Adverse pregnancy outcomes in obese nulliparous women

Elaine Maria Fyfe

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Abstract

The burgeoning obesity epidemic has become as profound a health problem as under-nutrition on the global scale. With the general rise of obesity, there has been a parallel vast increase in the incidence of overweight and obese women of reproductive age. There are consequent increasing rates of serious maternal, fetal and neonatal complications secondary to obesity.

Using retrospective analysis of prospectively collected data from the international multicentre Screening for Pregnancy Endpoints (SCOPE) study, and of routinely collected data from National Women's Health, Auckland, New Zealand from 2006 to 2009, we investigated the role of obesity as a risk factor associated with three common adverse pregnancy outcomes in obese nulliparous women: Caesarean section, postpartum haemorrhage and pre-eclampsia.

We reported two novel findings relating to Caesarean section. Firstly, being overweight or obese is an independent risk factor for Caesarean delivery in labour, but this elevated risk is confined to the first stage of labour. Obese women who progress to the second stage of labor are just as likely to birth vaginally as women with normal BMIs. Secondly, we found that although obesity is also associated with hyperlipidaemia and cholesterol inhibits myometrial contractility in vitro, elevated maternal serum cholesterol in early pregnancy is not a risk factor for first stage Caesarean for failure to progress in overweight or obese women. We found that nulliparous obese women have a twofold increase in risk of major postpartum haemorrhage (≥1000mls) compared to women with normal BMI regardless of mode of birth. Higher rates of postpartum haemorrhage among obese women are not attributable to their higher rates of Caesarean delivery. Finally we found that risk factors present at 14-16 weeks of gestation in obese nullipara that were associated with development of pre-eclampsia share similarities with those implicated in cardiovascular disease. This may in part explain the linkage between pre-eclampsia and later cardiovascular disease.

We have identified novel factors that will assist with risk assessment, and clinical management of obstetric care for obese women. Our findings provide direction for future research to assist in reduction of adverse pregnancy outcomes for obese women.

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Dr J Myers, University of Manchester

Professor PN Baker, University of Auckland

Professor JJ Walker, University of Leeds

Dr NAB Simpson, University of Leeds

Professor LC Kenny, University College, Cork

Statistical support

Dr AW Stewart, University of Auckland

Dr MA Black, University of Otago

Dr D Broadhurst, University of Edmonton

Ms EHY Chan, University of Auckland

SCOPE Project Managers

Mrs D Healy, University of Adelaide

Mrs A Briley, Kings College, London

Mrs N Murphy, Mrs E Snapes, University College Cork

What you get by achieving your goals is not as important as what you become by achieving your goals

Henry David Thoreau 1817-1862

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Abbreviations

aOR	Adjusted odds ratio
BMI	Body Mass Index
CI	Confidence interval
CS	Caesarean Section
CVD	Cardiovascular disease
GDM	Gestational diabetes mellitus
HDL	High density lipoprotein
IDL	Intermediate density lipoprotein
IL-6	Interleukin-6
IOL	Induction of labour
LDL	Low density lipoprotein
LMC	Lead Maternity carer
LGA	Large for gestational age
NWH	National Women's Health
NZ	New Zealand
OR	Odds ratio
PPH	Postpartum haemorrhage
SCOPE	Screening for Pregnancy Endpoints Study
SGA	Small for gestational age
TAG	Triglyceride
TNF-α	Tumour necrosis factor alpha
USA	United States of America
VLDL	Very low density lipoprotein
WHO	World Health Organisation

Chapter 1. Introduction

1.1. Background

1.1.1. *Prevalence of obesity*

An exponential rise in global rates of obesity has seen this state of malnourishment become so profound a health problem that it now shares the stage with traditional global health problems such as infectious diseases and undernutrition (World Health Organization, 2000). Recent statistics are alarming: more than one in ten of the world's adult population are obese, being overweight or obese is the fifth leading risk factor for global deaths, and is responsible for a consequent 2.8 million deaths each year (World Health Organisation, 2011). Obesity is no longer exclusive to the developed world - developing countries now carry a double edged sword as they are faced with malnourished populations that encompass both underfed and overfed (Gardner & Halweil, 2000). The obese population comprises not only adults but also an increasing proportion of children. Global health services are heavily burdened with this rising prevalence of childhood obesity, with an estimated 42 million children under the age of five overweight in 2010 (World Health Organization, 2009). In some countries this constitutes more than 25% of the child population.

1.1.2. *Causes of obesity*

The driving forces of the obesity epidemic are complex and multifactorial stemming from factors related to environments, behaviours and physiology. The epidemic is partly underpinned by changes in the global food system, with a rising energy supply of easily obtained, inexpensive "fast" food and the development of obesogenic environments (Swinburn et al., 2011). Systemic drivers such as policy systems related to taxation and economic policies dictating business operations affect the financial status of the population, and this can ultimately affect obesity prevalence. The larger the difference in income within a nation, the higher the rates of obesity (Swinburn, et al., 2011). Environmental drivers related to food supply and marketing promote high energy intake, and behaviour patterns of low physical activity levels and increased intake of high energy food are reflected in subsequent energy imbalance (Swinburn, et al., 2011).

1.1.3. *Health effects related to obesity*

Grave concerns about the escalating rates of obesity relate to the accompanying raft of serious co-morbidities. They include hyperlipidaemia, diabetes, cardiovascular disease, hypertension, respiratory disease, cancer and osteoarthritis (Malnick & Knobler, 2006; Sassi, 2010). Childhood obesity predisposes to adult obesity and increases the risk of developing health complications that are non-apparent until adulthood such as diabetes and cardiovascular disease (World Health Organisation, 2011). Furthermore, obese children are developing diabetes and have high blood pressure and

cholesterol, both risk factors for cardiovascular disease (CVD). In one study, 70% of obese children had at least one CVD risk factor, and 39% had two or more (Bofill et al., 1997; Rajasingam, Seed, Briley, Shennan, & Poston, 2009).

The current and future encumbrance on health services is enormous and potentially unmanageable. The need to develop intervention strategies to reduce the rates of obesity has been repeatedly voiced (World Health Organization, 2009), but evidence of effective interventions is limited and there is no "one size fits all' solution (Gortmaker et al., 2011). Concurrent with the need to reduce obesity rates is a need to optimally manage the health of the existing obese populations.

1.1.4. *Obesity among women*

Incumbent within the general rise of obesity, there has been a vast increase in the incidence of overweight and obese women of reproductive age. There are consequent increasing rates of serious maternal and fetal complications secondary to obesity including fetal anomalies, diabetes, hypertensive disorders, caesarean delivery, postpartum haemorrhage, large for gestational age babies and stillbirth (Barau et al., 2006; Bhattacharya, Campbell, Liston, & Bhattacharya, 2007; Bodnar, Ness, Markovic, & Roberts, 2005; Cedergren, 2004; Chu et al., 2007; Ramachenderan, Bradford, & McLean, 2008; Sebire et al., 2001; Stacey et al., 2011; Watkins, Rasmussen, Honein, Botto, & Moore, 2003).

The US National Health and Nutrition Examination Survey 2009–2010 reported one third of women age 20-39 to be obese (Ogden, Carroll, Kit, & Flegal, 2012). In New Zealand, more than half of the general female population and one third of women receiving obstetric care at National Women's Hospital (NWH) in Auckland are overweight or obese (Ministry of Health, 2008; National Women's, 2010). Although the rates of maternal obesity at NWH have remained stable over the past four years, just as they are not rising, neither are they falling. Although obesity is preventable and potentially reversible, dramatic weight loss during pregnancy is not a safe option. Although it is well established that maternal obesity is associated with adverse outcomes, there is an urgent need for evidence based knowledge to inform clinical practice for obstetric management of obese women. It is vital to establish best practice in management of pregnancy, labour and birth for obese women, to provide optimal birth outcomes, and to determine modifiable factors to facilitate such outcomes.

1.2. Aims of the research

The aim of this PhD thesis was to investigate the role of obesity as a risk factor associated with adverse pregnancy outcomes in obese nulliparous women and to identify factors that would assist with management and planning of antepartum and intrapartum care to modify outcomes.

The broad objectives of this research were to investigate three high risk obstetric complications, common among nulliparous, obese women:

association between Caesarean section (CS) rates, maternal obesity and lipid profile

association between the risk of postpartum haemorrhage (PPH) and maternal obesity

pre-eclampsia with a specific emphasis on risk factors in early pregnancy

1.3. Structure of thesis

This thesis begins with an overview of obesity: definition, prevalence, pathophysiology and medical complications. Following this are three chapters presenting a review of the existing literature that has investigated maternal obesity. The literature review has three major points of focus on common serious complications associated with maternal obesity: Caesarean section, postpartum haemorrhage and pre-eclampsia. These three chapters aim to provide a framework for the understanding of obesity and the complications associated particularly with obesity in pregnancy, and to provide a context for the research.

The body of the thesis is based upon four papers that report findings from research from four studies. Three papers report findings from the SCOPE pregnancy study, a multicentre prospective cohort study. The fourth paper reports findings from a study using a larger cohort from National Women's Hospital, Auckland, New Zealand. At time of submission, two of these papers have been published, one has been submitted and is being considered for publication, and the last SCOPE study paper is awaiting submission after publication of a main SCOPE paper.

The first paper, *Risk of first and second stage cesarean by maternal BMI among nullipara in labor at term (Obstetrics and Gynecology, 2011),* investigates whether CS rates are increased in both first and second stages of labour in overweight and obese women, and whether being overweight or obese are independent risk factors for all caesarean deliveries in the first and second stages of labour. This paper reports a novel and clinically important finding identifying when caregivers need to be alert to elevated risk of CS among obese women.

The second paper, *Early pregnancy maternal serum lipids are not associated with risk of intrapartum caesarean in overweight and obese nulliparous* women (submitted to *BMC:Pregnancy and Childbirth Nov 2012)* investigates the role of early pregnancy serum cholesterol and clinical risk factors associated with first stage CS for failure to progress among overweight and obese women. This paper reports novel findings exploring the relationship between serum cholesterol rates of CS in overweight and obese women.

The third paper, Maternal Obesity and Postpartum Haemorrhage after Vaginal and Caesarean Delivery among Nulliparous Women at Term: a retrospective cohort study (BMC:Pregnancy and Childbirth 2012) determines whether overweight and obesity are independent risk factors for major postpartum haemorrhage (PPH ≥1000ml) after vaginal and CS delivery. This paper explores the relationship between obesity and postpartum haemorrhage whilst accounting for many other risk factors for PPH, according to mode of delivery. The paper identifies novel and clinically applicable findings.

The fourth paper, *Early pregnancy risk factors for pre-eclampsia among obese nulliparous women* identifies risk factors in early pregnancy for development of preeclampsia in obese nullipara. This paper reports a novel finding that reduced concentrations of HDL-cholesterol are associated with pre-eclampsia among obese women, and that other risk factors identified are very similar to those for cardiovascular disease.

These papers are followed by a discussion of the research and considerations for future directions of research.

As stated, three of the studies in this thesis report findings from the SCOPE pregnancy study, within which I assumed a role as follows: I worked with the SCOPE study throughout it's duration in New Zealand for four years from Sept 2004 to June 2008. I was the senior research midwife and was the only midwife employed for the total duration of the study. My responsibilities included to recruit, interview, examine, complete data on and obtain specimens from participants and partners both during and at the end of pregnancy. I was responsible for follow up of participants and babies with specific responsibility for collating and completing data on recruits who developed the target pregnancy endpoints of pre eclampsia, fetal growth restriction and/or spontaneous preterm birth. In collaboration with others, I was responsible for data monitoring and data cleaning, and checking work as collaborative team member; assisting in ongoing review and updating of database datapoints. At times of annual and sick leave I was the acting project manager. I assisted in the development of a literature library and gave presentations and provided education for health professionals about SCOPE. When I had played a significant role in SCOPE, I was supported by the SCOPE principal investigators to use the data for a PHD project. I was successful in gaining a Senior Health Research Scholarship with the University of Auckland, which enabled the undertaking of doctoral study. The submission, describing my role in SCOPE and stating intent to use SCOPE data was approved by the Board of Graduate studies as part of the application process.

Chapter 2. Obesity: an overview

2.1. Definition of obesity

Overweight and obesity are defined as an "abnormal or excessive fat accumulation that may impair health" (World Health Organization, 2009). The most widely applied of various anthropometric measures used to calculate and classify adiposity is the Body Mass Index (BMI), calculated by dividing weight (kilograms) by square of height (metres). BMI is the most simple practical tool for adiposity classification. BMI, as used in adult populations, was developed using predominantly European ethnicities, and is unadjusted for age, gender or ethnicity. The association between health risk and increasing BMI is continuous for all populations, starting from BMI of <25. BMI categories were designed to be a tool to stratify risk, and also to compare populations and are applied for generalised use clinically and in research (*Table 2.1*) (World Health Organization, 2000).

BMI Classification	kg/m^2
Underweight	<18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese	≥30
Obese Class I	30-34.9
Obese Class II	35-39.9
Obese Class III	≥40

Table 2-1 World Health Organisation BMI classification

There are some acknowledged limitations of the use and categorisation of BMI. The World Health Organisation has acknowledged the contentious issue of BMI in relation to ethnicity. BMI may not correspond to the same degree of fatness in different ethnic groups due, in part, to different body fat percentage and distribution. Hence for some ethnicities, health risks increase before the cut off point of 25 kg/m² and the interpretation of BMI gradings in relation to risk may differ for different ethnicities (Jackson, Ellis, McFarlin, Sailors, & Bray, 2009; Ministry of Health, 2008; Rush et al., 2007). Of particular relevance to New Zealand, Asian, Maori and Pacific populations have been shown to have higher and lower proportions of body fat respectively compared to European adults with the same BMI. Therefore a level of health risk is different at the same BMI. There have been recommendations

to classify obesity at a higher BMI cut off (≥32kg/m^2) for Maori and Pacific ethnicities, however data is not available as yet to confirm or refute that these criteria correlate better with health risk compared with the WHO BMI cut-off of ≥30kg/m^2 (Rush, et al., 2007; Swinburn, 1998).

In 2004, a WHO expert consultation group made provision for public health action by recommending additional BMI cut off points (23, 27.5, 32.5, and 37.5kg/m^2) that would allow future international comparisons (World Health Organization, 2004). This was based on the premise that a continuous relationship exists between increasing BMI and increasing health risk, but that cut offs would be a useful tool in clinical and public health settings.

Despite its limitations, BMI is an acceptable proxy for degree of adiposity and has been associated with levels of morbidity and mortality universally among many different populations (World Health Organization, 2004). BMI is commonly used in health research and is the primary measure used in the studies described in this thesis.

2.2. Prevalence of obesity

The world is getting fatter. Over three decades since 1980, rates of obesity have risen from 8 to 14% and 5 to 10% for men and women respectively (World Health Organization, 2012). In 2008 it was estimated that 1.46 billion adults had a BMI of 25kg/m^2 or more, of whom one third were estimated to be obese (BMI ≥30kg/m^2). Since 1980, mean BMI has increased globally by 0.4kg/m^2 and 0.5 kg/m^2 per decade in men and women respectively (Finucane et al., 2011). The highest BMI rise is reported to be in Oceania, which incorporates New Zealand, notably with a 1.8 kg/m^2 increase in female BMI.

In 2008, approximately 300 million women aged over 20 years worldwide were obese (World Health Organization, 2012). Among high income countries, women in New Zealand, Australia and USA had the highest reported gain in BMI over the past three decades (Finucane, et al., 2011). The International Obesity Task Force have reported that more than 200 million school age children are overweight, and it is predicted, for the first time, that these children will have a shorter lifespan than their parents (International Obesity Task Force, 2012).

In New Zealand, one third of adults (age ≥15yrs) are overweight, and one quarter obese. There are significant differences in the rates of obesity among New Zealand's main ethnic groups. Those of Pacific Island ethnicity have the highest rates (64%), followed by Maori (42%), European/other (24%) and Asian (11%) using standard WHO BMI categories (Ministry of Health, 2008). Internationally, New Zealand sits alarmingly high in the female obesity hierarchy (*Figure 2.1*).

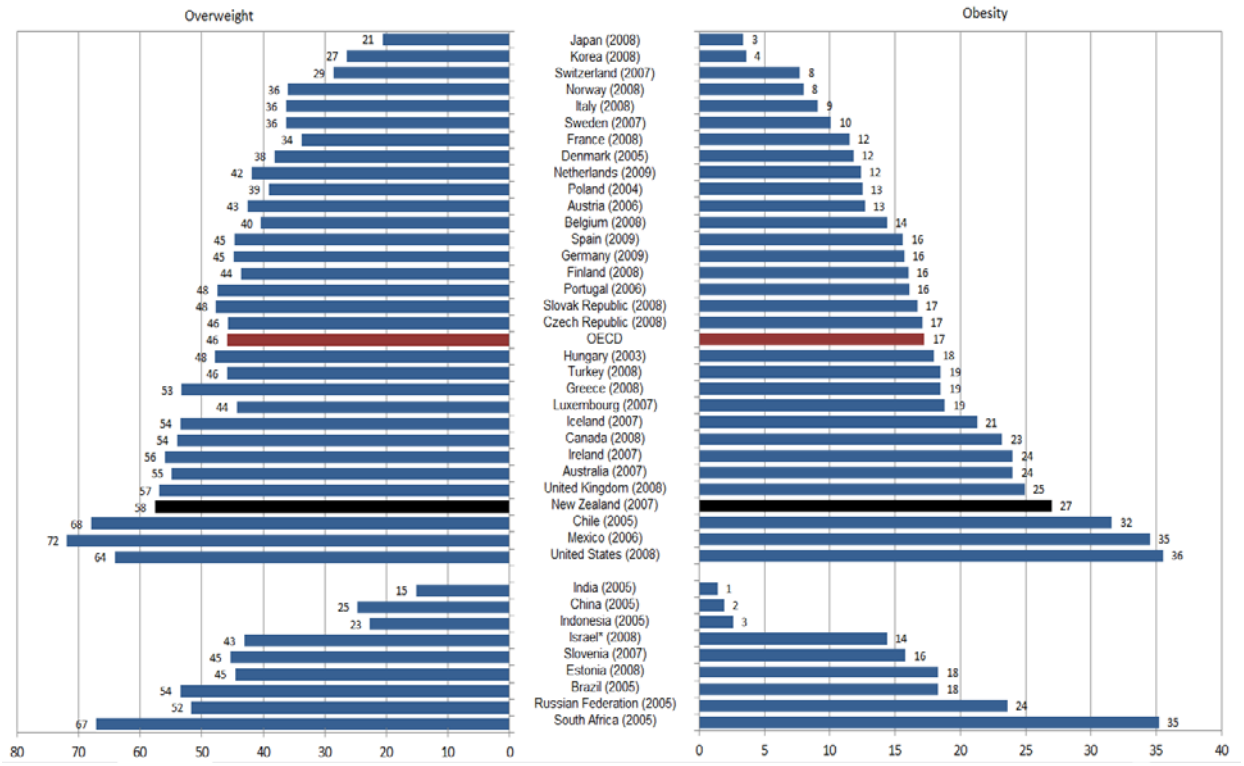

Figure 2-1 Female overweight and obese rates in OECD countries

Adapted from figure 2.1 Obesity and overweight in OECD and non-OECD countries from OECD (2010), Obesity and the Economics of Prevention: Fit not Fat, OECD Publishing. http://dx.doi.org/10.1787/9789264084865-en

The most recent New Zealand Health Survey (2006/7) reported adult female overweight and obesity rates of 29 % and 26% respectively. Rates of female obesity in Australia (24%) are comparable to NZ. The differences in New Zealand female overweight and obesity rates according to ethnicity mirror those of the whole adult population: Pacific women have the highest prevalence (88% [overweight 22%, obese 66%]), followed by Maori (72% [overweight 29%, obese 43%]). Compared to women in the "total population", Pacific and Maori women are respectively 2.5 and 1.7 times more likely to be obese, European women are about equivalent and Asian women are 50% less likely to be obese (Ministry of Health, 2008).

