]? _ _

14.4a Can you describe your baby's movements over the last 2 weeks, have there been any changes in the frequency or strength of movements?

What information were you given by your midwife/doctor about fetal movements?

14.5 During the last two weeks, did you notice any time that your baby was more vigorous than usual? ☐ *1=Yes 2=no*

14.6 If yes: ☐ *1= once 2=sometimes 3=often*

14.7 Were you concerned? ☐ *1=Yes 2=no*

14.8 If yes, did you seek medical advice? ☐ *1=Yes 2=no*

14.9 During the last two weeks, did you feel your baby having hiccups?
1=Yes 2=no 3=unsure

14.10 If yes☐ *1= once 2=sometimes 3=often 4=unsure*

14.11 During the last two weeks, did you feel uterine contractions / "pre-labor contractions" / "Braxton Hicks contractions" / "false labor"?
1=Yes 2=no

14.12 If yes:☐ *1= once 2=sometimes 3=often 4=unsure*

14.13 If yes, did you have regular tightenings that continued for longer than an hour?
1=Yes 2=no

---

20 **Time seeking advice**
1=0-11 hours 2=12-23 hours 3=24-47 hours 4=between 48 hours and a week 5=more than a week 6=several weeks.

14.14 If yes, were they painful? *1=Yes 2=no*

For case only:
14.15 Did this happen on the day the baby died? *1=Yes 2=no*

15. Injury

15.1 Did you experience any physical injury at any time during your pregnancy

1. No
2 slips and falls
3 MVA
4 blow to abdomen
5 self harm
6 other non-accidental
7 other accidental

15.2 If yes, did you seek medical help due to the injury?
Yes No

15.3 In the last 2 weeks of your pregnancy, did you experience any injury?

1. No
2 slips and falls
3 MVA
4 blow to abdomen
5 self harm
6 other non-accidental
7 other accidental

15.4 If yes, did you seek medical help?

This final question is a difficult and very sensitive one...

16. Family violence

(These must be asked only if the woman is on her own)

1. **During this pregnancy have you been hit, slapped, kicked or physically hurt by anyone?**

	Never	Once	2-5 times	More than 5 times
Husband/partner				
Ex husband/partner				
Family friend other than husband/partner				
Someone else				

2. **During this pregnancy were you ever physically forced to have sexual intercourse by anyone?**

	Never	Once	2-5 times	More than 5 times
HIusband/partner				
Ex husband/partner				
Family friend other than husband/partner				
Someone else				

3. **During this pregnancy were you ever afraid of anyone?**

	Never	Once	2-5 times	More than 5 times
Husband/partner				
Ex husband/partner				
Family friend other than husband/partner				
Someone else				

Comments:

17 Other

I would finally like to ask you, what was the first reason that you thought something was wrong with your pregnancy or that your baby was dying/had died?

1=I felt a reduction of kicks/movements
2=I felt kicks/movements stop
3=I felt abdominal pain
4=I had vaginal bleeding/hemorrhage
5=I had discharge of amniotic fluid/the membranes ruptured
6=I had a "feeling that something was wrong", but cannot specify
7=I had a trauma (involved in a physical accident)
8=I had other symptoms (specify below if possible)
9=I was told at an appointment for prenatal care
10=I was told when I was admitted for labor
11=I was told during labor
12=It was not discovered before the baby was born
13=I do not remember/know

Is there anything else that you would like to mention or talk to me about, or anything that you felt was significant about this pregnancy/different from a previous pregnancy?.....Thank you

Did you choose to have a post mortem?

If no, what was the main reason?

Would you make the same decision now?

....Please feel free to call me or email me if anything comes to mind that you think might be relevant.