In 2010, over one third of women receiving maternity care at National Women's Hospital (NWH), Auckland, were overweight or obese (underweight 6 %, normal BMI 59%, overweight 19%, obese 16%). Rates of obesity were particularly high among Pacific (57%) and Maori (33%) women, compared to NZ European women (10%), with difference in rates according to ethnicity mimicking the NZ general population. The rates of obesity at NWH have remained similar over the past 5 years.

It is also concerning that the relationship between BMI and age is "U' shaped, demonstrating higher rates of BMI ≥25kg/m^2 not only among older mothers (>40yrs) but also among younger mothers (<25yrs) (National Women's, 2010). Being overweight prepregnancy increases risk for excessive

postpartum weight retention (Gore, Brown, & West, 2003), so as younger mothers start their child bearing years in an obese state, the future burden of obesity is compounded as these mothers' BMI measures increase concurrently with increasing parity.

2.3. Pathophysiology of obesity and adipose tissue

In broad terms, the basic physiological cause of obesity is exceedingly simple. Obesity occurs as a result of energy imbalance, reflecting a persistent state of energy intake exceeding energy expenditure. Excess energy is stored as fat or adipose tissue. The consequences of excess fat storage are diverse and involve intricate adjustments to metabolism, commonly resulting in hyperlipidaemia, hypertension and insulin resistance which, if combined in a non-pregnant state, comprise what is termed "metabolic syndrome" (Eckel, Grundy, & Zimmet, 2005).

In order to understand the pathophysiology and effects of obesity in pregnancy, firstly it is useful to understand the basic anatomy, physiology and metabolism of normal adipose tissue. As the contents of this thesis relate to metabolic changes associated with hyperlipidaemia and with hypertension, it is these changes that will be predominantly described. However, as there are inextricably linked complex interplays between the numerous metabolic roles of adipose tissue, other roles such as glucose metabolism will also be described.

2.3.1. *Anatomy and physiology of adipose tissue*

Adipose tissue is the largest endocrine and energy storage organ in the body. One third of adipose tissue comprises adipocytes (fat cells), the remaining two thirds comprises of connective tissue, small blood vessels, nerve tissue, immune cells, fibroblasts, macrophages and preadipocytes (Ahima, 2006; Avram, Avram, & James, 2005; Kershaw & Flier, 2004).

There are two cytotypes of adipocytes differentiating adipose tissue into white and brown. In humans, brown adipose tissue is primarily functional only in the neonatal period, comprising about 5% of the body mass and has a vital role in heat generation. The amount of brown adipose tissue is vastly reduced by adulthood. White adipose predominates in mammals, with the largest deposits found subcutaneously and around viscera. In normal weight men it contributes 9-18% of body weight, and 14-28% in women (Cinti, 2006). It is white adipose tissue that is referred to henceforth.

A single white adipocyte is unilocular, with a single lipid droplet, consisting of triglycerides (TAGs) occupying most of the intracellular space surrounded by a thin rim of cytoplasm containing the nucleus (*Figure 2.2*) (Cinti, 2006).

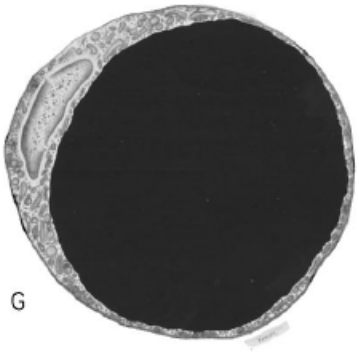

Figure 2-2 A single white adipocyte

Historically, fat was considered to be largely metabolically passive, useful only for energy storage. The recognition of adipose tissue as a highly active organ, with vital endocrinological and immunological roles, has led to it's identification as a major site for production of many cytokines (cell to cell signalling proteins), called adipokines. The first adipokine, identified in 1994, was leptin, a satiety regulating protein. To date there are in excess of 100 different adipokines and they include fatty acids, prostaglandin, and hunger and metabolism regulating hormones. The major protein molecules produced by adipose tissue include adiponectin, resistin and angiotensin, all components of the blood pressure and fluid balance regulating "rennin-angiotensin" system; leptin, insulin mimicking vistafin; and pro-inflammatory tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (Ahima, 2006; Fischer-Posovszky, Wabitsch, & Hochberg, 2007; Stehno-Bittel, 2008). Concentrations of these cytokines are altered in obesity related metabolic complications such as hypertension and hyperlipidaemia. Adipose tissue also produces enzymes involved in the metabolism of steroid hormones, such as oestrogen and testosterone (Callaway, O'Callaghan, & McIntyre, 2009; Kershaw & Flier, 2004; Stehno-Bittel, 2008; Zhang et al., 1994). As well as being a primary source of cytokine production, adipose tissue also acts in response to hormone and central nervous systems signals.

2.3.1.1. Basic metabolism of white adipose tissue

As an active organ, adipose tissue plays a major role in both lipid and glucose metabolism providing equilibrium of energy expenditure and storage. As well as storing fat, it also releases fatty acids and glycerol to be utilised by other tissues when they require energy. Glucose metabolism in other tissues is highly influenced by the metabolic activity of adipocytes. Increased lipolysis (lipid hydrolysis) of triglycerides (TAGs) in adipocytes increases circulatory concentrations of free fatty acids and glycerol. The released free fatty acids regulate glucose homeostasis in other tissues. After eating, secretion of insulin increases, resulting in glucose intake by adipocytes and lipid storage; increased protein and glycogen production and glucose intake by muscle cells, and increased lipid and protein synthesis along with decreased glucose production in the liver (*Figure 2.3*). When fasting, adipose tissue

releases fatty acids to provide energy, resulting in reduced glucose intake in adipocytes and muscle, and increased hepatic glucose production (*Figure 2.4*) (Callaway, et al., 2009).

Immune system cells are an important integral constituent of adipose tissue. These immune cells include a small number of either inactive or anti-inflammatory macrophages. Adipose tissue influences immune function, as a result of production of cytokines such as resistin, leptin, TNF-α and IL-6 and adiponectin. Receptors for leptin and adiponectin have been shown to be present in the immune and cardiovascular systems (Guzik, Mangalat, & Korbut, 2006). Leptin maintains immune system up regulation, adiponectin reduces the levels of inflammatory molecules that are released and resistin stimulates inflammation. In a non-obese state, adipocytes produce low concentrations of leptin, vistafin, and fatty acids, high concentrations of adiponectin and probably very small amounts of TNF-α and resistin (Stehno-Bittel, 2008).

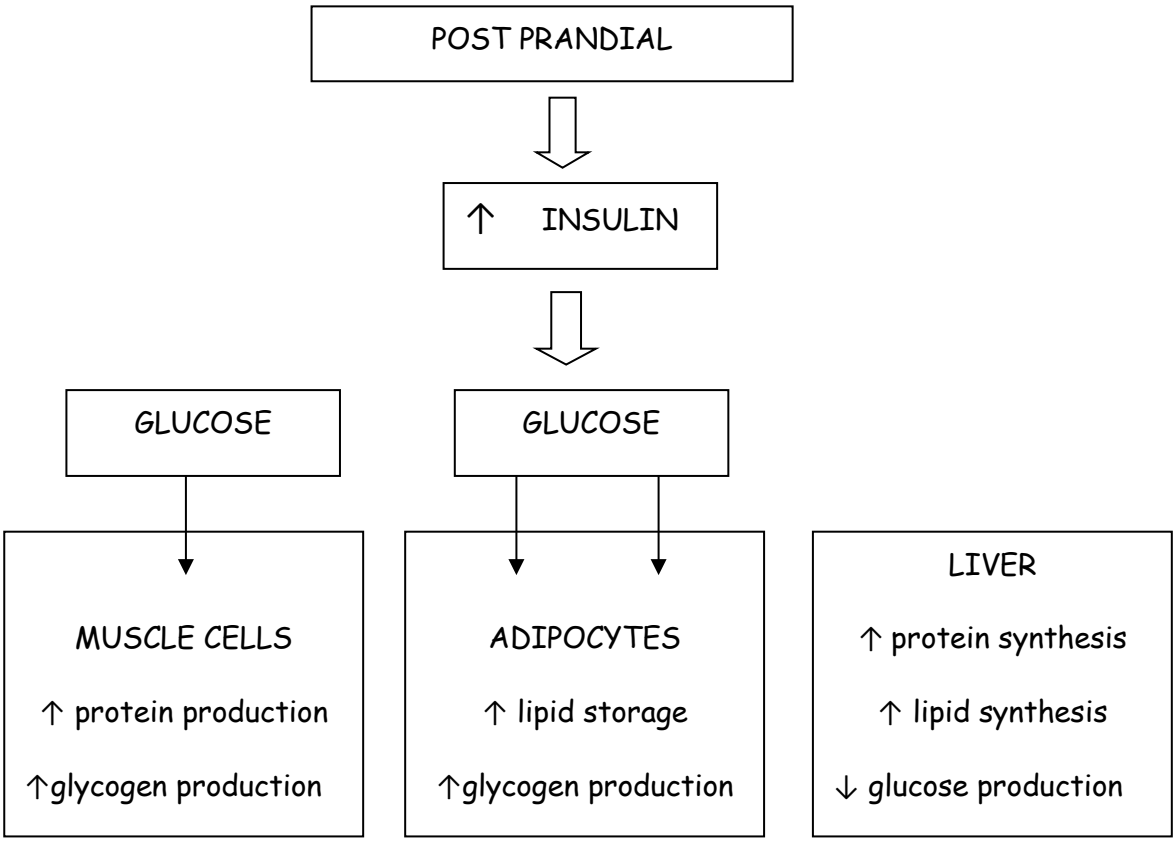

Figure 2-3 Post prandial metabolism

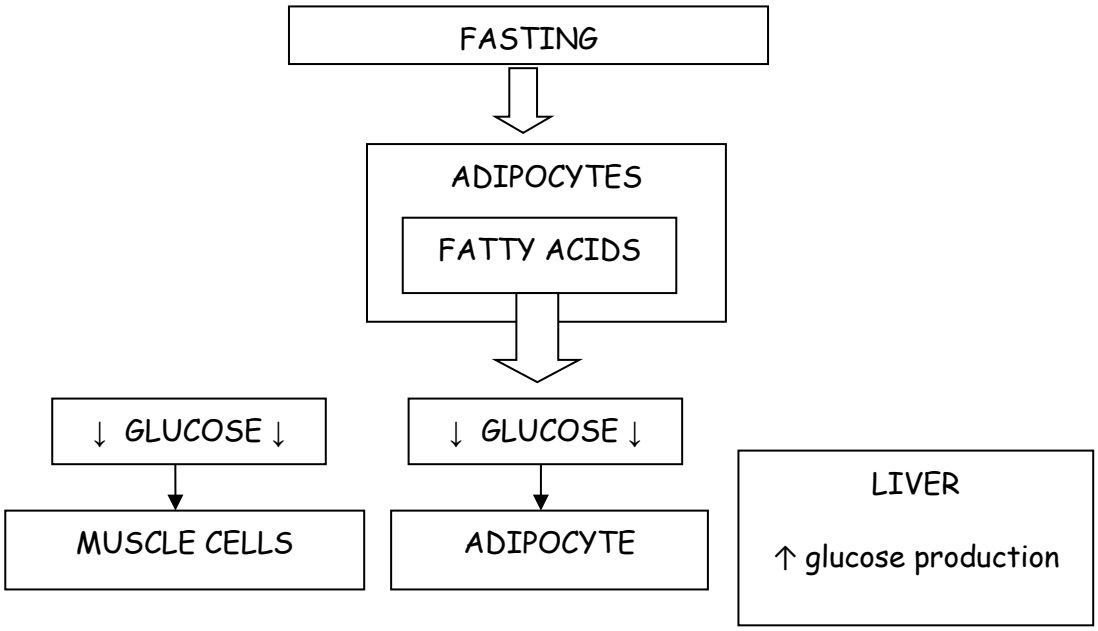

Figure 2-4 Fasting metabolism

2.3.2. *Normal physiology of lipid metabolism*

The main fuel molecules in fats are fatty acids which provide long term energy storage. Fatty acids are sourced primarily from circulating lipids derived from ingested dietary triacylglycerols, or secondarily from de novo lipogenesis (conversion of dietary carbohydrate into fat).

There are four major lipoproteins used to transport lipids in plasma:

chylomicrons

very low density lipoprotein (VLDL)

low density lipoprotein (LDL)

high density lipoprotein (HDL)

Lipoproteins each have a similar structure of phospholipids, apoprotein, triacylglycerols and cholesterol, with differing percentages of each of the structural components. The trend progressing from chylomicrons to HDL (as in the above order) is increasing protein, increasing density and decreasing size.

Each lipoprotein has a different function. Chylomicrons transport TAG to other tissues (except to the kidneys) (*Figure 2.5*). VLDL binds TAGs in the liver and carries them to adipose tissue. LDL carries cholesterol to peripheral tissue. HDL is bound to plasma cholesterol and transports cholesterol to the liver (Hardy, 2010; Myant, 1971).

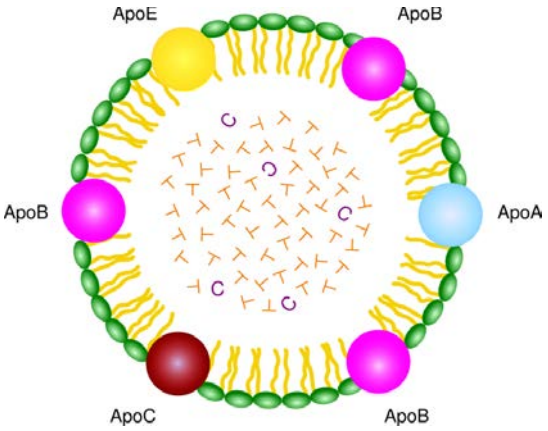

Figure 2-5 A single chylomicron

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There are three main pathways involved in the production and transport of lipids, which all interact to balance energy requirements: exogenous lipid pathway (dietary), endogenous pathway and reverse cholesterol transport. There is also de novo lipogenesis.

2.3.2.1. Exogenous lipid pathway (dietary)

After eating, fats enter the small intestine from the stomach and are then hydrolysed (made water soluble) into non-esterified fatty acids and monoglycerols to enable their metabolism. This emulsification occurs through the detergent action of pancreatic secretions and bile acids. The resultant hydrolysed mix is a fine suspension of "micelles" (*Figure 2.6*) and is carried by bile salts to the mucosal cells (enterocytes) lining the small intestinal wall where micelle contents are released.

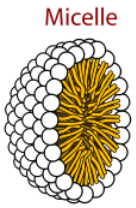

Figure 2-6 A single micelle

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Once in the intestinal mucosa, glycerol and short chain fatty acids enter the mesenteric blood. Longer chain free fatty acids undergo re-esterification as the fatty acids and glycerol released from the micelles are reassembled into TAGs in the form of chylomicrons (McMurray, 2005). The spherical

chylomicrons consist of an outer membrane of phospholipids and protein, encompassing cholesterol and triglycerides inside.

A full circle has now been completed. Ingested TAGs have been broken down by hydrolysis, and then after absorption through the intestinal wall, the products of this hydrolysis, fatty acids and glycerol, have been re-esterified to reform TAGs. The TAGs initially pass through the lymphatic system via the thoracic duct into the systemic bloodstream in plasma and to the liver as “nascent or immature” chylomicrons. Once in the bloodstream, maturation of the chylomicrons occurs with donation of apoproteins from HDLs.

Chylomicrons are responsible for transporting all dietary lipids in the circulation. They repeatedly pass through the capillary beds of all tissues. Uptake of incumbent fatty acids within the chylomicrons by adipocytes and other cells is an active process as fatty acids cannot diffuse passively through plasma membrane. This is enabled through the action of an enzyme called lipoprotein lipase (LPL), which is located on the surface of the capillaries in adipose tissue and also particularly in skeletal and cardiac tissue. LPL is activated by Apoprotein CII on the chylomicron, and allows the fatty acids encompassed within to be broken down. The TAG of chylomicrons is hydrolysed to form glycerol and fatty acids, which enter the tissue cells, and are oxidised or converted to intracellular TAG. Unused intracellular TAGs are stored (Hardy, 2010; McMurray, 2005).

2.3.2.2. Endogenous pathway

Following chylomicron breakdown, cholesterol rich chylomicron remnants remain in the plasma, and are removed from the bloodstream by the liver. The apoprotein on the chylomicron remnant binds to its receptor on the liver surface and is ingested. Once in the liver, the remnants are used to make a new protein, VLDL, which has high lipid content. The liver secretes VLDL into the blood stream, and in the same way it acts on chylomicrons, lipoprotein lipase on the capillary surface of the tissues acts on VLDL, freeing the fatty acids and glycerol to enable their uptake and subsequent reconversion to triacylglycerols for energy storage. Processed VLDL becomes VLDL remnants, most of which are taken up by the liver. Remaining particles become intermediate density lipoprotein (IDL), a smaller denser lipoprotein than VLDL. IDLs are also reabsorbed by liver or are hydrolysed to form low density lipoprotein (LDL), a smaller denser particle than IDL. LDL is the main carrier of circulating cholesterol in the body. It is used for cell membrane and steroid hormone synthesis and bile acid synthesis. LDL is associated with plaque formation in blood vessels, and has a high TAG and cholesterol content, and thus is often known as “bad cholesterol”. Fatty acids and glycerol from LDL are absorbed by adipose and other tissues for energy storage, and remaining LDL particles are taken up by liver where they are resupplied with TAGs, phospholipids, and cholesterols and sent out again as VLDL (Kingsbury & Bondy, 2003; Large, Peroni, Letexier, Ray, & Beylot, 2004).