Appendix C The Auckland Stillbirth Study: Clinical data

The Auckland Stillbirth Study

ID: _ _ _ _ _ Clinical data collection Date: __/__/____

A. Inclusion criteria

A.1: Gestational age: ⌐⌐.⌐ (weeks/days)

A.2: Singleton pregnancy: *yes* ⊏ *no* ⊏

A.3: Major congenital abnormality: *yes* _ *no* ⌟

A.4: Consent signed: *yes* *no*

B. Maternal demographics

B.1: Date of birth: __/__/____

B.2: Country of birth[21]:.....

B.3: If not New Zealand: Number of years in New Zealand: ⌐

B.4: Citizen/Permanent resident: *yes* ⌟ *no* ¯

B.6: Fluent in English: *yes* _ *no* ⌴

B.7: Interpreter required: yes ⌟ no ⌞ language: .....

B.8: Usual address at time of delivery:

Number

Street:_____

Suburb: _____

C. Maternal medical history

C.1: Pre-existing medical conditions:

None ☐

a. Anaemia ☐

b. Asthma ☐

c. Cervix surgery ☐

d. Depression ☐

e. Epilepsy ☐

f. Heart condition – congenital ☐

g. Heart condition rheumatic ☐

h. Hypertension (Ess/Chronic) ☐

i. Hyperthyroid ☐

j. Hypothyroid ☐

k. Inflammatory bowel disease ☐

l. major psychiatric disorder(other than depression) ☐

m. Other autoimmune ☐

n. Renal disease ☐

o. Systemic lupus erythematosus ☐

p. Thalassaemia trait ☐

q. Thrombophilia ☐

r. Urinary tract infection ☐

s. Uterine abnormality ☐

t. Uterus surgery ☐

u. venous thromboembolism ☐

v. other: . (please specify) ☐.....

C.2: Allergies: yes ☐ no ☐

C.3 If yes, describe: .....

D. Past obstetric history

Miscarriage <12 ☐ Termination <12 ☐

Date of birth	*Gestation*	*Birthweight*	*Pregnancy complication*[22]	*Delivery method*[23]	*Outcome*[24]

E. Current pregnancy

E. 1: EDD: __/__/____

E.2: Method for establishing EDD[25]: ☐☐

E.3: Consanguinity: yes ☐ no ☐

E.4: Height (in cms): ☐☐☐ not recorded: ☐

E.5 Weight at booking (in kgs): ☐☐ not recorded: ☐☐

E.6 Weight at last visit (in kgs): ☐☐☐ not recorded: ☐

E.7: BMI calculated at booking: ☐☐

22 **Pregnancy complication**
01: abruption 02. cervical stitch 03. fetal anomaly 03.gestational diabetes 04.IUGR <10% 05.placenta praevia 06. multiple birth 07 pre-eclampsia 00 none/not recorded 99. other .....

23 **Delivery method**
01 Normal vaginal birth 02 Cesarean section 03 Operative delivery 04 vaginal breech 00 not recorded

24 **Outcome**
01 Alive and well 02 Child death 03 congenital abnormality 04 ectopic 05 spontaneous miscarriage 06 molar pregnancy 07 neonatal death 08 post neonatal death 09 stillbirth 10 termination of pregnancy -00 not recorded

25 **Method for establishing EDD**
01 certain LMP/regular cycle 02 u/s scan < 16 weeks 03 u/s scan 16-21 weeks 04 u/s scan > 21 weeks 05 clinical assessment 99 other

F. Antenatal care

F.1: Date of first visit: __/__/____
F.2: Estimated gestational age at first visit: ☐☐.☐ (weeks/days)
F.3 Initial lead maternity carer type[26]: ☐☐

F.4: Referral to specialist services: No
a Obstetric specialist
b maternal fetal medicine
c physician
d mental health specialist
e drug & alcohol service
f social work
g Physio
h Other: (please specify) .....

Reason for referral (other than obstetric):
.....