2.3.2.3. Reverse cholesterol transport

The third main pathway of lipid metabolism and transport is reverse cholesterol transport involving the removal of cholesterol and lipoproteins from the tissues, and transport of cholesterol to the liver for degradation. This role is fulfilled by HDL, the smallest and densest lipoprotein, often referred to as "good" cholesterol. HDL is formed by a maturation process whereby precursor particles (nascent HDL) secreted by the liver and intestine go through a series of conversions (HDL cycle) to attract cholesterol from cell membranes and free cholesterol to the HDL particle core.

2.3.2.4. De novo lipogenesis

As well as synthesising new lipoproteins through repackaging of lipoprotein remnants, after eating, the liver also fulfils a role of de novo lipogenesis (conversion of glucose into fatty acids). Lipogenesis is regulated by nutritional status. After eating, glucose from the blood enters the liver and converts to glucose-6-phosphate.Some of this is used as fuel and some becomes glycogen. When liver glycogen stores are full, excess glucose is converted into fatty acids. They are packaged as VLDL and enter the bloodstream to be uptaken and stored in adipose tissue. Adipose tissue is the major storage point for fatty acids. The fatty acids are uptaken and stored as TAGs in the adipose tissue. In order to reassemble the fatty acids as TAGs within the adipocyte, glycerol-3-phophate is required. This has to come from glucose. Therefore, it is not possible to store fat unless there is an excess of glucose in the body (Hardy, 2010).

2.3.3. *Pathophysiology of obesity*

Contrary to earlier beliefs, it is now known that adipocytes can increase and decrease in both number and size throughout life, and there is evidence that apoptosis of fat cells occurs (Fischer-Posovszky, et al., 2007). In a state of obesity hypertrophy of adipocytes occurs primarily, but when the adipocytes attain a critical size, an unknown trigger provokes the differentiation of precursor cells into mature adipocytes, causing adipocyte hyperplasia (Cinti, 2006). Thus, in lesser states of obesity, the increase in adipose tissue mass is hypertrophic in nature, whereas in more severe obesity, the changes are both hypertrophic and hyperplastic.

The increased adipose tissue mass has a profound effect on metabolic function, adversely affecting the liver, pancreas, beta cells, skeletal muscle (lipid accumulation and peripheral insulin resistance) and heart (Avram, Avram, & James, 2005; de Ferranti & Mozaffarian, 2008). The primary metabolic effects are dyslipidaemia, hypertension and insulin resistance resulting in hyperglycaemia. Endothelial dysfunction, oxidative stress, endoplasmic stress, inflammation and prothrombotic changes are some of the mechanisms underpinning the deranged metabolic function.

2.3.3.1. Dyslipidaemia in obesity

Obesity is associated with increased concentrations of VLDL, LDL and total cholesterol, whereas HDL concentrations are reduced. The raised plasma concentrations of free fatty acids and consequent

increase in free fatty acids transporting to the liver result in insulin resistance and increased hepatic production of VLDLs. It is likely this is the primary cause of obesity related hypertriglyceridaemia. In an obese insulin resistant state, LDLs have an increased triacylglycerol content, and are broken down into fatty acids and glycerol by hepatic lipase at a rapid rate, resulting in smaller, denser LDL particles. These smaller LDL's are able to infiltrate the endothelium and contribute to inflammation and atherosclerosis (Van Gaal, Mertens, & De Block, 2006). HDL cholesterol content is decreased in hypertriglyceridaemia, as a result of decreased cholesterol ester within the lipoprotein core, and HDL becomes smaller and denser. Consequently, HDL is cleared from the circulation at a higher rate and plasma concentrations are decreased (Callaway, et al., 2009; Eckel, et al., 2005; Van Gaal, et al., 2006).

At a more refined level, adipocyte cellular dysfunction contributes significantly to the deranged lipidaemic metabolic function. The cellular dysfunction in obesity stems partly from endoplasmic reticulum stress. The smooth endoplasmic reticulum in the adipocyte is involved with the formation of its lipid droplet within, sensing and regulating cholesterol, and synthesising proteins (de Ferranti & Mozaffarian, 2008). In vivo studies have found that endoplasmic reticulum stress affects lipid synthesis and is detrimental to the cholesterol sensing regulation (Gregor & Hotamisligil, 2007). Consequently, there is an increased release of systemic free fatty acids and inflammatory mediators. The increased concentration of free fatty acids is associated with lipid accumulation in the liver, skeletal muscle, heart, and pancreas.

It is speculated that lipid accumulation, particularly cholesterol, may also occur in smooth muscle, such as uterine myometrium (Noble, Zhang, & Wray, 2006; Zhang, Kendrick, Quenby, & Wray, 2007). This lipid accumulation is specifically related to disruption in microdomains within the muscle cell membrane called lipid rafts. The lipid raft dysfunction appears to be specific to smooth muscle. An association between increased membrane cholesterol in smooth gallbladder muscle and impaired contractility was reported a decade ago, and, notably, withdrawal of cholesterol from the smooth muscle cell plasma membrane reinstated normal contractile function (Chen, Amaral, Biancani, & Behar, 1999). Subsequently, a similar effect was demonstrated in uterine myometrium (Zhang, et al., 2007). Further detail relating to the potential effects of obesity related hypercholesterolaemia on uterine myometrium and effects on myometrial contractility are presented in Chapter 3.

2.3.3.2. Hypertension

The associations between obesity and hypertension are complex, multi factorial and not yet fully understood. It is likely that principal inter-related causal pathways are associated with vascular resistance, vasoconstriction, adipocyte pro inflammatory cytokine release (e.g.IL-6, TNF-α) and sodium retention, resulting from individual and inter action of insulin, leptin and free fatty acids. The manifestations of endothelial dysfunction, insulin resistance and sympathetic nervous system activity have a compounding effect on blood pressure (Montani, Antic, Yang, & Dulloo, 2002; Poirier et al., 2006). Increased blood volume in obesity resulting in increased cardiac output (due to higher stroke

volume) is also associated with hypertension (Alpert, 2001; Callaway, et al., 2009; Poirier, et al., 2006).

Further detailed description of the association between maternal obesity in pregnancy and hypertension will be presented in Chapter 5.

2.3.3.3. Insulin resistance

Obesity is undoubtedly associated with insulin resistance. Increased circulating concentrations of non-esterified fatty acids released from TAGs in adipose tissue are a primary contributing factor. As adipocytes hypertrophy, there is a physiological decrease in their insulin sensitivity. Insulin acts as an inhibitor of lipolysis in adipose tissue, consequently as insulin sensitivity decreases, lipolysis increases, and the adipocytes release increased amounts of fatty acids, resulting in increased hepatic TAG and VLDL production, and decreased HDL production (Callaway, et al., 2009).

In skeletal muscle, the effect of fatty acids on insulin sensitivity restrains glucose uptake and glycogen and TAG storage. The resultant increased plasma concentrations of glucose and fatty acids lead to increased insulin production in the pancreas and thus hyperinsulinaemia. The increased glucose and fatty acid concentrations eventually cause impaired glucose tolerance and diabetes (Callaway, et al., 2009). As insulin is a lipolytic inhibitor, there is an ongoing persistent cycle of deteriorating insulin sensitivity and consequently raised fatty acid concentrations.

The inflammatory state of the increased adipose tissue mass of obesity also contributes to insulin resistance as increased release of pro-inflammatory cytokines such as TNF-α provoke fatty acid release, and inhibit insulin receptor signalling (Xu et al., 2003). Reduced adiponectin is also associated with insulin resistance, as it has an insulin sensitising effect (Fischer-Posovszky, et al., 2007).

2.3.3.4. Vasculopathy, inflammation, coagulatory dysfunction

Vascular endothelial cells maintain vascular homeostasis with involvement in barrier function, vasoconstriction and dilation, thrombosis and inflammation. Obesity related changes of cytokine concentrations such as TNF-α cause disruption of endothelial function and consequently of vascular homeostasis. Manifestations of endothelial dysfunction include hypertension, atherosclerosis and vasculopathy. There are numerous contributory factors to endothelial dysfunction, including dyslipidaemia, chronic inflammation, insulin resistance, increased oxidative stress and altered prothrombotic factors (Callaway, et al., 2009; Montani, et al., 2002).

Adipocyte cellular inflammation also contributes to metabolic dysfunction. In obesity, large numbers of proinflammatory macrophages independently enter adipose tissue, there is an increase in inflammatory pathway activity and increased production of proinflammatory adipokines such as IL-6, and TNF-α, and a decrease in anti-inflammatory adiponectin. Adipokines such as leptin and resistin also attract inflammatory macrophages, and in a self-serving circle of inflammation, the macrophages

themselves release inflammatory stimulating factors including resistin and TNF-α. The consequence is a chronic state of inflammation (Gregor & Hotamisligil, 2007; Stehno-Bittel, 2008).

Obesity is associated with increased serum viscosity. Raised concentrations of fibrinogen and plasminogen activator inhibitor-1, which inhibits the breakdown of fibrin, result in a hypo-fibrinolytic state (Van Gaal, et al., 2006). These changes increase the risk of thrombosis.

Summary of pathophysiology and effects of obesity

- hypertrophy ± hyperplasia of adipocytes
- dyslipidaemia: increased levels of VLDL, LDL and total cholesterol, reduced levels of HDL
- lipid accumulation in liver, skeletal muscle, heart, pancreas and possibly smooth muscle
- hypertension
- insulin resistance
- endothelial dysfunction
- chronic state of systemic inflammation
- coagulatory dysfunction

2.4. Physiological metabolic adaptation in normal pregnancy

Physiological changes in maternal metabolism in pregnancy occur to accommodate the increased nutritional and energy needs of both the maternal and feto-placental unit. They increase nutrient availability to ensure adequate fetal growth and development in utero, to provide energy stores and substrates for the fetus to utilise after birth, and for the mother to utilise for demands of pregnancy, labour and lactation. Major change occurs in the metabolism of lipid, glucose and protein resulting in relative hyperlipidaemia, alteration in insulin sensitivity, and transport and oxidation of amino acids (Hadden, 2008; von Versen-Hoeynck & Powers, 2007).

There are basically two stages of maternal metabolism during pregnancy; anabolic and catabolic. The initial anabolic stage during the first two trimesters enables development of fat stores to meet later feto-placental and maternal demand. A catabolic state ensues for the third trimester with increased insulin sensitivity resulting in increased availability of nutrients for rapid fetal growth as maternal free fatty acid concentrations and glucose rise (Freinkel, 1972; Lain & Catalano, 2007; von Versen-Hoeynck & Powers, 2007).

2.4.1. *Gestational lipid metabolism*

There is a physiological state of hyperlipidaemia in pregnancy. The catabolic state of later pregnancy enables lipid availability for maternal use as an energy source, and glucose and amino acids for fetal use (von Versen-Hoeynck & Powers, 2007). There are increasing concentrations of plasma free fatty acids. Insulin inhibits the action of lipase which reduces hydrolysis of TAGs, but the physiological insulin resistance of pregnancy means lipase action is less inhibited and consequently there are increased concentrations of TAG hydrolysis and hence increased plasma concentrations of free fatty acids and glycerol. The liver uptakes a large proportion of the free fatty acids and glycerol, and hepatic re-esterification results in production of VLDL. There are massive increases in gestational plasma lipid levels. Total TAG concentrations increase by 200-400% and total cholesterol concentrations by 25-50%. By mid gestation LDL has increased by 50% and HDL by 30%. HDL decreases slightly at term (Lain & Catalano, 2007). As insulin resistance causes reduction of lipoprotein lipase action, there is a consequent reduction in clearance of plasma lipoproteins and an increase in circulating TAGs (von Versen-Hoeynck & Powers, 2007).

2.4.2. *Gestational glucose metabolism*

As pregnancy progresses beyond the first trimester, fasting glucose concentrations decrease, despite an increase in hepatic glucose production. There is a concurrent increase in fasting insulin. In a non-pregnant state, hepatic glucose production is reduced by insulin, but in pregnancy a physiological state of insulin resistance develops. It has been demonstrated that pregnant women produce extra insulin following a fixed glucose challenge, but plasma glucose levels remain high, showing reduced insulin sensitivity (Lind, Billewicz, & Brown, 1973). Although the insulin induced reduction of hepatic glucose production in pregnancy is less than in a non-pregnant state, glucose tolerance in pregnant women usually remains within normal limits. The consequence of decreased insulin sensitivity is increased postprandial plasma glucose and lipid concentrations, providing increased nutrients for transfer to the fetus (Lain & Catalano, 2007). The precise mechanism underpinning gestational insulin resistance is still unclear but pro-inflammatory cytokines such as TNF-α have a contributory role, as they interfere with insulin signalling (von Versen-Hoeynck & Powers, 2007).

2.4.3. *Inflammatory state of pregnancy*

It is now known that normal pregnancy is a controlled systemic state of inflammation (Sargent, Borzychowski, & Redman, 2006). In 1998 increased concentrations of peripheral leukocytes in pregnancy compared to the non-pregnant state were first reported, indicating an inflammatory response (Sacks, Studena, Sargent, & Redman, 1998). Part of this inflammatory response comprises production of pro-inflammatory cytokines including TNF-α and IL-6 (Sargent, et al., 2006). Among women with uncomplicated pregnancy TNF-α has been reported to be modestly elevated throughout pregnancy compared to non-pregnant women (Kraus et al., 2010; Kupferminc et al., 1994). C reactive protein, a marker of inflammation, has also been shown to be moderately increased from the first trimester (Sargent, et al., 2006).

2.4.4. *Endothelial function in pregnancy*

Healthy pregnancy is characterised by vasodilation and reduced vascular resistance (Cockell & Poston, 1997). These endothelial dependent vasodilation responses improve with increasing gestational age, despite gestational hyperlipidaemia (Saarelainen et al., 2006). Peripheral vascular resistance and arterial pressure fall from very early pregnancy (5 weeks) until between 20 and 32 weeks gestation, and then increase gradually until term (Silversides & Colman, 2007).

Summary of physiological metabolic adaptation in normal pregnancy

Normal pregnancy is associated with:

- anabolic metabolism first two trimesters
- catabolic metabolism third trimester
- physiological state of gestational hyperlipidaemia
- physiological state of insulin resistance
- activation of a systemic inflammatory response
- vasodilation and reduced vascular resistance

2.5. Effect of obesity on physiological metabolic changes in normal pregnancy

The physiological metabolic adjustments to normal pregnancy described above are exaggerated by obesity. Compared to normal weight women, obese women are more likely to enter into pregnancy in a pre-existing state of hyperlipidaemia, inflammation and insulin resistance. Consequently obesity is associated with higher rates of metabolic complications of pregnancy such as preeclampsia and diabetes (King, 2006). Obese women have an increased basal metabolic rate (BMR) during pregnancy compared to non-obese women. They already have existing energy reserves, and in contrast to non-obese women don't require an additional accumulation of fat during pregnancy. The increased BMR may serve to expel surplus energy and reduce the accumulation of unnecessary fat reserves (King, 2006). Maternal adiposity and gestational weight gain correlate with total energy costs of pregnancy.

2.5.1. *Gestational lipid metabolism in obesity*

Obesity exacerbates physiological gestational hyperlipidaemia. To recap, in normal pregnancy, the dominant lipid metabolism is lipogenic in early pregnancy (hydrolysis of lipids into free fatty acids and

glycerol), and lipolytic in late pregnancy (fat forming). However, in obesity, lipogenesis is only evident pre-pregnancy, and lipolysis predominates throughout pregnancy (Lain & Catalano, 2007). Obese women have increased concentrations of free fatty acids entering into pregnancy compared to those who are non-obese, and their enhanced inability to suppress lipolysis serves to further increase plasma free fatty acid concentrations. Obesity related dyslipidaemia in pregnancy has been demonstrated to be specifically associated with hypertriglyceridaemia and reduced concentrations of HDL. The magnified gestational hyperlipidaemia in obesity is not only due to increased insulin resistance, but also to elevated concentrations of oestrogen, as adipose tissue is the main source of oestrogen (King, 2006). Oestrogen impairs glucose tolerance, and causes a rise in VLDL concentrations.

2.5.2. *Gestational glucose metabolism in obesity*

In obese parturients with normal glucose tolerance, insulin is less able to suppress hepatic glucose production, resulting in exaggerated insulin resistance compared to non-obese women (Lain & Catalano, 2007). Obese pregnant women demonstrate a reduced insulin response to intravenous glucose compared to normal weight women, which is likely due to persistent insulin resistance causing hyperinsulinaemia (Catalano, Huston, Amini, & Kalhan, 1999). The consequence of obesity related insulin resistance is abnormally high concentrations of circulating plasma lipids and glucose after eating, as it decreases suppression of fat formation (lipolysis).

2.5.3. *Gestational inflammatory state in obesity*

Elevated concentrations of IL-6 and C reactive protein have been reported in obese pregnant women compared to those who are not obese, demonstrating increased inflammation (Madan et al., 2009; Ramsay et al., 2002).

2.5.4. *Gestational endothelial dysfunction in obesity*

Using an in vivo assessment of endothelial-dependent and independent microvascular function using laser Doppler imaging, Ramsay et al (2002) found a reduced response to administration of acetylcholine and to sodium nitroprusside both of which are endothelial dependent. This demonstrated for the first time that microvascular endothelial function in pregnancy is impaired in obese women compared to lean women (Ramsay, et al., 2002).

Summary of the effect of obesity on physiological metabolic adaptation in normal pregnancy

- increased metabolic rate
- lipolysis predominant throughout gestation
- exacerbation of physiological gestational hyperlipidaemia
- exaggerated insulin resistance and hyperinsulinaemia
- heightened systemic inflammatory state

2.6. Chapter summary

This chapter has summarised the anatomy and physiology of adipose tissue, pathophysiology of obesity, metabolic adaptations to normal pregnancy and the effects of obesity on those metabolic adaptations. This has provided the background for the next three chapters which detail three of the most common obesity related complications of pregnancy: Caesarean section, postpartum haemorrhage and pre-eclampsia.

Chapter 3. Literature review: Obesity related complications of pregnancy

The following three chapters present literature reviews for Caesarean section, postpartum haemorrhage and pre-eclampsia. Electronic databases MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews were searched. Searches were limited to English-language studies and were not time limited. References of published articles were searched for other eligible studies. Multiple search strategies were developed for weekly searches of MEDLINE from 2009 to present. Keywords were: obesity, BMI, pregnancy, labour, hypertension, postpartum haemorrhage, obstetric haemorrhage, uterine contraction, muscle contraction, uterus, myometrium, lipids,cholesterol.
Details of relevant manuscripts were entered into spreadsheets, detailing study and population demographics. Studies were then critiqued for quality reviewing factors including study method, population, bias, missing data and relevance and applicability to my own research hypotheses and utilised accordingly. The details of the studies were recorded in excel spreadsheets.
This literature review chapter focuses on the first of three common obesity related pregnancy complications relevant to this thesis: **Caesarean section (CS).**

3.1. Overview of obesity and Caesarean section

Compelling evidence from a large number of studies published over the past decade has demonstrated a dose dependent increased risk of CS associated with increased BMI (Barau, et al., 2006; Bergholt, Lim, Jorgensen, & Robson, 2007; Cedergren, 2006; Heslehurst et al., 2008; Schrauwers & Dekker, 2009). As the rate of obesity rises internationally, so does the percentage of CS attributable to obesity, reportedly increasing threefold over a 20 year period (Lu et al., 2001). A retrospective study has reported BMI to be an independently associated factor involved in changes in caesarean delivery rates among nulliparous women in two study periods ten years apart (Andreani et al., 2011).

Caesarean delivery among obese women is associated with increased morbidity and mortality compared to procedures undertaken in non-obese women for various reasons. Anaesthesia is more likely to be complicated, for example failed epidural, difficult emergency intubation and difficult intravenous access. Obese women have a greater gastric volume and lower gastric pH exacerbating their risk of gastric aspiration, a factor contributory to their increased anaesthesia related maternal mortality (Perlow, 2004).

Surgical access is more difficult, optimal incision choice has to be considered, retraction of a large panniculus may cause cardiorespiratory compromise and surgical field visualisation may be reduced (Perlow, 2004). Fundal pressure to facilitate delivery may be less effective due to dissipation of

pressure throughout a large abdomen. This challenging surgery results in prolonged operative time which is associated with adverse maternal outcomes such as increased blood loss, adverse fetal outcomes such as umbilical arterial pH<7.1 and adverse neonatal outcomes including low Apgar scores at 5 minutes (Doherty et al., 2008). The postoperative risk of infectious morbidity, such as chest or wound infection is also elevated, as is the risk of postoperative thromboembolism (Alexander & Liston, 2006; Sebire, et al., 2001; Soens, Birnbach, Ranasinghe, & van Zundert, 2008; Vallejo, 2007). These complications, haemorrhage, sepsis and thromboembolism, are prominent in maternal mortality reports.

In the 2007 Confidential Enquiry into Maternal and Child Health (CEMACH) report, haemorrhage and thromboembolism were leading causes of maternal death. Among women who died from haemorrhage or thromboembolism, 47% and 65% respectively had a BMI >25. Three quarters of the women who died from sepsis also had a BMI >25 (Lewis, 2007). The Perinatal and Maternal Mortality Review Committee (PMMRC) in New Zealand reported 20 direct maternal deaths from 2006-2010, but cause of death outcomes have not yet been reported in relation to maternal BMI due to small numbers (Perinatal and Maternal Mortality Review Committee, 2011). Based on the CEMACH maternal mortality figures, it can be speculated that approximately 5 or 6 of 8 women who died from haemorrhage, thromboembolism or sepsis in NZ would have had a BMI >25.

3.1.1. *Health care costs*

Caesarean section not only increases risk of morbidity for individual women but also increases the burden on healthcare services, necessitating use of additional resources. Uncomplicated vaginal birth is the least costly birth option when considering resources required for staffing and length of stay, and vaginal operative birth and CS increases these costs (Heslehurst, et al., 2008). Additional complications further increase costs. Determining modifiable risk factors in obese women that are associated with both increased and decreased incidence of CS is likely to influence costs.

3.1.1.1. Differentiation and definition of types of CS

The inconsistency between studies with regard to categorisation and definition of CS warrants some discussion, as lack of clarity in this area limits interpretation of some study results. For our CS study stringent criteria were used to categorise CS.

3.1.1.2. Differentiation of types of CS

Caesarean section can be subdivided into two main groups: those performed prior to labour (usually planned and hence elective) and unplanned emergency CS (usually in labour). Most studies have not differentiated between elective/emergency or prelabour/in labour CS and have reported only total CS rates (Abenhaim, Kinch, Morin, Benjamin, & Usher, 2007; Baeten, Bukusi, & Lambe, 2001; Sheiner et al., 2004). However, whilst not differentiating categories of CS, some studies have investigated indications for CS such as failure to progress (FTP) or cephalopelvic disproportion (CPD) which are emergency CS in labour (Doherty, Magann, Francis, Morrison, & Newnham, 2006; Kaiser & Kirby,

2001). Others have investigated indications for CS that could be applicable to either prelabour or in labour such as elective primary, breech presentation, medical indication or non-reassuring fetal heart rate (Haeri, Guichard, Baker, Saddlemire, & Boggess, 2009) or applicable to either elective or emergency CS such as previous CS or malpresentation (Sheiner, et al., 2004).

3.1.1.3. Definition of type of CS

Overall, there is no standard definition in the literature for categories of CS. Differences between studies in definitions of category of CS make comparison complex. Among those that did differentiate between elective or emergency CS, most have then not provided a definition for each of these categories (Bhattacharya, et al., 2007; Schrauwers & Dekker, 2009; Usha Kiran, Hemmadi, Bethel, & Evans, 2005). Studies reporting CS alone as an adverse pregnancy outcome among obese women more frequently provided a definition for each category of CS, but definitions varied between studies and were often unclear. For example, Cnattingius (1998) defined elective CS as "CS before onset of labour" and emergency CS as "CS after onset of labour" , whereas elsewhere, elective CS has been defined as "planned" and emergency CS "unplanned" (Graves, DeJoy, Heath, & Pekow, 2006; Vahratian, Siega-Riz, Savitz, & Zhang, 2005). Neither of these definitions can be applied when a CS is before the onset of labour but is unplanned.

In the absence of a definition, exactly what constitutes emergency CS may be open to interpretation as it may or may not incorporate both CS in labour and unplanned pre labour. Caesarean sections performed prior to labour may not be exclusively elective or planned. Emergency or unplanned CS may be undertaken prior to labour due to pregnancy complications such as preeclampsia and antepartum haemorrhage.

3.1.2. *Caesarean section rates*

3.1.2.1. Total CS rates in general obstetric populations

Among the studies reporting "total" CS rates which comprise both elective and emergency CS (or prelabour and in labour), most investigators have reported an increased overall risk among obese women compared to women with a normal BMI. Odds ratio's (OR) for total CS range from 1.4 to 2.42 (Abenhaim, et al., 2007; Callaway, Prins, Chang, & McIntyre, 2006; Doherty, et al., 2006; Sahu, Agarwal, Das, & Pandey, 2007; Seligman et al., 2006; Vahratian, et al., 2005). Some studies have cited higher ORs (2.9 -3.05) but for a referent group, they have either used or included a low underweight BMI, which may result in an inappropriately elevated OR (Barau, et al., 2006; Dempsey et al., 2005). A meta-analysis has reported total CS OR1.46 (95% CI:1.34-1.6), 2.0 (95% CI:1.86-2.27) and 2.9 (95% CI:2.28-3.79) among overweight, obese and severely obese women respectively compared with normal weight women (Chu et al., 2007).

3.1.2.2. Elective and emergency CS rates

Overall, irrespective of how type of CS is defined, most studies have reported that an increased BMI is more consistently associated with increased risks of emergency CS but the risk of elective CS is not consistently elevated. For emergency CS in labour, Bergholt et al (2007) reported OR1.9 (95% CI: 1.3-2.8) and 3.8 (95% CI: 2.4-6.2) for BMI >30 and >35 respectively compared to BMI <25. Sarkar et al (2007) reported a significant positive correlation between increasing BMI and emergency CS (p=0.003) but not elective CS (Sarkar et al., 2007). Another study reported a twofold increase in the rate of emergency CS for BMI >30 compared to BMI <30 (OR 2.0, 95% CI: 1.2-3.5) (Usha Kiran, et al., 2005). In a meta-analysis investigating the relationship between increased BMI and labour and birth outcomes in both nulliparous and multiparous women, Heslehurst et al (2008) confirmed the increased risk of emergency CS for obese and morbidly obese versus ideal BMI (OR 1.6, 95% CI: 1.4-1.9) but found no significantly increased odds for elective CS. However, a meta-analysis investigating the association between increasing BMI and elective/emergency CS among cohort studies of only nulliparous women reported an increased risk for elective CS for obese compared to normal weight women (OR1.87, 95% CI: 1.6-2.1), but the risk for emergency CS was even greater (OR 2.23, 95% CI: 2.1-2.4) (Poobalan, Aucott, Gurung, Smith, & Bhattacharya, 2009).

In the CS study for this thesis, type of CS has been clearly defined and these data will be a valuable addition to the small number of prospective studies that have investigated an association between increasing BMI and elective and/or emergency CS among nulliparous women.

3.1.3. *Adjustment for confounding factors for CS*

Obesity has been independently associated with both total CS (including elective and emergency) and emergency CS in labour in numerous studies following adjustment for factors such as maternal height, age, parity, education, induction of labour, weight gain during pregnancy, hypertensive disease, infant birth weight and gestational age at birth (Barau, et al., 2006; Bergholt, et al., 2007; Sheiner, et al., 2004; Vahratian, et al., 2005). While the majority of the above studies investigated populations of Caucasian women, the elevated risk of CS amongst women with elevated BMI has also been demonstrated in different ethnic groups such as African American and Chinese (Kaiser & Kirby, 2001; Leung et al., 2008). Leung (2008) found the odds ratio for total CS according to BMI groups among a Chinese cohort was similar to those reported in studies using Caucasian cohorts which defined obese as BMI ≥30 (OR 2.42, 95% CI:2.02-2.91).

Summary of obesity and risk of CS and definition of CS

- obesity is consistently associated with increased rates of emergency CS in labour, but an association with elective CS is not well established
- CS among obese women is associated with increased morbidity and mortality compared to non-obese women, and likely increased health care costs
- in studies to date, definition of types of CS is absent or unclear. Lack of differentiation between types of CS makes interpretation of findings difficult

3.2. BMI and timing of CS in labour

There is commonly a lack of reporting throughout the literature regarding the stage of labour at which CS was performed according to BMI.

Active first stage of labour is defined by regular, painful contractions with progressive cervical effacement from cervical dilatation 3cms to full dilatation, 10cms. Second stage of labour is from full dilatation of the cervix ending with birth of the baby (Chamberlain, 2001).

Most studies report reasons why CS was undertaken, but the reasons cited most commonly for CS i.e. labour dystocia, FTP, cephalopelvic disproportion and fetal distress are applicable to CS in either 1^{st} or 2^{nd} stage of labour, and the timing of CS is rarely reported. Among studies investigating maternal obesity and CS, only four were found that reported findings related to stage of labour and CS. Bergholt (2007), investigating nulliparous women with a singleton cephalic presentation in spontaneous labour at 37^0 - 42^6 weeks gestation, reported that overall most CS were performed in 1^{st} stage of labour (82%), but these were not stratified according to BMI. Reasons for CS were reported (62% for FTP, 34% for fetal distress, and 4% for other reasons) and an increase in BMI significantly increased risk of CS for FTP and suspected fetal distress, however reasons for CS were not subdivided according to 1^{st} and 2^{nd} stage CS (Bergholt, et al., 2007). Vahratian (2005) investigated the risk of CS at term in 641 nulliparous women, and computed 1^{st} stage CS. This study did not adjust for gestational diabetes, pre-eclampsia or gestational hypertension as these were considered to be intermediate factors and not potential confounders (Vahratian, et al., 2005). Like Bergholt (2007), results included findings that most CS were performed in 1st stage and for reasons of dystocia and fetal distress. Compared to normal weight women (BMI 19.8-26.0 kg/m), overweight and obese women were more likely to have 1^{st} stage CS, with an adjusted risk ratio (adjusted for height,

education, pregnancy weight gain, and IOL) of 1.4 (95%CI: 0.95-2.2), but risk of 2nd stage CS was not calculated. This study does not define its population according to labour status, and therefore may have included women who had a CS in the latent labour phase or failed to establish labour following induction, and were thus inaccurately categorised as failure to progress in the 1st stage of labour. The study also acknowledges in its limitations the possibility of random error due to small cell numbers.

A retrospective study investigating maternal obesity as a risk factor for CS among nulliparous and multiparous women reported risk of failure to progress in 1st or 2nd stage of labour among obese (BMI ≥30) compared to non-obese (BMI <30) women (Sheiner, et al., 2004). Obese women were more likely to fail to progress in 1st stage of labour (OR 4.0, 95%CI: 3.2-4.9) but not in the 2nd stage. Multivariable analysis showed failure to progress in 1st stage of labour to be significantly associated with maternal obesity (OR 3.2, 95%CI: 2.9-3.5). A small prospective study investigating pregnancy outcomes among obese nulliparous and multiparous women also reported a significantly higher rate of non-progressive labour in the 1st stage, but not in the 2nd stage of labour (Burstein, Levy, Mazor, Wiznitzer, & Sheiner, 2008). However, both of these latter studies combined normal and overweight into the non-obese group, likely resulting in an underestimation of the risk for obese women, as overweight women also have an increased risk for CS compared to normal weight women (Chu, et al., 2007; Poobalan, et al., 2009). Burstein (2008) and Sheiner (2004) both had study populations confined to Jewish or Bedouin Arabs ethnic groups, who may have a lower or higher rate of CS compared to other ethnicities.

Overall, findings from these studies reported an increased risk of both CS in 1st stage of labour and CS for FTP among obese women compared to non-obese women. Most studies have used populations of mixed parity, not specifically nulliparous populations.

3.3. Mechanisms of increased CS rates among overweight/obese women.

What remains unclear is why or how obesity increases the risk of CS in labour. There have been various theories proposed over the past decade.

3.3.1. *Macrosomia*

Macrosomia has various definitions including birth weight >4kgs (Bhattacharya, et al., 2007) or >4.5kgs (Kaiser & Kirby, 2001). There is a well described association between maternal obesity and macrosomia, particularly in univariable analysis (Cedergren, 2004; Usha Kiran, et al., 2005). Macrosomia or a large for gestational age (LGA) baby has frequently been reported as a risk factor for CS in general obstetric populations (Boulet, Alexander, Salihu, & Pass, 2003; Jolly, Sebire, Harris, Regan, & Robinson, 2003). Increased infant weight has thus been suggested as a reason for increased CS in obese women (Castro & Avina, 2002; Sebire, et al., 2001). However, several studies have reported a persisting association between increased BMI and CS after adjustment for macrosomia (Bergholt, et al., 2007; Bianco et al., 1998; Young & Woodmansee, 2002). This suggests that factors in addition to fetal size are important. The definition of macrosomia/ large for gestational

age (LGA) differs between studies, for example birth weight >4kgs, (Bhattacharya, et al., 2007) or >4.5kgs (Kaiser & Kirby, 2001), making comparison between studies difficult.

In our study, size at birth is assessed using customised centiles with LGA defined as birthweight >90th customised centile, which will add novel data to the existing information about birth weight/ macrosomia in relation to maternal BMI and mode of birth.

3.3.2. *Pelvic fat deposition*

Fat deposition in the maternal pelvis has been proposed as a possible reason for soft tissue labour dystocia by several authors (Crane, Wojtowycz, Dye, Aubry, & Artal, 1997; Dietz, Callaghan, Morrow, & Cogswell, 2005; Naftalin & Paterson-Brown, 2008; Sebire, et al., 2001). This theory currently remains speculative as it is unconfirmed by direct evidence of increased pelvic fat deposition demonstrated on medical imaging. Also, soft tissue dystocia is an unlikely explanation for the nearly fourfold increase in the CS rate among women who have a lean prepregnancy BMI, and a high pregnancy weight gain (Young & Woodmansee, 2002). Even with increased weight gain (over 16kgs), lean women (BMI<20) can still remain within a normal BMI range (18.5-24.9) and yet have an increased CS rate, and it is unlikely deposition of pelvic fat explains this.

3.3.3. *Maternal and fetal monitoring difficulties*

Difficulty monitoring uterine contractions or fetal well-being due to maternal habitus among obese women has also been postulated as a reason for increased CS rates (Bergholt, et al., 2007). In the face of difficulty monitoring or lack of reassurance regarding fetal well-being, a lower threshold for proceeding to CS may result. However, in contrast to the above theory Vahratian (2005), found a longer median time from diagnosis of failure to progress to CS for overweight and obese women, suggesting that following diagnosis of failure to progress care providers were not proceeding to CS sooner for overweight and obese women compared to normal weight women.

3.3.4. *Failure to progress in labour*

The predominant reason for CS in labour among obese women is dysfunctional labour or failure to progress (Bergholt, et al., 2007; Dempsey, et al., 2005; Ehrenberg, Durnwald, Catalano, & Mercer, 2004; Jensen, Agger, & Rasmussen, 1999; Sheiner, et al., 2004; Zhang, Bricker, Wray, & Quenby, 2007). Ehrenberg (2004) found women with BMI >30 had a significantly higher CS rate for the indication of dystocia than women with normal BMI (29.3% v 19.9%, *P* =0 .001). Odds ratios for CS for failure to progress among obese women range from 1.6-3.3. Sheiner et al (2004) reported a threefold increase in risk for women with BMI ≥30 compared to <30 (OR 3.1, 95% CI: 2.5-3.8) and Zhang (2007) reported a twofold increase with the same comparison (OR 1.8, 95% CI: 1.4-2.4). Bergholt et al (2007) reported an odds ratio of 1.6 (95% CI: 1.0-2.7) and 3.3 (95% CI: 1.9-5.9) for BMI 30-35 and >35 respectively.

It is worth noting that definitions differed between studies, or studies did not define terms relating to labour dysfunction. Bergholt (2007) defined FTP as “no progress at the cervical dilatation rate of 1cm per hour, with inefficient uterine action completely excluded”, whilst others cited deviations from Friedman’s plots (Sheiner, et al., 2004), and others simply stated labour dystocia or CPD with no clarification of definition or diagnosis (Seligman, et al., 2006). To determine that CS was truly due to labour dysfunction, data analysis must include only women who were in active labour, however this could not always be determined when reviewing studies. Of relevance is a comment by Ehrenberg (2004) regarding the limitations of using retrospective data, with misdiagnosis of labour complications due to coding inconsistencies.