F.5: Reason for obstetric referral: NA
a APH
b Maternal request
c Breech
d Multiple pregnancy
e Cardiac (maternal)
f Other medical
g Cholestasis
h PPROM
i Diabetes
j SRM >24 hrs >37 weeks
k Fetal anomaly (current)
l Previous LSCS
m Hypertension
Chronic
Gestational
Preeclampsia
Eclampsia
PE on chronic HT
n Previous perinatal death
o Renal disease
p Surgical problem
q Suspected large fetus
r Suspected small fetus
s Infection (specify) .....
u Unstable lie
u Maternal age > 35 years

---

26 **Lead maternity carer**
01. Hospital team midwife 02. Independent midwife 03. Hospital clinic 04. Private Obstetrician 05. GP 06 Community clinic 07. No antenatal care 99. Other

v Maternal age < 18 years
w Preterm labour/threatened preterm labour
x Other (please specify):

F.6: Change of LMC: yes | no

F.7: If yes: reason:
a. pre-existing condition .....
b. complication of pregnancy .....
c. maternal request
e. change in personal circumstances
f. Stillbirth
g. Other (please specify) .....

F.8 Booked place of birth[27]: .....
F.9 Transfer to new care facility: yes no

F.10 If yes: a. reason for transfer[28]: ..... b. gestation at transfer: (weeks/days) c. timing of transfer[29]:

F.11 Actual place of birth[30]:

F.12 Number of antenatal visits in 1st trimester:

F.13 Number of antenatal visits in 2nd trimester:

F. 14 Number of antenatal visits in 3rd trimester:

F15 Gestation at first visit with health practitioner re pregnancy:

F16: Type: midwife/GP/Obstetrician

F17: Additional visits (not with LMC):

---

27 **Booked place of birth:**
01 NWH 02 MMH 03 NSH 04 WTK 05 Birthcare 06 Papakura 07 Botany 08 Pukekohe 09 Home 99 Other -9 not recorded

28 **Reason for transfer**
01 pre-existing condition 02 complication of pregnancy 03 maternal request 04 change in personal circumstances 05 Stillbirth 99 Other -9 Not recorded

29 **Timing of transfer**
01 Antenatal non acute 02 Antenatal acute 03 In labour 04 Post delivery -9 not recorded

30 **Actual place of birth**
01 NWH 02 MMH 03 NSH 04 WTK 05 Birthcare 06 Papakura 07 Botany 08 Pukekohe 09 Home 99 Other -9 not recorded

G Screening and management this pregnancy

G.1 Procedures this pregnancy: None ¦

a Scan at ≤ 20/40 ¯

b CVS ¬

c Cervical Suture ¬

d Amniocentesis ¬

e Doppler studies ¦

f FBS ¦

g Fetal transfusion ¬

h Feticide (in multiple pregnancy) ¯

I Amnio reduction ¬

j Laser fetal surgery ¬

k Maternal blood transfusion ¬

l serum screening

m nuchal translucency ¬

n ECV ¬

0 Other ¬ .....

G.1: Blood pressure at booking: systolic _ _ ¬ diastolic ¬¬ _

G.2: Lowest recorded systolic: ¯ ¯ ¬
(with diastolic ¯ ¬¬): gestation ¬ ¯.¯ (weeks/days)

G.3: Lowest recorded diastolic: ¬¬ ¬
(with systolic ¬ ¬¬): gestation ¬ ¬.¬ (weeks/days)

G.4: Highest recorded systolic: ¬ _ _
(with diastolic ¦¦): gestation . (weeks/days)

G.5: Highest recorded diastolic: ¦¦
(with systolic ¯ ¬¬): gestation ¬ ¯.¯ (weeks/days)

G.6: Hypertension[31]: ¬ ¬

G.7: Highest degree of proteinurea in pregnancy[32]: ¦

G. 18 Bleeding in pregnancy[33]: ¬¬

G. 19 If yes, cause[34]: ¬¬

G. 20 Was fetal growth restriction clinically suspected?
Yes ¦ No ¦¦

G.20 a If yes, gestation first suspected ¯ ¬.¬

---

31 **Hypertension**
01 Nil 02 chronic essential 03 chronic secondary eg renal disease 04 chronic unspecified 05 gestational 06 pre-eclampsia 07 pre-eclampsia superimposed on chronic -9 Unknown