A recent prospective study assessed whether non-elective CS due to either obstructed labour or ineffective uterine contractility or fetal distress was associated with maternal BMI (Cedergren, 2009). The three indications for CS were selected from ICD-10 codes: ICD 062 ineffective uterine contractility and ICD 063 long labour. ICD 064 obstructed labour due to malposition and malpresentation of the fetus; ICD 065 obstructed labour due to maternal pelvic abnormality and 066 other obstructed labour. ICD 068 labour and delivery complicated by fetal distress. ICD classification of the CS was done by the responsible obstetrician and each study participant could have multiple codes. The risk of CS due to obstructed labour was not significantly associated with maternal BMI, in contrast to a significantly increased risk of CS due to ineffective uterine contractility or fetal distress. Risk due to ineffective uterine contractility increased with increasing BMI, quadrupling among morbidly obese women (BMI ≥40) (OR 4.0, 95% CI: 3.1–5.0). A retrospective case control study of women of mixed parity reported a significantly higher rate of arrest of dilatation among obese BMI >35kg/m^2 compared to lean BMI <26 (Verdiales, Pacheco, & Cohen, 2009).

An important factor that should be considered is the characteristics of labour progression among obese women and health care provider decision making re timing of intervention for emergency CS for failure to progress. In a study investigating duration of labour among nulliparous women according to BMI, labour progression was significantly slower before 7cms of cervical dilatation in obese women compared to normal weight women (Vahratian, Zhang, Troendle, Savitz, & Siega-Riz, 2004). Therefore, is the higher rate of intrapartum CS among obese women partly explained by health care providers intervening and performing CS for what is perceived to be failure to progress, when it may be normal for obese women progress more slowly? There is evidence that this is not so. Vahratian et al (2005) investigated this as part of a study examining the effect of overweight and obesity on the risk of term caesarean delivery in nulliparous women. They calculated the mean duration of time that women were stalled at their last cervical dilation measurement prior to a first stage CS based on an indication of dystocia. They found median wait times were longer for overweight and obese women compared to normal weight women, and also that care providers waited longer than the 2-hour minimum for arrest of dilation before deciding to perform a CS.

3.3.5. *Suboptimal myometrial contractility*

A hypothesis that suboptimal myometrial contractility underlies dysfunctional labour among obese women has been proposed by Zhang et al (2007). They demonstrated that myometrial specimens obtained during CS at term from obese women contracted with less force and less frequency in vitro than specimens obtained during CS at term from women with a normal BMI (Zhang, et al., 2007). In addition the rate of cervical dilation in labour is slower in overweight and obese women (Kominiarek et al., 2011). There is speculation that the underlying mechanism of myometrial dysfunction might be explained by elevated cholesterol (Zhang, et al., 2007).

Cholesterol has an important role in smooth muscle contractility. Serum cholesterol, which is increased in pregnancy, is further increased in obesity. The plasma membrane of smooth muscle contains special microdomains called lipid rafts (*Figure 3.1*). These regions have less fluidity due to the high cholesterol content, thus the term lipid "rafts" as the lipids "float". When cholesterol binding protein caveolin-1 is associated with these rafts, specific "caveolae" rafts are formed, characterised by U shaped invaginations of the surface membrane *(Figure 3.2*). Recent research shows evidence that raft/caveolae signalling mechanisms are utilised in uterine myometrium (Wray, 2007). Function of oxytocin and oestrogen receptors located in the caveolae is modulated by the amount of cholesterol in the myometrium (Gimpl & Fahrenholz, 2000; Zhang, et al., 2007).

Extraction of cholesterol from myometrium and consequent caveolae disruption has been demonstrated to greatly enhance spontaneous muscle contractions in vivo (Smith, Babiychuk, Noble, Draeger, & Wray, 2005). Obesity related dyslipidaemia may result in changes to the caveolae, altering regulatory components of cell signalling. It has been speculated that changes in calcium ion channel expression and sarcoplasmic reticulum function requisite for successful labour may not occur adequately in those women with dysfunctional labour (Noble, et al., 2006).

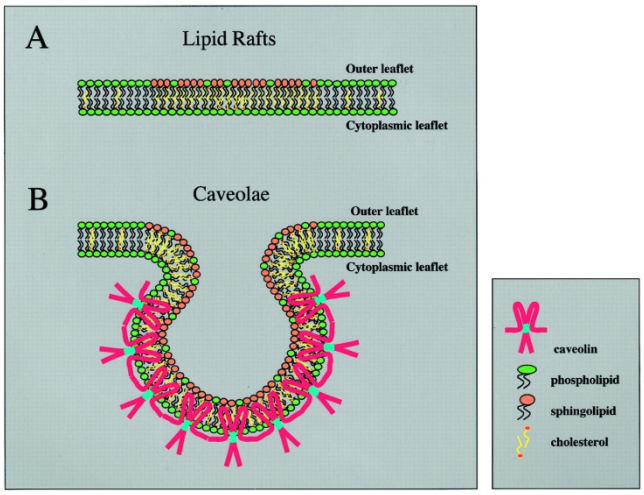

Figure 3-1 Diagram showing structure of a lipid raft and a caveolae

Reproduced with permission from Caveolae: From Cell Biology to Animal Physiology Razani, B, Woodman S.E. and Lisanti M.P.

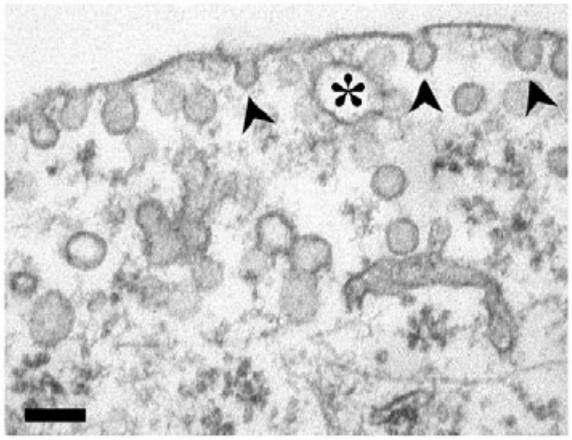

Figure 3-2 Electron micrograph showing caveolae (arrowheads)

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There are currently no studies of serum cholesterol and it's relationship with labour outcomes in humans. In our study, we explored the relationship between cholesterol concentrations and labour outcomes and investigated whether there is an association between lipid concentrations and mode of birth.

Summary of timing and underlying mechanisms of CS among obese women

- timing of emergency intrapartum CS among obese women has not been well studied. No studies have prospectively investigated prevalence and risk of CS among nulliparous women at term according to 1st or 2nd stage of labour according to BMI
- mechanisms underlying increased CS rates in labour among overweight/obese women have been postulated but this remains unclear
- suboptimal myometrial contractility may underlie dysfunctional labour, and be associated with elevated cholesterol in myometrium
- currently there are no studies of serum cholesterol and it's relationship with labour outcomes in humans

Chapter 4. Literature review: Obesity related complications of pregnancy

This chapter focuses on the second of three common obesity related pregnancy complications relevant to this thesis: **postpartum haemorrhage**.

4.1. Overview of postpartum haemorrhage

Globally, postpartum haemorrhage (PPH) remains a leading cause of maternal mortality in both developing and developed countries, responsible for one quarter of all maternal deaths and a major contributor to maternal morbidity and long term disability (Arulkumaran, Mavrides, & Penney, 2009; World Health Organisation, 2009). In the latest report of the Confidential Enquiries into Maternal Deaths in the United Kingdom, postpartum haemorrhage was the sixth most common cause of direct maternal death (Centre for Maternal and Child Enquiries, 2011), and in New Zealand it was the third most common (PMMRC, 2012).

4.1.1. *Definition*

Primary PPH is most commonly defined as a blood loss of 500 ml or more from the genital tract within 24 hours after birth, and may be classified as minor (500–1000mls) or major (more than 1000mls) (Arulkumaran, Mavrides, & Penney, 2009; World Health Organization, 2012). Secondary PPH is defined as abnormal or excessive bleeding from the birth canal between 24 hours and 6 weeks postnatally. All future reference to PPH in this thesis relates to primary PPH.

Other criteria have been used to define PPH such as decrease in haematocrit or need for blood transfusion (Combs, Murphy, & Laros, 1991a; Driessen et al., 2011; Magann et al., 2005). A lack of consistency in definitions of PPH among studies makes comparison between them difficult. Use of blood loss of 500mls as a cut off to define PPH has been critiqued as this amount of blood loss is common, is not associated with adverse outcomes in the majority of healthy women and may be considered an average blood loss (ACOG, 2006; Drife, 1997; Gilstrap & Ramin, 1994).

4.1.2. *Prevalence*

Primary PPH, greater than 500mls after vaginal birth, occurs in approximately 5% of births (ACOG, 2006). In developed countries, the incidence of postpartum haemorrhage has been increasing, with reported rates rising by over one third during the past two decades (Callaghan, Kuklina, & Berg, 2010; Knight et al., 2009; Rossen, Okland, Nilsen, & Eggebo, 2010). There are consistent reports from various developed countries, USA, Canada and Australia, that the increase in PPH is not accounted for by adjustment for corresponding changes in risk factors such as higher rates of CS and induction of labour, and advanced maternal age (Bateman, Berman, Riley, & Leffert, 2010; Ford, Roberts, Simpson, Vaughan, & Cameron, 2007; Joseph et al., 2007).

A local Australian study (New South Wales) predicted that PPH rates should remain constant over an eight year period after adjustment for covariates that may have affected rates, such as maternal age, induction of labour and caesarean section (P=0.28). BMI was not included in the covariates. Contrary to this prediction, rates did not remain constant and the observed PPH rates actually increased from 4.7% to 6.0% per 100 births (P<0.001) (Ford, et al., 2007).

A systematic review reported an overall primary PPH prevalence of 6.09% (95% CI: 6.06-6.11) (Carroli, Cuesta, Abalos, & Gulmezoglu, 2008). The rise in global maternal obesity, which has been concurrent with the rise in PPH rates, has raised speculation that maternal obesity may be responsible for this reported increase in PPH rates (Ford, et al., 2007; Joseph, et al., 2007; Knight, et al., 2009).

4.1.3. *Estimation of blood loss*

Accurate estimation of blood loss is difficult to achieve. Most studies use visual estimation as the method of assessing blood loss after vaginal birth (Larsson, Sissel, Wiklund, Pahlen, & Andolf, 2006). Whilst the accuracy of estimated blood loss is limited, it is widely accepted that visual estimation generally underestimates true loss, and the degree of underestimation increases with increasing volumes of blood loss (ACOG, 2006; Duthie et al., 1990; Prasertcharoensuk, Swadpanich, & Lumbiganon, 2000; Stafford, Dildy, Clark, & Belfort, 2008). In a systematic review, overall prevalence of PPH increased from 6.1% to 10.6% when measurement method was not specified versus when blood loss was measured objectively, demonstrating underestimation of blood loss with subjective (visual) measurement (Carroli, et al., 2008). Critique of the accuracy of PPH rates using visual estimation may therefore be valid, but concern that rates are consequently overestimated is not.

There have been intervention trials to try and improve accuracy of blood loss estimation and achieve earlier detection of excessive blood loss. In a large cluster randomised trial, it was hypothesised that earlier recognition of excessive blood loss by using a transparent plastic collector bag to measure blood loss after vaginal birth would trigger earlier intervention, thus reducing the incidence of the severe postpartum haemorrhage. However, this was not found to be the case (Zhang et al., 2010). The recently published “World Health Organization recommendations for the prevention and treatment of postpartum haemorrhage” report that there is insufficient evidence to recommend the measurement of blood loss over clinical estimation of blood loss (World Health Organization, 2012).

4.1.4. *Causes and risk factors for PPH*

PPH is usually prevented by physiological contraction of the myometrial muscle fibres around the large blood vessels at the placental site following delivery of the placenta in the third stage of labour.

4.1.4.1. Uterine atony

The predominant cause of primary PPH is uterine atony, accounting for more than 70% of cases (ACOG, 2006; Oyelese & Ananth, 2010). There are known risk factors associated with uterine atony.

Labour related factors include induction of labour, prolonged first second or third stage of labour augmentation of labour, precipitate labour, CS, and retained placenta (Al-Zirqi, Vangen, Forsen, & Stray-Pedersen, 2008; Driessen, et al., 2011; Stones, Paterson, & Saunders, 1993).

4.1.4.2. Overdistension of the uterus

Overdistension of the uterus is also a significant cause of PPH and commonly occurs in the context of multiple pregnancy, large for gestational age fetus and polyhydramnios (Magann, et al., 2005; Oyelese & Ananth, 2010).

4.1.4.3. Genital tract trauma

Another major category of primary PPH is genital tract trauma, namely CS, episiotomy and perineal or cervical lacerations (Combs, et al., 1991a; Driessen, et al., 2011).

4.1.4.4. Other physical risk factors

Rarely, blood disorders such as coagulation defects are associated with PPH (ACOG, 2006; Magann, et al., 2005). Other risk factors for PPH include placenta praevia, a history of antepartum haemorrhage from other causes and placental abruption (Bateman, et al., 2010; Harlev et al., 2008; Magann, et al., 2005).

4.1.4.5. Ethnicity

An association between Asian ethnicity and PPH has been reported (Al-Zirqi, et al., 2008; Combs, Murphy, & Laros, 1991b; Magann, et al., 2005). It has been speculated that this may be explained by larger proportions of older women and higher rates of CS, placenta praevia and perineal trauma among Asian women, but this has not been well investigated (Al-Zirqi, et al., 2008; Combs, et al., 1991b).

4.1.4.6. Parity

Multiparity

Despite a commonly held view that grand multiparity is associated with increased rates of PPH, this is not confirmed by the literature. Al-Zirqi et al (2008) reported no association after adjustment for confounders between multiparity of greater than or equal to 5 compared to parity of 1 to 4 (aOR 1.19, 95% CI 0.76-1.86) (Al-Zirqi, et al., 2008). Similarly, others have reported no association, comparing grand multiparity with either nulliparity (Combs, et al., 1991b) or with lower parity (Humphrey, 2003).

Nulliparity and risk of PPH

Studies investigating specific risk factors for PPH have demonstrated that nulliparous women have elevated rates compared to those who are multiparous, and that nulliparity is an independent risk factor for PPH (Al-Zirqi, et al., 2008; Driessen, et al., 2011; Magann et al., 2008; Rossen, et al., 2010).

Among studies that have reported risk of major PPH in nulliparous women, the degree of risk varies. A population based cohort study including women with severe PPH (defined by a peripartum change in haemoglobin of 4g/dL or more, considered equivalent to the loss of 1,000 mL or more of blood) reported a twofold increase in risk in nulliparous compared to multiparous women with no previous CS (aOR 1.9, 95%CI: 1.5-2.3) (Driessen, et al., 2011). Another population based cohort study including women with severe PPH (defined as visually estimated blood loss of >1500 ml intrapartum) also reported an increase in risk for nulliparous compared to multiparous women, but the magnitude of risk was smaller (parity 1-4) (aOR 1.1, 95%CI: 1.0-1.4) (Al-Zirqi, et al., 2008).

Although studies have reported an association between PPH and parity, and found nulliparity to be a risk factor, few have investigated PPH further specifically among this prevalent higher risk nulliparous population.

4.2. Maternal BMI and risk of PPH

4.2.1. *Obesity as a risk factor for PPH*

A number of studies have investigated a range of specific potential risk factors for PPH, including maternal characteristics such as maternal age, ethnicity and parity (Al-Zirqi, et al., 2008; Bais, Eskes, Pel, Bonsel, & Bleker, 2004; Combs, et al., 1991b; Driessen, et al., 2011; Magann, et al., 2005; Naef 3rd et al., 1994; Sheiner, Sarid, Levy, Seidman, & Hallak, 2005; Sosa, Althabe, Belizan, & Buekens, 2009). However, despite attention being drawn to the potential association between obesity and PPH in early research (Stones, et al., 1993), BMI has rarely been included as a potential risk factor in subsequent studies. Only two papers included data on BMI and the results are conflicting. A recent cohort study using data from 106 French hospitals investigated severe postpartum haemorrhage (defined by a peripartum change in haemoglobin of 4g/dL or more considered equivalent to the loss of ≥1,000 ml) due to uterine atony after vaginal birth. They reported no association with maternal BMI (overweight or obese) (Driessen, et al., 2011). Conversely, in an earlier small study investigating prediction of PPH at Caesarean delivery, obesity was independently associated with PPH (defined as blood loss >1500mls, or decrease in haematocrit ≥10%, or need for blood transfusion) (Naef 3rd, et al., 1994). In this latter study obesity was defined as weight >250lbs (114kgs), limiting comparison with other studies. Differences in PPH definitions and use of maternal weight versus BMI categories make comparison between studies difficult.

4.2.2. *Obesity and risk of PPH among populations of women of mixed parity*

In studies of populations of women of mixed parity, investigating the relationship between obesity and general birth outcomes, such as pre-eclampsia, CS, birthweight and including PPH, an independent positive association has frequently been reported between obesity and PPH (Cedergren, 2004; Doherty, et al., 2006; Heslehurst, et al., 2008; Sebire, et al., 2001). In a large retrospective analysis, obesity (BMI ≥30) was associated with a 40% increase in risk of PPH (aOR 1.39, 99%CI:1.32–1.46) (Sebire, et al., 2001) and a smaller prospective study using Australian data reported a comparable

risk (aOR 1.71, 95%CI: 1.20–2.44) (Doherty, et al., 2006). Another retrospective analysis reported a twofold increase in risk of PPH (estimated blood loss >600mls) among obese women with a spontaneous vaginal birth in univariable analysis (OR 2.1, 95%CI: 1.2-3.8) (Zhang, et al., 2007).

There is only one study that has specifically investigated the relationship between maternal BMI and PPH (Blomberg, 2011). Defining obesity by class (Class I 30-34.9, Class II 35-39.9 and Class III ≥40) compared normal BMI as a referent group, and defining PPH as major (greater than 1000mls), Blomberg reported a small increased risk for PPH in women of all obesity classes following vaginal birth, However, PPH risk was variable in obese classes following CS, and was increased only in Class II obese women (aOR 1.30, 95% CI 1.02-1.65). This study was performed in a population of mixed parity including preterm birth. It used data derived from ICD codes from a birth registry, and therefore was only able to adjust for very limited confounders (year of infant birth, maternal age, parity and smoking).

4.2.3. *Obesity and risk of PPH among nulliparous women*

No studies have primarily investigated an association between PPH and maternal BMI among nulliparous women. Among the few previous publications reporting the relationship between maternal obesity and general birth outcomes in nulliparous women, comparisons are difficult due to absent or differing definitions of PPH, and none have assessed the risk of PPH after vaginal and cesarean birth separately. Findings from these studies are also inconsistent, and only one has adjusted for confounding variables. Two retrospective studies reported higher rates of PPH among obese women compared to those with normal BMI. Mantakas et al (2010) reported increased risk of major PPH (estimated blood loss >1000mls) among obese (BMI≥30) and morbidly obese (BMI≥40) (OR 1.6, 95%CI 1.1-2.2 and 2.1, 95%CI 1.1-4.1 respectively) (Mantakas & Farrell, 2010). Denison et al (2008) reported similar findings but slightly lower odds for obese (BMI≥30) and morbidly obese (BMI≥35) (OR 1.2, 95%CI 1.1-1.3 and 1.4, 95%CI 1.2-1.6 respectively) than Mantakas and Farrell (2010) (Denison, Price, Graham, Wild, & Liston, 2008). In a further study, increased rates of PPH (blood loss > 500mls) after vaginal birth in nulliparous obese women compared to those with a BMI of 20-30 were reported, but the magnitude of risk was not quantified (Usha Kiran, et al., 2005).

Two studies in nullipara have reported no association between obesity and PPH (defined as estimated blood loss of greater than or equal to 1500mls or use of blood transfusion) but these studies were underpowered (Athukorala, Rumbold, Willson, & Crowther, 2010; Haeri, et al., 2009).

Only one study of nulliparous women and birth outcomes including PPH adjusted for confounding factors, and reported a two fold increase in risk of major PPH (including vaginal and Caesarean delivery) in obese women (BMI ≥30) compared to normal weight women (BMI 20–24.9) (aOR 1.5 95%CI:1.3-1.7) (Bhattacharya, et al., 2007). No significant increase was reported among morbidly obese women (aOR 1.3, 95%CI:0.8-1.9), however they only comprised 0.6% of the study population so this result may be related to lack of power. Additionally, no adjustment was made in this study for perineal trauma or birthweight which are both consistently reported as risk factors for PPH.

Summary of risk of PPH, nulliparity and obesity

- PPH remains a leading cause of maternal morbidity and mortality internationally
- changes in well recognised risk factors such as maternal age and CS do not account for increasing rates of PPH and a contemporaneous rise in maternal obesity rates may be explanatory
- nulliparity is an independent risk factor for PPH
- an independent positive association has frequently been reported between obesity and PPH in populations of women of mixed BMI
- findings are inconsistent with regard to an association between increased BMI and PPH in nulliparous women
- no studies have primarily investigated an association between PPH and BMI among nulliparous women

4.3. Theories about association between obesity and PPH

The mechanism underlying increased rates of PPH among obese women remains unclear. It has been suggested that the increase in risk is at least partly explained by a concurrent increased CS rate (Bhattacharya, et al., 2007; Mantakas & Farrell, 2010). CS has been consistently associated with increased rates of PPH (Al-Zirqi, et al., 2008), and maternal obesity is associated with increased rates of CS (Fyfe et al., 2011). However, this is speculation as no studies among nulliparous women have analysed risk for PPH separately for vaginal birth and CS. Increased rates of other factors associated with PPH such as increased birthweight may also contribute to higher rates of PPH among obese women. An independent positive association between obesity and PPH among nulliparous women has been reported by one study after adjustment for other risk factors, but adjustment did not include birth weight (Bhattacharya, et al., 2007).

It is possible that the increased risk of PPH among obese women may be related to suboptimal myometrial contractility. Uterine atony, the leading cause of PPH, has been associated with slow progress in labour, a likely surrogate for impaired intrapartum myometrial contractility (Driessen, et al., 2011). Maternal obesity is associated with an elevated risk of intrapartum CS, predominantly for failure to progress (Bergholt, et al., 2007; Fyfe, et al., 2011; Zhang, et al., 2007), the mechanism of which is thought to be due to reduced uterine contractility (Zhang, et al., 2007). Among nulliparous women in labour at term, we found that the elevated risk of intrapartum CS is confined to the first stage of labour, as obese women who progress to the second stage of labour are just as likely to birth vaginally as women with normal BMI (Fyfe, et al., 2011). Thus, it appears that obese women who achieve second stage of labour and birth vaginally may not have any impairment of contractility. We speculate therefore that obese women who birth vaginally may have normal myometrial contractility, and thus will not have increased rates of PPH compared to women with normal BMI who birth vaginally.

Chapter 5. Literature review: Obesity related complications of pregnancy

This literature review chapter focuses on the first of three common obesity related pregnancy complications relevant to this thesis: **pre-eclampsia**.

5.1. Physiological cardiovascular and haemodynamic changes in normal pregnancy

Normal pregnancy is characterised by a progressive increase in circulating blood volume beginning at 6 weeks gestation and increasing by 50% by term (Knock & Poston, 1996; Silversides & Colman, 2007; Weiner & Thompson, 1997). There is a physiological fall in blood pressure from early pregnancy, reaching its lowest at approximately 20-24 weeks gestation and then subsequently increasing until term (James & Nelson-Piercy, 2004; Ochsenbein-Kolble et al., 2004). Stroke volume and cardiac output increase to compensate for the reduced resistance, but this is not fully achieved until late in the second trimester, hence the decrease in blood pressure until this time.

The fall in pressure is attributable to reduced systemic vascular resistance due to the development of a high flow low resistance uteroplacental circulation and peripheral vasodilation. The factors and mechanisms underlying the systemic vasodilation are not fully understood, but probably include reduced vascular reaction to vasoconstrictive angiotensin II and norepinephrine, increased endothelial nitric oxide synthesis stimulated by oestradiol, increased prostacyclin production, and decreased aortic rigidity (Edouard, Pannier, London, Cuche, & Safar, 1998; Knock & Poston, 1996; Weiner & Thompson, 1997). There may be other influential hormonal factors yet to be established including progesterone, prolactin and oestrogens (Fu & Levine, 2009; Silversides & Colman, 2007). The haemodynamic changes precipitate activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Consequently there is a physiological rise in vasoconstrictive renin and angiotensin concentrations in pregnancy despite the increase in blood volume. Reduced peripheral vascular resistance prompts a response from the sympathetic nervous system. It has been postulated that in the third trimester this enables normalisation of arterial blood pressure (Greenwood, Scott, Stoker, Walker, & Mary, 2001; Silversides & Colman, 2007).

5.2. Definition of pre-eclampsia

Pre-eclampsia is a common multisystem complication of pregnancy, occurring after 20 weeks gestation, affecting 5-7% of healthy nulliparous women (Sibai, Dekker, & Kupferminc, 2005). It is traditionally defined as de novo hypertension after 20 weeks gestation with systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, returning to normal postpartum and proteinuria (Roccella, 2000). Diastolic blood pressure is determined as the disappearance of sound (Korotkoff

phase V), unless Korotkoff V persists in which case muffling of Korotkoff IV is used. Measuring the blood pressure successively may result in different readings, as the first may be elevated due to white coat hypertension. Therefore it is recommended that gestational blood pressure elevation be defined on the basis of at least two determinations (Roccella, 2000), and to discard the first.

Proteinuria is defined as the urinary excretion of ≥ 0.3 g protein in a 24-hour specimen. This will usually correlate with a protein/creatinine ratio of ≥30 mg/dL (≥1+ reading on dipstick) in a random urine determination with no evidence of urinary tract infection. However, because of the discrepancy between random protein determinations and 24-hour urine protein concentrations in pre-eclampsia (which may be either higher or lower) it is recommended that the diagnosis be based on a 24-hour urine sample if at all possible or that it be based on a timed collection corrected for creatinine excretion if the former procedure is not feasible (Roccella, 2000). Although proteinuria is the most commonly recognised additional feature of pre-eclampsia after hypertension, it should not be considered mandatory to make the clinical diagnosis. As this classification is based on clinical data, it is possible that women with another condition will sometimes be classified incorrectly as having pre-eclampsia during pregnancy. However, this is not usually a clinical problem as the diagnosis of pre-eclampsia should lead to increased observation and vigilance which is also appropriate for conditions which may mimic pre-eclampsia (Society of Obstetric Medicine of Australia and New Zealand, 2008).

A diagnosis of pre-eclampsia can be made when hypertension arises after 20 weeks gestation and is accompanied with multisystem involvement including one or more of the following:

renal involvement: serum or plasma creatinine > 90 µmol/L or oliguria

haematological involvement: thrombocytopenia; haemolysis; disseminated intravascular coagulation

liver involvement: raised serum transaminases; severe epigastric or right upper quadrant pain

neurological involvement: convulsions (eclampsia); hypereflexia with sustained clonus; severe headache; persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm); stroke

pulmonary oedema

fetal growth restriction

placental abruption (Society of Obstetric Medicine of Australia and New Zealand, 2008)

5.3. Pathophysiology of pre-eclampsia

Although precise knowledge of the pathophysiology underlying the syndrome of pre-eclampsia is still evolving, there is currently much that is already understood. It is acknowledged that the placenta has a causal role and that the way in which pre-eclampsia develops and presents is dependent on individual maternal response. In pre-eclampsia there is an exaggerated maternal systemic vascular inflammatory response to trophoblastic particles released into the maternal circulation, resulting in

endothelial dysfunction, platelet clustering, increased vascular resistance, and activation of clotting factors (Redman & Sargent, 2005; Sibai, et al., 2005). The timing, progression, severity and clinical presentation of this response is hugely diverse, individual and difficult to predict (Redman & Sargent, 2005; Sibai, et al., 2005).

Recent findings identify two broad sub-phenotypes of pre-eclampsia that manifest typically as either a preterm and fetal or a term predominantly maternal syndrome. Preterm pre-eclampsia is usually associated with initial poor placentation, due to inadequate trophoblastic cell invasion and subsequent suboptimal development of maternal spiral arterioles. The result is a poorly perfused hypoxic placenta that suffers oxidative stress, and often gives rise to fetal growth restriction.

Conversely, the maternal syndrome occurring at term is usually associated with normal placental flow and normal fetal growth is usual. It is thought to be an exaggeration of the physiological systemic maternal inflammatory response to pregnancy. The actual presence of a placenta and the maternal response to placentation (whether it is abnormal or normal) is the cause of pre-eclampsia rather than placentation itself (Huppertz, 2008; Vatten & Skjaerven, 2004). The differentiation of phenotypes of pre-eclampsia is not always distinct. These fetal and maternal phenotypes can overlap, and the maternal syndrome is heterogenous, and dependent on individual response and pre-existing risk factors.

5.4. Complications of pre-eclampsia

Pre-eclampsia is a key obstetric problem. It is associated with significant maternal and neonatal morbidity and is a major cause of maternal mortality (15-20%) in developed countries (*Figure 5.1*). The associated degree of effect is dependent upon various factors: severity of pre-eclampsia, gestational age at onset, presence of co-morbidities and management. Adverse maternal and perinatal outcomes are increased if the onset pre-eclampsia is earlier (<34 weeks) and if there are other pre-existing medical disorders (Sibai, et al., 2005).

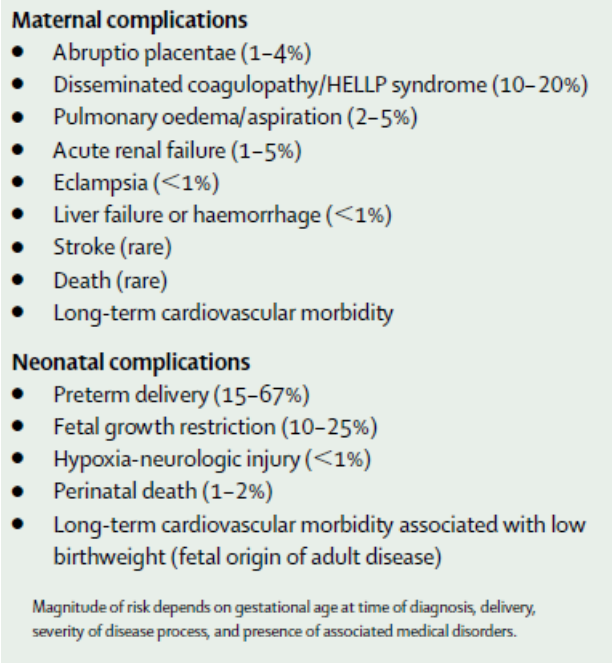

Figure 5-1 Maternal and neonatal complications of pre-eclampsia

Reprinted from *Lancet, 365* (9461) Sibai et al. Pre-eclampsia 785-799 (2005). with permission from Elsevier

5.5. Pathophysiology of obesity and pre-eclampsia

The mechanisms underpinning the relationship between increased BMI and pre-eclampsia are complex and not yet fully understood. As described in Chapter 2, the pathophysiology associated with obesity is complex involving a number of hormonal and biochemical pathways, including insulin resistance, endothelial cell activation, dyslipidaemia, and a pro-inflammatory milieu with elevated cytokines such as tumour necrosis factor α (King, 2006; Moynihan, Hehir, Glavey, Smith, & Morrison, 2006). These same biochemical pathways are also integral to the pathogenesis of pre-eclampsia. Differences in these maternal biochemical parameters have been identified prior to pregnancy, (Magnussen et al., 2007) in early pregnancy before the onset of pre-eclampsia, (Chappell et al., 2002; Enquobahrie et al., 2004) and on follow-up months to years after pre-eclampsia (Girouard, Giguere, Moutquin, & Forest, 2007; Sattar, Ramsay, Crawford, Cheyne, & Greer, 2003).

5.6. Clinical manifestations of pre-eclampsia

Typical clinical presentation of the maternal syndrome includes hypertension and proteinuria, plus or minus other multisystem complications (Huppertz, 2008; Redman & Sargent, 2005; Sibai, et al., 2005). However, pre-eclampsia is notoriously atypical and may manifest without notable hypertension. Proteinuria may be an early or a late sign, or may not be present all in women with multisystem disease. Most women presenting with pre-eclampsia are usually asymptomatic, however

when symptoms occur, they may include headache, visual disturbances, nausea, vomiting, general feeling of malaise and epigastric tenderness. Signs of pre-eclampsia may include proteinuria, oedema, abruption and fetal growth restriction.

Multisystem complications may include: abnormal renal function signified by raised serum creatinine; abnormal liver function signified by elevated liver function tests specifically aspartate transaminase or alanine transaminase; abnormal neurological function evident by imminent or occurring eclamptic seizure or cerebral haemorrhage; abnormal haematological function, specifically thrombocytopaenia, haemolysis or disseminated intravascular coagulation (Society of Obstetric Medicine of Australia and New Zealand, 2008).

5.7. Clinical risk factors for pre-eclampsia

There are numerous well established risk factors for pre-eclampsia. Those specific to this thesis, namely obesity; nulliparity; dyslipidaemia; central adiposity and gestational weight gain are described in more detail in the latter part of this section.

5.7.1. *Demographic factors*

5.7.1.1. Maternal age

Increasing maternal age increases the risk of pre-eclampsia, with a reported doubling of risk for those women who are ≥ 35yrs of age (aOR 2.5, 95%CI: 1.5-4.1) (Hartikainen, Aliharmi, & Rantakallio, 1998). A systematic review of controlled studies found no association with young maternal age, however many included studies did not control for confounding factors (Duckitt & Harrington, 2005). A recent study of low risk nulliparous women reported younger maternal age to be associated with pre-eclampsia in univariable analysis, but this did not persist after adjustment (Myatt et al., 2012).

5.7.1.2. Ethnicity

A US study reported higher rates of pre eclampsia among Black and Hispanic women compared to white women after controlling for diabetes, socioeconomic status, age and geographic location (Tanaka et al., 2007). However, in a New Zealand population, Anderson et al (2012) found no ethnic difference in risk for preeclampsia after adjustment for BMI (Anderson, Sadler, Stewart, Fyfe, & McCowan, 2012).

5.7.2. *Pre-existing medical conditions*

5.7.2.1. Diabetes mellitus

The relationship between insulin resistance and pre-eclampsia is strong and unsurprising, as they both have associations in common with features such as obesity, hypertension and dyslipidaemia. In a prospective case control study investigating a nulliparous cohort of women, early pregnancy insulin resistance (measured by glycoprotein SHBG concentrations) was independently associated with subsequent pre-eclampsia (Wolf et al., 2002) and pre-existing insulin dependent diabetes mellitus predisposes to a three to fourfold increase in risk of pre-eclampsia (RR3.6, 95% CI: 2.5-5.0) (Duckitt & Harrington, 2005).

5.7.2.2. Chronic hypertension

Chronic hypertension is a well established high risk factor for pre-eclampsia, and in particular has been reported to confer a large increase in risk for severe pre-eclampsia and requirement for preterm birth. High rates of pre-eclampsia among nulliparous women with pre-existing hypertension (16.7%), have been reported with an associated threefold increase in risk (OR3.4, 95% CI: 2.8–4.1) (Catov, Ness, Kip, & Olsen, 2007; Sibai et al., 1998). A recent study reported prepregnancy "prehypertension" (systolic BP >120mm/Hg and/or diastolic BP >80mm/Hg) to be the strongest predictor, following adjustment for confounders, for subsequent hypertensive disorder of pregnancy (Hedderson, Darbinian, Sridhar, & Quesenberry, 2012).

5.7.2.3. Renal disease

An increase in risk for pre-eclampsia associated with renal disease is well established but chronic renal disease covers a range of conditions, and it is thought that the degree of renal insufficiency rather than the underlying renal disease itself is the determining factor for maternal and fetal outcomes (Duckitt & Harrington, 2005; Mirza & Cleary, 2009).

5.7.2.4. Auto immune disease, pre-existing thrombophilias

Women with auto immune disease such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS) are more likely to develop pre-eclampsia (Salmon et al., 2011). A systematic review of controlled studies reported the presence of antiphospholipid antibodies to increase the risk of developing pre-eclampsia (Duckitt & Harrington, 2005). Women who develop pre-eclampsia have been reported to be more likely to have pre-existing thrombophilias such as Factor V Leiden mutation or protein C or S deficiency compared to controls, however many of these studies are old, poorly designed and too small to accurately determine the size of the association (Alfirevic, Roberts, & Martlew, 2002). More compelling recent data from a multicentre prospective study suggest that there is no positive relationship between inherited thrombophilia and preeclampsia (Kahn et al., 2009). Data relating to the risk of pre-eclampsia in women with inherited thrombophilia is conflicting and inconsistent relationships have been reported.

5.7.3. *Gynaecological and obstetric factors*

5.7.3.1. Assisted reproductive technology (ART)

In vitro fertilisation has been reported to be associated with increased risk of pre-eclampsia (Hartikainen, et al., 1998; Lorentzen, Endresen, Clausen, & Henriksen, 1994). A higher incidence of pre-eclampsia among women conceiving with intrauterine insemination using donor sperm versus partner sperm has been reported (Enquobahrie, et al., 2004). It is likely this is related to immune maladaptation (Dekker & Robillard, 2005) (refer below: *nulliparity and pre-eclampsia*).