32 **Proteinuria**
01 Not tested 02 Nil 03 Trace 04 1+ 05 2+ 06 3− -9Unknown

33 **Bleeding in pregnancy**
01 No bleeds 02 single episode < 20 weeks 03 recurrent bleeds < 20 weeks 04 Single >20 weeks 05 recurrent bleeds >20 weeks 06 Recurrent bleeds throughout -9 unknown

34 **Cause of bleeding**
01 placenta praevia 02 abruption 03 vasa praevia 04 cervical cause 05 cause unknown 06 Fetal 07 Other cause -9 no record

G.20 b Was a customized growth chart used? *Yes* ¬ *No* ¯

G.20 c Was there clinical evidence of growth restriction not identified by LMC?
Yes _ *No*⊔

G. 21 Was a growth scan done? *Yes* *No*

G.21 a Was there evidence on the growth scan of FGR?
Yes ac <10% ⊔ *Yes EFW <10* _ *No*⊔
G.22 Method of confirmation[35]: ⊔ _

G.23 Management of FGR: (blank if FGR not diagnosed)
a. increase routine A/N checks ¯
b serial CTG ¬
c Dopplers ¬
d thrombophilia studies ⊥
e anti coagulant treatment |
f admit |
g deliver ¬
h Other (please specify) ¬.....

G.24 Preterm prelabour rupture of membranes: Yes ⊔ No _ Not known ⊥

G.25 If yes, gestation: .

G. 26 Threatened preterm labour:

No.	*Gestation*	*Admitted*
	⊔⊔._	

G. 27 Decreased fetal movements reported[36]: ⊏ ⊐

G.28 If yes:

No.	*Gestation*	*Action taken*
	⊔⊔.⊔	1 palpation & auscultation _ 2 CTG || 3 growth scan 4 scan w Doppler ¯ 5 start FM counting ⊏ 6 admit for observation ⊔ 7 deliver ⊥ 8 Other | 9 NA |

35 **Confirmation method**
01 Serial USS 02 Single USS 03 USS at IUFD only 99 Other

36 **DFM reported**
01 no 02 only at IUFD diagnosis 03 yes -9 No documentation/not known

G.29 Medications in pregnancy:

a. None ┘
b. Antibiotics ┘
c. Antidepressants │
d. Antihypertensives │
e. Antiepileptics ┐
f. Aspirin ┐
g. Clexane/Heparin ┘
h. Corticosteriods ┘
i. Insulin │
j. Metformin │
k. Prednisone ┐
l. Tocolytics ┐
m.Other (specify type) ┐
n.Not recorded/don't know ┘

G.30 If corticosteroids administered:

1st C/steroids □ Gestation □□.□ Course completed □
2nd C/steroids └ Gestation ┘└┘.└┘ Course completed ┘

G.15 Medical conditions in pregnancy:

a. Anaemia ┐
b. Asthma ┐
c. Cervix surgery ┐
d. Depression ┘
e. Epilepsy │
f. Heart condition - congenital │
g. Heart condition – rheumatic ┐
h. Hyperthyroid ┐
i. Hypothyroid ┐
j. Inflammatory bowel ┘
k. major psychiatric disorder(other than depression │
l. Other autoimmune │
m. Renal disease ┐
n. Rheumatic heart ┐
o. Systemic lupus erythematosus □
p. Thalassaemia trait ┘
q. Thrombophilia ┘
r. Urinary tract infection │
s. Uterine abnormality ┐
t. Laporotomy ┐
u. Venous thromboembolism ┐
v. Other ┘ .....