5.7.3.2. Previous history of pre-eclampsia

The risk of recurrent pre-eclampsia in women is related to the presence or absence of any other risk factors, and also the gestational age at onset of pre-eclampsia in previous pregnancy. Consequently, a broad range of rates of recurrence have been reported (11-65%) and women who have a history of pre-eclampsia in the second trimester have the highest recurrence rate (up to 65%) (Barton & Sibai, 2008). Hnat et al (2002) reported a three to four fold increase in pre-eclampsia rates among women who had pre-eclampsia in a previous pregnancy compared with nulliparous women (17.9% v 5.3%, p=<.0001), and that recurrent pre-eclampsia is more likely to be severe and preterm compared to nulliparous pre-eclampsia (Hnat et al., 2002).

5.7.3.3. Family history of pre-eclampsia

A history of pre-eclampsia in a mother or sisters increases the risk of pre-eclampsia two to three fold. A recent SCOPE study reported that among healthy nulliparous women, a family history of pre-eclampsia (in mother and sisters) to double the risk of developing the disease (aOR 2.0, 95% CI: 1.3-3.0) (North et al., 2011). A systematic review estimated a threefold increase in risk (RR2.9, 95% CI: 1.7-4.9) reviewing studies of family history in mother or sister or mother and grandmother (Duckitt & Harrington, 2005).

5.7.3.4. Gestational weight gain and pre-eclampsia

Among studies reporting risk of pre-eclampsia associated with gestational weight gain, just over half have reported a positive association, but the evidence is inconclusive as interpretation of the findings of these studies is limited (Institute of Medicine and National Research Council, 2009; Viswanathan et al., 2008). A recent Institute of Medicine report “Weight Gain During Pregnancy: Reexamining the Guidelines” highlights the difficulty in interpreting study findings due to use of total weight gain during pregnancy, rather than weight gain prior to a pre-eclampsia diagnosis, and due to lack of a consistent definition of pre-eclampsia (Institute of Medicine and National Research Council, 2009). Use of total weight gain during pregnancy complicated by pre-eclampsia may not be an accurate measure of increased adiposity. Development of pre-eclampsia-related oedema in late pregnancy due to increased vascular permeability and decreased plasma oncotic pressure, may lead to excessive weight gain in late gestation, and hence not all weight gain is associated with increased adiposity.

Results from a large population based cohort study investigating total gestational weight gain during pregnancy and pregnancy outcomes among obese women showed increasing risk of pre-eclampsia with increasing weight gain in each obesity class. They also reported that reduced gestational weight gain or weight loss was associated with decreased risk of pre-eclampsia (Kiel, Dodson, Artal, Boehmer, & Leet, 2007). In a large retrospective study, increasing BMI combined with increasing rate of weight gain resulted in increased rates of pre-eclampsia (Mbah et al., 2010). Thus there is evidence suggesting that total weight gain and average weight gain rate during pregnancy among obese women may be influential in risk for pre-eclampsia.

5.7.4. *Factors specific to this thesis*

The following section details risk factors for pre-eclampsia that are of specific relevance for this thesis – nulliparity, obesity, dyslipidaemia and central adiposity, each of which are associated with a two to three-fold increase in risk.

5.7.4.1. Nulliparity and pre-eclampsia

Pre-eclampsia is more prevalent in nulliparous compared to parous women, which is likely explained by the immune maladaptation theory, underpinned by the protective effect of prolonged sperm exposure and the primipaternity concept (Dekker & Robillard, 2007; Duckitt & Harrington, 2005). It has been shown that sperm cause a maternal immune inflammatory response, and paternal antigen tolerance increases with increased duration of sperm exposure (Dekker, 2002). Shorter duration of sperm exposure is more common in nulliparous women who develop pre-eclampsia compared to women with uncomplicated pregnancies (Kho et al., 2009). Among multiparous women, pre-eclampsia in second and subsequent pregnancies is far less common if the same partner has fathered the pregnancy compared to a new partner (Robillard et al., 1993).

5.7.4.2. Dyslipidaemia and pre-eclampsia

The pathological dyslipidaemia of pregnancy is exaggerated in pre-eclampsia (Belo et al., 2002) and an association between dyslipidaemia and pre-eclampsia is well established. In 1994, Lorentzen et al demonstrated for the first time that increases in free fatty acids and triglycerides at 16-18 weeks gestation preceded later manifestation of pre-eclampsia (Lorentzen, et al., 1994). Subsequent studies have confirmed these findings (Enquobahrie, et al., 2004; Gratacos et al., 1996; Lorentzen, Drevon, Endresen, & Henriksen, 1995).

There are various theories about the association between dyslipidaemia and the underlying pathophysiology of pre-eclampsia. The endothelium appears to be an important factor in the pathogenesis of pre-eclampsia, and it is hypothesised that the link may be endothelial cell disruption and oxidative stress. This is similar to the hypothesis underlying dyslipidaemia and atherosclerosis risk, and there is an association between pre-eclampsia and subsequent development of risk factors for cardiovascular disease in later life including dyslipidaemia, and endothelial dysfunction. It is hypothesised that the inflammatory activation of endothelium and circulating blood cells generates

free radicals, and the effect of these are exaggerated by dyslipidaemia (Roberts, Pearson, Cutler, & Lindheimer, 2003). Women with pre-eclampsia have been reported to have increased lipolytic activity, which results in increased uptake of free fatty acids by the endothelium which are then esterified into triglycerides (Lorentzen, et al., 1995). Women with pre-eclampsia not only have higher concentrations of circulating FFA's but also higher concentrations of oxidised LDL particles, which is contributory to vascular endothelial cell damage (Wakatsuki, Ikenoue, Okatani, Shinohara, & Fukaya, 2000).

The pre-pregnancy presence of characteristics of the metabolic syndrome may also be contributory factors to the pathogenesis of pre-eclampsia. Elevated BMI, dyslipidaemia, elevation of blood pressure, and central adiposity have been associated with pre-eclampsia (Barden, Beilin, Ritchie, Walters, & Michael, 1999; Magnussen, et al., 2007). Bodnar (2005) investigated the effect of inflammatory markers and lipids on the association between maternal BMI and pre-eclampsia and reported that inflammation and triglycerides mediated approximately one third (36%) of the total effect of BMI on risk of pre-eclampsia. The predominant effect arose from inflammation (31%), measured by maternal serum C-reactive protein (CRP). However, an association between elevated CRP concentrations evident before clinically apparent pre-eclampsia and development of the disease is not consistently reported (Djurovic et al., 2002; Wolf et al., 2001).

A few prospective studies have investigated early pregnancy maternal lipid concentrations and an association with pre-eclampsia. The prospective design of these studies confirms that the dyslipidaemia evident in pre-eclampsia is not a late consequence of the developed disease. Hypertriglyceridemia is reported as the dyslipidaemic factor most consistently associated with pre-eclampsia (Clausen, Djurovic, & Henriksen, 2001; Ray, Diamond, Singh, & Bell, 2006). In the earliest studies, pre-eclampsia was associated with increased triglycerides in univariable analysis among nulliparous women (Lorentzen, et al., 1995; Lorentzen, et al., 1994).

Subsequent studies have investigated other lipids including LDL, HDL and lipid ratios. In a case control study, Clausen et al (2001) reported a positive association between early onset pre-eclampsia and increased triglycerides at 18 weeks gestation (adjOR 5.0, 95% CI: 1.5-16.6) but not total cholesterol, HDL or non-HDL after adjustment for age, BMI, nulliparity and smoking (Clausen, et al., 2001). Findings in a recent study were similar, reporting increased adjusted OR's for trigycerides and pre-eclampsia (aOR1.1, 95% CI: 1.1–1.2; p=0.004) but no similar association for cholesterol or HDL (Demirci, Tugrul, Dolgun, Sozen, & Eren, 2011). One study reported an association between hypertriglyceridaemia and development of pre-eclampsia in obese nulliparous women, but this cohort included a large subgroup of women with hypertension or diabetes (Rajasingam, et al., 2009). Enqhuobahrie et al (2004) reported a positive association between pre-eclampsia and higher concentrations of LDL cholesterol, triglycerides, and LDL/HDL ratios, but not HDL after adjustment for confounders (Enquobahrie, et al., 2004). Results from other studies are consistent with these findings (Van den Elzen, Wladimiroff, Cohen-Overbeek, Bruijn, & Grobbee, 1996; Wiznitzer et al., 2009). Overall, reduced concentrations of HDL have not been associated with increased risk of pre-eclampsia after adjustment for confounding factors.

5.7.4.3. Central adiposity and pre-eclampsia

It is well established that central adiposity is associated with increased risk of metabolic syndrome, type 2 diabetes and cardiovascular disease in non-pregnant populations. (Cameron et al., 2009; Eckel, et al., 2005; Huxley, Mendis, Zheleznyakov, Reddy, & Chan, 2010). A WHO expert consultation group report on waist circumference and waist hip ratio reported that both measures are associated with increased disease risk in diverse populations (World Health Organization, 2008). Waist circumference is the best simple marker and predictor for visceral fat whereas BMI is not a good indicator of visceral fat (Han, Sattar, & Lean, 2006).

Although not widely investigated, waist circumference may also be a useful anthropometric measure in pregnancy to assess risk for adverse outcomes. Use of waist circumference has been considered as limited due to increasing abdominal girth particularly in later pregnancy, however several prospective studies have reported an association between increased waist circumference in early pregnancy and adverse pregnancy outcomes. A large study of a population of women of mixed BMI and parity with singleton pregnancies reported increased waist circumference measured at 20-28 weeks gestation to be predictive of increased risk of pre-eclampsia and have similar predictive capacity to BMI (Wendland, Duncan, Mengue, Nucci, & Schmidt, 2007). In another study of primigravid women of mixed BMI, Sattar et al (2001) reported that waist circumference was unrelated to gestational age up to 16 weeks and predictive of pre-eclampsia after adjustment for BMI, age, parity and smoking status (Sattar et al., 2001). A smaller study reported a 'hypertriglyceridaemic-waist phenotype', defined as the simultaneous presence of abdominal obesity and hypertriglyceridemia, in the first trimester of pregnancy to be associated with increased risk of glucose intolerance in later pregnancy among women of mixed parity and BMI (Brisson, Perron, Guay, Gaudet, & Bouchard, 2010). The proportion of variance in waist circumference explained by height is minimal, thus does not need to be considered as a confounder (Han, et al., 2006; Sattar, et al., 2001).

There is evidence that central adiposity measured by waist circumference in early pregnancy is associated with risk of pre-eclampsia among populations of women with mixed BMI. No studies have investigated this association in obese pregnant women to determine if assessment of central adiposity in early pregnancy is useful to determine risk for adverse outcomes such as pre-eclampsia.

Summary of risk factors for pre-eclampsia

- dyslipidaemia in early pregnancy, particularly hypertriglyceridaemia, has been associated with risk of pre-eclampsia among populations of women of mixed BMI
- central adiposity measured by waist circumference in early/mid pregnancy has been reported to be associated with risk of pre-eclampsia among populations of women with mixed BMI
- no studies have investigated risk factors for pre-eclampsia in an obese otherwise healthy nulliparous population of women

5.8. Rates of pre-eclampsia

5.8.1. *Prevalence of pre-eclampsia and general obstetric population*

Background prevalence of pre-eclampsia in general obstetric populations is approximately 2-3% (Hutcheon, Lisonkova, & Joseph, 2011; Redman & Sargent, 2005). At National Women's Hospital, Auckland, NZ in 2011, overall rate of pre-eclampsia was 2.4% (National Women's, 2011).

5.8.2. *Prevalence of pre-eclampsia and nulliparous women*

The background rate of pre-eclampsia among healthy nulliparous women is approximately 5% (North, et al., 2011; Sibai, et al., 2005; Vatten & Skjaerven, 2004).

5.8.3. *Prevalence and risk of pre-eclampsia associated with obesity*

As worldwide rates of obesity among women of reproductive age continue to rise, it is likely there will be an increasing overall prevalence of pre-eclampsia (Andreasen, Andersen, & Schantz, 2004; Bhattacharya, et al., 2007; Bodnar, Siega-Riz, Simhan, Himes, & Abrams, 2010; Cedergren, 2004; McIntyre, Gibbons, Flenady, & Callaway, 2012; Sibai, et al., 2005). LaCoursiere et al (2005) reported concurrently increasing rates of maternal obesity and pre-eclampsia over a ten year period in a US cohort (LaCoursiere, Bloebaum, Duncan, & Varner, 2005).

5.8.4. *Obesity and pre-eclampsia in a general obstetric population*

Increased rates of pre-eclampsia have been consistently associated with elevated BMI. Among studies of women who are obese and of mixed parity, rates are increased to 8.7% - 10.5% (Fortner, Pekow, Solomon, Markenson, & Chasan-Taber, 2009; Gaillard, Steegers, Hofman, & Jaddoe, 2011; Mbah, et al., 2010; O'Brien, Ray, & Chan, 2003). The Generation R study investigating "associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders" reported a two and a half fold increase in risk of pre-eclampsia among obese women compared to women of normal weight (Gaillard, et al., 2011). A systematic review of risk factors for pre-eclampsia identified a raised BMI pre-pregnancy or at booking versus a normal BMI nearly doubled the adjusted odds ratio for development of pre-eclampsia (Duckitt & Harrington, 2005).

5.8.5. *Obesity, pre-eclampsia and nulliparity*

Among obese women who are nulliparous, rates of pre-eclampsia are further increased from a background rate of 5% among a general population of nulliparous women to 8-12% (Anderson et al., 2012; Bhattacharya, et al., 2007; North, et al., 2011; Sohlberg, Stephansson, Cnattingius, & Wikstrom, 2012). A three to four fold increase in risk for pre-eclampsia among nulliparous women comparing obese to normal weight is consistently reported, persisting after adjustment for confounding factors such as maternal age, education and smoking status. Exploring the dose dependent relationship between pre-pregnancy BMI and risk of pre-eclampsia among primiparous

women, Bodnar (2005) reported the risk of pre-eclampsia nearly tripled for obese women (BMI 30kg/m^2) compared to a BMI of 21 kg/m^2 (aOR 2.9, 95% CI: 1.6-5.3) whereas a lower BMI (19 kg/m^2) was protective (aOR 0.66, 95%CI: 0.5-0.9) (Bodnar, et al., 2005). Sohlberg (2012) reported a three to four fold increase in risk for term pre-eclampsia among nulliparous obese (BMI 30-34.9 kg/m^2) and morbidly obese women (BMI>35 kg/m^2) (aOR 2.7, 95% CI: 2.6-2.9] and 4.0 95% CI: 3.8-4.4 respectively) compared to women with normal BMI (Sohlberg, et al., 2012). Liu (2009), investigating pre-eclampsia risk among a nulliparous Chinese population using a lower ethnic specific classification for obese BMI (≥28 kg/m^2), reported a fivefold increase compared to a normal BMI of 18.5-24 kg/m^2 (aOR 5.7, 95% CI: 4.0-8.1) (Liu & Sia, 2004).

5.9. Stratifying risk of pre-eclampsia among nulliparous obese women

Obesity is highly correlated with other factors that increase risk for pre-eclampsia, including insulin resistance, dyslipidaemia, and chronic hypertension, however obesity is a persisting risk factor for pre-eclampsia after either exclusion of or adjustment for these other factors (Ehrenthal, Jurkovitz, Hoffman, Jiang, & Weintraub, 2011; O'Brien, et al., 2003). Obese women comprise a large proportion of nulliparous women who are otherwise healthy, (16% of the cohort in the SCOPE study) and have high rates of pre-eclampsia of 10-15% (Dixon et al., 2011). This high prevalence of obesity in obstetric populations means that specialist referral is not feasible for all obese women, and a background rate of pre-eclampsia of 10% is also not generally considered high enough to warrant prophylactic treatment with low dose aspirin or calcium to reduce the risk of pre-eclampsia (North, et al., 2011). Currently, referral in early pregnancy for specialist consultation if BMI ≥35 is only recommended if there is also any other predisposing risk factors present (*Figure 5.2*) (Milne et al., 2005; National Collaborating Centre for Women's and Children's Health, 2010).

Many of these risk factors for pre-eclampsia are not applicable to "otherwise healthy" obese nulliparous women, for example previous history of pre-eclampsia, chronic hypertension or pre-existing diabetes mellitus. Identification of subgroups of obese nulliparous women at higher risk for pre-eclampsia would enable prudent referral for specialist care and consideration of prophylactic treatment.

So are there risk factors that can differentiate obese nulliparous women with no underlying medical conditions who develop pre-eclampsia from those who do not? Identification of such factors might enable stratification of obese nulliparous women into low and high risk categories, and enable referral of those at higher risk of pre-eclampsia for specialist led care and consideration of antenatal preventative treatment. There are no data defining risk factors for pre-eclampsia among obese populations of who have no medical complications such as diabetes, renal disease or hypertension.

PRECOG RECOMMENDATION Offer pregnant women with the following predisposing factors for pre-eclampsia referral early in pregnancy for specialist input to their antenatal care plan The factors indicate an underlying pathology, concomitant condition, or otherwise high level of obstetric risk related to pre-eclampsia, which would benefit from specialist input: this may be for further specialist investigation, for clarification of risk, or to advise on early intervention or pharmacological treatment.

BOX 2: Factors for referral in early pregnancy for specialist input to care

Multiple pregnancy

Underlying medical conditions

- Pre-existing hypertension or booking diastolic BP ≥ 90 mmHg
- Pre-existing renal disease or booking proteinuria (≥ 1+ on more than one occasion or quantified at ≥ 0.3g/ 24 hour)
- Pre-existing diabetes
- Antiphospholipid antibodies

• Pre-eclampsia in any previous pregnancy

• Any two other pre-disposing factors from Recommendation

- first pregnancy
- age 40 years or more
- BMI ≥ 35
- family history
- booking diastolic BP ≥ 80 mmHg < 90mmHg

Figure 5-2 Pre-eclampsia community guideline (Milne, Redman et al. 2005)

Obese women already have pathophysiologic factors predisposing to risk of pre-eclampsia, entering pregnancy in a pre-existing state of increased adiposity, and many may be dyslipidaemic. Among obese women, the degree of dyslipidaemia and adiposity may be influential in determining risk of pre-eclampsia. Adiposity can be measured not only by BMI but also by a measure of central adiposity (waist circumference). It is feasible that obese women may have different risk factors related to pre-eclampsia in early pregnancy compared to those present in a general population of women. One study has investigated risk of pre-eclampsia among obese nullipara but the study population included a large subgroup of women with additional risk factors of hypertension and diabetes (Rajasingam, et al., 2009). Risk factors for pre-eclampsia among obese “otherwise healthy” nulliparous women have not been investigated previously.