H Laboratory Results

H.2 Karyotype[37]: ☐☐

H.3 If yes: result: ☐☐☐☐

H.4 First trimester ultrasound

a. Performed: yes ☐ no ☐

b. If yes, gestation by LMC: ☐☐.☐ (weeks/days)

If yes, findings:

Indication[38]	*GA weeks/days by USS*	*CRL*	*NT*	*BPD*	*HC*	*AC*	*FL*
	☐☐.☐						

d. Correlation to LMP[39]: ☐☐

H.5 Anomaly ultrasound

a Performed: yes ☐ no ☐

b. If yes, findings:

GA weeks/days	*BPD*	*HC*	*AC*	*FL*	*AFV*	*Other findings*

H.6 Further USS

Indication[40]	*GA weeks/days*	*BPD*	*HC*	*AC*	*FL*	*EFW*	*AFV*	*Umbilical doppler RI*
	☐☐.☐							

H.7 Other doppler studies yes no ☐

b.If yes, result: .....

c. Other comment:.....

H.8 Polycose: Not tested ☐ result: ☐☐.☐

H.9 If yes, gestation: 1st gestation ☐☐. (weeks/days)

last gestation ☐☐. (weeks/days)

H.10 Glucose tolerance test: Not tested ☐

Result: ☐☐.☐/☐☐.☐/☐☐.☐

---

37 **Karyotype**

01 Not performed 02 Yes: amniocentesis 03Yes: CVS 04 Yes cordocentesis -9 not recorded

38 **Indication**

01 unsure dates, 02 vaginal bleeding, 03 Trisomy 21 screen, 04 Elective 05 unknown, 06=cervical length, 07=viability, 08=abdominal pain, 10=suspected ectopic 11=no early scan 99=other

39 **Correlation to LMP**

01 NA 02 Yes 03 No >7 days less than LMP 04 No >7 days more than LMP 05 LMP unknown

40 **Indication**

01 suspected SGA 02 Suspected LGA 03 reduced FM 04 fetal position 05 No further USS 99 other -9 unknown

H.11 If yes, gestation: gestation _ _/_ (weeks/days)

H.12 Diabetes[41]: ⌋⌊

H.13 Blood group: ⌈

H.13a IIcp B positive yes ⊏ no ⊐

H.13 b HIV yes ⌊ no ⌋ not tested ⌊

H.14 (Leave blank if not done)

	Haemoglobin	***PCV***
Booking		
28 weeks		

H. 16 Midstream urine culture
(Leave blank if no MSU)

No:	***GA w +d***	***Infection[42]***	***Organism[43]***	***Treatment[44]***
1.	⌜ ¯.¯	⌝⌐	⌐⌜	⌝⌐

H. 17 Vaginal swab
(Leave blank if no swabs)

No:	***GA w +d***	***Organism[45]***	***Treatment***
1.	⌈ .	⌈	⌈

41 **Diabetes**
01 Nil 02 NIDDM on oral hypoglycemics 03 NIDDM on insulin 04 IDDM 05 gestational diabetes requiring insulin 06 gestational diabetes not requiring insulin 07 Not tested -9 Not known

42 **Infection**
01=negative 02=single organsism 10x2-10x5/mL 03=UTI >10x5/mL 04=mixed growth 05=sterile pyuria 6 not cultured -9 not known/no record

43 **MSU Organism**
00=no UTI 01=E coli 02= GBS 03=staph sap 04=klebsiella 05=proteus 06=enterococci 07=staph aureus 08 chlamydia 09 other 10 mixed growth 11 NA -9 not known/no record

44 **Treatment**
1−none 2−metronidazole 3−erythromycin 4−amoxil 5−augmetin 6−anti-fungal 7−other -9 not known/not recorded

45 **Swab organism**
01=normal flora 02=bacterial vaginosis 03=GBS 04=candida 05=chlamydia 06=staph aureus 07=E Coli 08=gonorrhea 09=trichmonas vaginalis 10=ureaplasma 11=other -9=not known/not recorded

I Baby

Baby date of birth: ||| /| /|

1.1:Birthweight in grams: ⊓⌜ ¯ ⌝

I.2 Best estimate of gestation: ⊔⌊.⌊

I.2a:Customized centile

I.3: Sex of baby: Male ⊓ Female ⌜

I.4: Head circumference (in cms): _ ⌟

I.5 Length (in cms): |

I.6: Amniotic fluid volume[46]: ⊓⌜

I.7: Amniotic fluid colour[47]: ⊔⌊

I.8 Method of birth[48]: ||

I.9 Examination of the cord:

a Normal ⌋
b tight knot / occluded ⌋
c loose knot ⌟
d cord round neck tightly |
e cord round neck loosely |
f cord round limbs/body loosely ⌝
g cord around limbs/body tightly ⌋
h torsion or spring like cord ⌋
i marginal / velamentous insertion ⌟
j thin cord |
k meconium stained |
l tear ⌝
m 2 vessels ⌋
n other ⌋
o Not examined ⌟
p Other ..... |

I.10. Length of cord(in cms): ⊓⌜ not measured ⊓

I.11 Examination of the placenta:

a. Normal ⌟
b retroplacental clot |
c gritty/ calcified |

---

46 **AFV:** 01 Normal 02 Reduced 03 Increased -9 Not recorded

47 **AFC:** 01=Clear 02=Meconium 03=Blood stained 04=Purulent -9=Not recorded

48 **Method of birth:** 01=Spontaneous vaginal 02=Ventouse 03=Forceps 04=Elective LSCS 05=Emergency LSCS 06=Vaginal breech -9=Not recorded

d vasa praevia ☐
e offensive odour ☐
f succenturiate lobe ☐
g Extrochorial ☐
h circumvallate ☐
i bilobate placenta ☐
j Placenta accreta ☐
k Not examined ☐

I.12 Who examined the placenta[49]: ☐☐ .....

I.13 Weight of placenta in gms: ☐☐☐ not weighed

I.14 Clinical examination of baby:
a. Normal ☐ b. Abnormal (please specify) ☐.....

Who examined baby[50]? ☐☐☐

J Details of stillbirth (cases only)

J.1 Date of diagnosis of fetal death: __/__/____
J.2: Reason for presentation at diagnosis of FD[51]: ☐☐

J.3: Date of last consult prior to death where fetus confirmed alive: __/__/____

J.4: New findings at consult prior to diagnosis of fetal death:
a No new findings ☐
b SGA ☐
c LGA ☐
d Hypertension ☐
e Oligohydramnios ☐
f Polyhydramnios ☐
g APH ☐
h Diabetes ☐
i Decreased fetal movements ☐
j urinary tract infection ☐
l NA - not seen recently ☐

J.5: When did death occur:
Antepartum ☐

---

49 **Who examined placenta**
01 Midwife 02 Obstetrician 03 Pathologist 99 Other

50 **Who examined baby**
01=Midwife 02=Obstetrician 03=Obstetric registrar 04=Obstetric house Surgeon 05=Neonatologist 06=Peadiatric registrar 07=NNP 08=Geneticist 99=Other -9=Not recorded

51 **Reason for presentation**
01=routine scheduled visit 02=decreased fetal movements 03=labour 04=was in hospital 05=Mother unwell 06=APH 99=Other -9=not recorded/unknown

Intrapartum
Unknown whether antepartum/intrapartum
J.6: Interval from diagnosis of FD to birth: (days/hours)

K Stillbirth investigations

K.1: Postmortem:
Consent given for PM Yes No

K.2 Consent for Full partial

K.3 Maternal blood tests results
Haemeglobin
Platelets
Antibodies
Kleihauer
Uric acid
Creatinine
AST
ALT
HbA1c
B19 serology
Rubella
Syphilis serology
Thrombophilia tests
Anticardiolipin antibodies IGG titre
IGM titre
Lupus anticoagulant
APC Resistance

K.4 Surface swabs: .....

K.5 Ultrasound findings: .....

K.6 Postmortem findings: .....

K.7 PSANZ classification: .....