Summary of prevalence of pre-eclampsia and risk of pre-eclampsia among obese women

- pre-eclampsia remains a prevalent disease and a major cause of maternal, fetal and neonatal morbidity and mortality
- rates of pre-eclampsia are predicted to rise concurrent with increasing rates of obesity. An association between both nulliparity and obesity and risk for pre-eclampsia is well established
- numerous established risk factors for pre-eclampsia, such as previous history of pre-eclampsia, are not applicable to a nulliparous population of women, nor to an obese population of women who have no underlying medical pathology such as chronic hypertension
- identification of subgroups and risk stratification of obese nulliparous women into lower or higher risk for preeclampsia would enable prudent referral for specialist care and consideration of prophylactic treatment
- no studies have investigated risk factors for pre-eclampsia among a nulliparous "healthy" obese population of women

Chapter 6. Obesity and caesarean section

This chapter presents results on the association between first and second stage CS and maternal BMI

Title:

Risk of first and second stage cesarean by maternal BMI among nullipara in labor at term.[1]

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Authors:

Elaine M FYFE, Ngaire H ANDERSON, Robyn A NORTH, Eliza HY CHAN, Rennae S TAYLOR, Gustaaf A DEKKER, Lesley ME MCCOWAN.

Contribution:

EF participated in the conception and design of the study, carried out the data collection, conducted statistical analysis of the data, interpreted the data and drafted the manuscript.

NA assisted with interpretation of the data and helped to draft and revise the manuscript

RN participated in the conception and design of the study, assisted with interpretation of the data and helped to draft the manuscript.

EC assisted with statistical analysis and interpretation of the data and helped to edit the manuscript.

RT assisted with interpretation of the data and helped to edit the manuscript.

GD helped to edit the manuscript

LM participated in the conception and design of the study, assisted with interpretation of the data and helped to draft the manuscript.

[1] All spelling in this chapter is American as this paper was published in a American journal

Abstract

Objective

To estimate in a cohort of nulliparous women in labor at term whether cesarean delivery rates are increased in first and second stages of labor in overweight and obese women and whether being overweight or obese is an independent risk factor for cesarean delivery.

Methods

Nulliparous women recruited to the prospective Screening for Pregnancy Endpoints (SCOPE) study who went into labor after 37 weeks of gestation were categorized according to ethnic-specific body mass index (BMI) criteria as normal, overweight or obese. Normal BMI was the referent. Multivariable analyses, adjusting for known confounders for obesity and cesarean delivery, was performed to determine if being overweight or obese was associated with an increased risk of cesarean in labor (all cesarean deliveries and in first stage of labor).

Results

Of 2629 participants, 1416 (54%) had normal BMI's, 773 (29%) were overweight and 440 (17%) were obese. First stage cesarean delivery was increased in overweight (n=149, 19%) and obese (n=137, 31%) women compared with normal weight women (n=181, 13%) *P*=.0002, whereas second stage cesarean delivery was similar [normal BMI 76 (6.2%), overweight 45 (7.2%), obese 23 (7.6%), *P*=.87]. Being overweight or obese was an independent risk factor for all cesarean deliveries in labor with adjusted odds ratio (OR) 1.34, 95% confidence interval (CI) 1.07-1.67 and 2.51, 95%CI 1.94-3.25, respectively. Similarly, being overweight (adjusted OR 1.39, 95%CI 1.09-1.79) or obese (adjusted OR 2.89, 95%CI 2.19-3.80) was associated with increased cesarean during the first stage. Risks of cesarean delivery were similar regardless of whether ethnic specific or World Health Organization (WHO) BMI criteria were used.

Conclusion

Among nulliparous women in labor at term, being overweight or obese by either WHO or ethnicity-specific BMI criteria is an independent risk factor for cesarean delivery in the first stage, but not the second stage of labor.

Paper II

Risk of first and second stage cesarean by maternal BMI among nullipara in labor at term.

Introduction

Increasing maternal body mass index (BMI, calculated as weight (kg)/[height(m)]^2) is associated with a dose dependent increased risk of cesarean delivery, particularly emergency cesarean delivery in labor (Bergholt, et al., 2007; Heslehurst, et al., 2008; Sarkar, et al., 2007; Schrauwers & Dekker). Cesarean delivery in obese women is associated with increased rates of morbidity and mortality compared to cesarean delivery in women with normal BMIs, and also with increased use of limited healthcare resources (Doherty, et al., 2006; Heslehurst, et al., 2008). Potential limitations when defining obesity by standard World Health Organization (WHO) BMI criteria recently have been highlighted, with both underrecognition of obesity in some ethnicities and over diagnosis in other ethnic groups (World Health Organization, 2004). Ethnicity-specific BMI criteria have been developed to account for differing proportions of body fat between different ethnicities (Swinburn, Ley, Carmichael, & Plank, 1999; World Health Organization, 2004), but these criteria have rarely been used to study the relationship between obesity and pregnancy outcome (Leung, et al., 2008).

Although indications for cesarean delivery in labor among obese women have often been reported (Vahratian, et al., 2005; Young & Woodmansee, 2002), few studies have reported the timing of cesarean with respect to the first and second stages of labor (Burstein, et al., 2008; Sheiner, et al., 2004; Vahratian, et al., 2005; Zhang, et al., 2007). The only prospective study of obese nulliparous women in labor at term reported a tendency to increased first and second stage cesarean delivery compared to women with normal BMIs, but this study was underpowered (Vahratian, et al., 2005). Because obese nulliparous women have a particularly high rate of caesarean delivery during labor, better understanding of whether cesarean occurs during first or second stage in these women would assist clinical management.

In this prospective study of nulliparous women in labor at term, we hypothesized that 1) cesarean delivery rates would be increased in the first and second stages of labor in overweight and obese women; and 2) being overweight or obese according to ethnicity specific criteria would be an independent risk factor for cesarean delivery in the first and second stages of labor.

Materials and methods

Participants were healthy, nulliparous women recruited to the Screening for Pregnancy Endpoints Study from Auckland, New Zealand and Adelaide, Australia between November 2004 and October 2008. The Screening for Pregnancy Endpoints Study is a multicenter prospective cohort study with the primary aim of developing screening tests for prediction of preeclampsia, spontaneous preterm birth and small for gestational age neonates. Ethical approval was obtained from local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008) and all women provided

written informed consent. Detailed methods have been described previously (McCowan et al., 2009). The final study population comprised women who labored at term (*Figure 6.1*).

Because the focus of the current study was obesity, underweight women (BMI<18.5) were excluded. Maternal BMI was calculated using maternal height and weight, measured to the nearest centimeter and kilogram, respectively, by research midwives at 15 ± 1 of weeks gestation. Women were classified into normal, overweight and obese groups according to conventional WHO (World Health Organization, 2006) and ethnic specific criteria (Swinburn, et al., 1999; World Health Organization, 2004). WHO criteria were 18.5-24.9 kg/m^2 (normal), 25-29.9 kg/ m^2 (overweight) and ≥ 30 kg/ m^2 (obese). In the ethnicity specific classification, different criteria were used for Asian (normal 18.5-22.9 kg/m^2, overweight ≥23 kg/m^2, obese ≥27.5 kg/$m^{2)}$ and Pacific Island/Maori women (normal 18.5-25.9 kg/m^2, overweight ≥26 kg/m^2 and obese >32 kg/m^2). For women who were not of Asian, Pacific Island or Maori ethnicity, WHO criteria were used. Normal BMI was the referent.

The primary outcome measure was cesarean delivery in labor at term, further classified as cesarean delivery in first and second stage of labor. Secondary outcomes were gestation at delivery, delivery gestation ≥41 weeks, induction of labor and duration of labor.

Estimated date of delivery (EDD) was calculated from a certain last menstrual period date and only adjusted if either a scan at less than16 weeks' gestation found a difference of seven or more days between the scan gestation and that calculated by the last menstrual period, or at a 20 week scan a difference of 10 or more days was found between the scan gestation and that calculated from the last menstrual period. If the last menstrual period date was uncertain, scan dates were used to calculate the estimated date of delivery (Australian New Zealand Clinical Trials Registry, 2007).

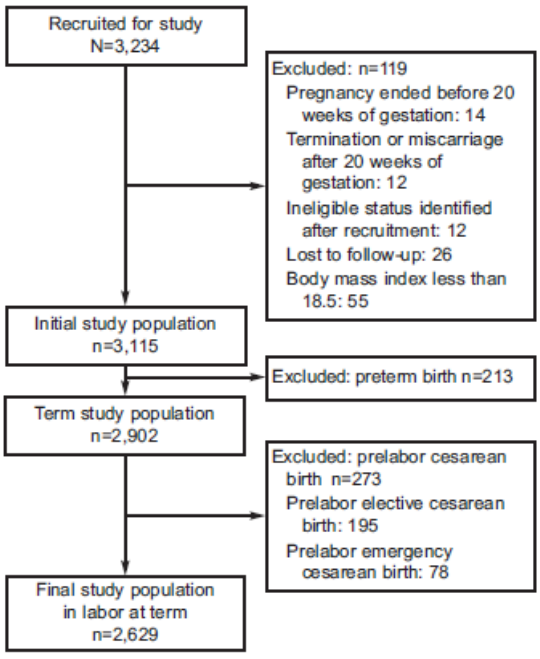

Figure 6-1 Recruitment flow chart

Socioeconomic index was a measure of socioeconomic status derived from maternal occupation (Galbraith, Jenkin, Davis, & Coope, 1996). Active labor was defined as regular, painful uterine contractions with progressive cervical effacement and dilation and cervical dilatation 3cms or more (Chamberlain, 1995). Prelabor elective cesarean delivery was a planned procedure before the onset of labor or following the onset of labor, when the decision for cesarean was made before labor (National Centre for Classification in Health (Sydney), 2004). Prelabor emergency cesarean delivery was a delivery required because of an emergency situation (e.g. fetal distress) before the onset of active labor when the cesarean was performed having not been previously considered necessary. Emergency cesarean delivery in labor was delivery required because of an emergency situation in active labor (e.g. obstructed labor, fetal distress) when the cesarean was performed having not been previously considered necessary (National Centre for Classification in Health (Sydney), 2004). Duration of first stage labor was from the onset of active labor to full cervical dilatation (Chamberlain, 1995). Duration of second stage of labor was from full cervical dilatation until delivery of the neonate (Chamberlain, 1995). Term delivery was delivery at 37 or greater gestational weeks. Pre-eclampsia was defined as gestational hypertension (systolic BP≥140 mmHg and/or diastolic BP ≥90 on at least two occasions four hours apart either after 20 weeks gestation but before the onset of labor, or postpartum) with proteinuria (≥ 300mg/24hr or spot urine protein: creatinine ratio ≥30mg/mmol creatinine or urine dipstick protein ≥2+) or any multisystem complication of preeclampsia (Australian New Zealand Clinical Trials Registry, 2007). A small for gestational age (SGA) baby had a birthweight <10th customized centile (adjusted for infant sex, gestation at delivery and maternal characteristics: parity, ethnicity, height and booking weight) (McCowan, Stewart, Francis, & Gardosi, 2004). A large for gestational age (LGA) infant had a birthweight >90th customized centile (adjusted for infant sex, gestation at delivery and maternal characteristics: parity, ethnicity, height and booking weight) (McCowan, et al., 2004).

Data were entered into an Internet-accessed, auditable database. Data analysis was performed using the statistical software package SAS version 9.1. Univariable analysis was performed to compare maternal characteristics and pregnancy and birth outcomes between ethnicity specific BMI groups. 'Normal BMI' was the referent group.

The chi-square test was used for analysis of categorical variables. Analysis of variance and Dunnett's test were performed to compare continuous variables as appropriate. Multivariable analysis was performed to estimate whether overweight and obesity are independently associated with risk of cesarean delivery (all cesarean deliveries, and in first stage of labor) after adjusting for confounders associated with cesarean, obesity or both. The covariates adjusted for were maternal age, height, socioeconomic index, smoking, conception with artificial reproductive technology, gestational hypertension, preeclampsia, gestational diabetes, induction of labor, gestation at delivery, maternity care provider (public or private), small for gestational age and large for gestational age. Ethnicity specific BMI criteria and then WHO BMI criteria were used to define overweight and obesity in the multivariable analysis.

Results

Between November 2004 and Oct 2008, 3234 women were recruited to the Screening for Pregnancy Endpoints Study in Auckland and Adelaide and follow up was complete in 99% of participants (*Figure 6.1*). The initial study population (n=3115) included 213 (6.8%) women with preterm births and 273 (8.8%) prelabor cesarean deliveries performed at any gestation. The overall rate of preterm birth did not differ between BMI groups [normal 106 (6.4%), overweight 64 (7.0%) and obese 43 (7.9%), *P*=.49], nor did the type of preterm birth, either spontaneous [normal 76 (4.6%), overweight 47 (5.1%), obese 26 (4.8%), *P*= .82] or iatrogenic [normal 30 (1.8%), overweight 17 (1.9%), obese 17 (3.1%), *P*=.41]. Prelabor cesarean delivery was higher in obese women [normal 133 (8.6%), overweight 76 (8.9%) and obese 64 (12.6%), *P*=.02] as a result of a higher rate of prelabor emergency cesarean delivery [normal 29 (1.9%), overweight 21 (2.5%) and obese 28 (5.6%), *P*=.00005]. Elective prelabor cesarean rates were similar across BMI groups.

The final study population (n=2629) comprised women who labored at term either spontaneously (n=1832) or after induction of labor (n=797). Overweight and obese women differed in a number of demographic characteristics compared to those with normal BMI (*Table 6.1*). Obese women were younger, shorter, had lower socioeconomic indices, and were more likely to be single, to smoke and to receive public antenatal care. Hypertensive disorders of pregnancy and gestational diabetes were also more common.

	Body Mass Index (kg/m^2)			
	Normal (n=1,416)	Overweight (n=773)	Obese (n=440)	*P*
Maternal characteristic				
Ethnicity				<.001
European	1,242 (87.7)	651 (84.2)	385 (87.5)	
Asian	70 (4.9)	34 (4.4)	15 (3.4)	
Maori or Pacific	41 (2.9)	47 (6.1)	15 (3.4)	
Indian	24 (1.7)	27 (3.5)	10 (2.3)	
Other	39 (2.8)	14 (1.8)	15 (3.4)	
Age (y)	27.9±5.8	27.9±5.7	26.7±5.5	<.001
Height (cm)	165.7±6.5	164.9±6.6	164.5±6.3	<.001
Primigravid	1,088 (76.8)	586 (73.5)	321 (73.0)	.052
Unmarried	101 (7.1)	52 (6.7)	44 (10.0)	.003
Socioeconomic index	43±17	41±16	35±15	<.001
Smoking at 15 wk	140 (9.9)	69 (8.9)	71 (16.1)	<.001
Public obstetric care	1,166 (82)	672 (87)	409 (93)	<.001
Pregnancy complications				
Gestational hypertension	57 (4.0)	74 (9.6)	57 (13.0)	<.001
Preeclampsia	39 (2.8)	34 (4.4)	38 (6.7)	<.001
Gestational diabetes*	17 (1.2)	14 (1.8)	31 (7.0)	<.001

Data are n (%) or mean±standard deviation unless otherwise specified.
P values are for comparisons between all body mass index groups.
* Unknown n=159.

Table 6-1 Maternal Characteristics and Antenatal Outcomes for Nulliparous Women in Labor at Term

There was no difference in mean gestation at delivery across BMI groups and no increase in prolonged pregnancy (≥ 41^0 weeks) among obese women (*Table 6.2*). Induction of labor was more common in overweight and obese women. The rate of cesarean delivery in labor also increased with increasing maternal BMI (*Figure 6.2*). Obese women were twice as likely to have cesarean delivery in labor compared with women with normal BMIs as a result of an increased rate of cesarean in the first stage of labor (*Table 6.2*). In contrast, the rate of cesarean in the second stage of labor was similar across BMI groups.

Outcome	Body Mass Index (kg/m²)			*P*
	Normal (n=1,416)	Overweight (n=773)	Obese (n=440)	
Gestation at delivery (wk)	40.0±1.2	40.1±1.2	40.0±1.2	.48
Delivery gestation 41 wk or more	349 (24.7)	216 (27.9)	115 (26.1)	.24
Duration of labor				
Vaginal birth (min)				
Duration first stage	429±238	432±264	424±258	.90
Duration second stage	78±55	82±59	69±54	.007
Total duration	507±253	515±281	493±272	.53
Mode of delivery				
Vaginal (n=2,018)	1,159 (81.8)	579 (74.9)	280 (63.6)	<.001
Spontaneous (n=1,405)	795 (56.1)	394 (50.1)	216 (49.1)	<.001
Operative (n=613)	364 (25.7)	185 (23.9)	64 (14.6)	<.001
Cesarean delivery in labor (n=611)	257 (18.1)	194 (25.1)	160 (36.4)	<.001
First-stage cesarean	181 (12.7)	149 (19.3)	137 (31.1)	<.001
Second-stage cesarean	76 (5.4)	45 (5.8)	23 (5.2)	.99

Data are mean±standard deviation or n (%)unless otherwise specified.
P values are for comparisons among all body mass index groups.

Table 6-2 Labour and Delivery Outcomes for Nulliparous Women in Labor at Term

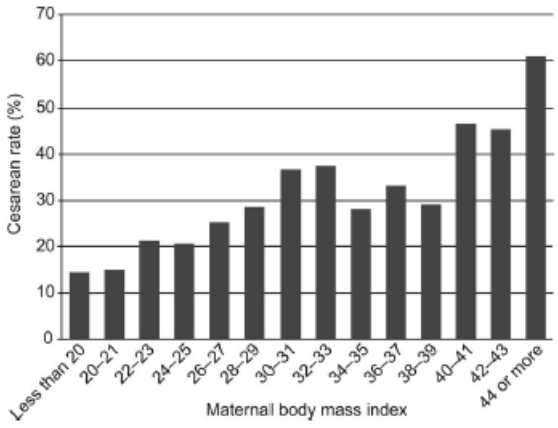

Figure 6-2 Rate of Caesarean Delivery in Labor at Term by BMI

After adjusting for potential confounding factors for both BMI and cesarean delivery, overweight and obesity were independent risk factors for all cesarean deliveries in labor and cesarean delivery in first stage of labor (*Table 6.3*). The results were similar whether ethnicity specific or WHO BMI criteria

were used to define obesity. Other independent risk factors for all cesarean deliveries in labor at term and cesarean delivery in first stage of labor included maternal age, height, gestational hypertension, induction of labor, final gestation at delivery and large for gestational age infant. An additional risk factor for cesarean delivery in first stage of labor was preeclampsia.

Risk Factor	Ethnicity-Specific Body Mass Index	World Health Organization Body Mass Index
All cesarean deliveries in labor		
Obesity	2.51 (1.94–3.25)	2.54 (1.96–3.30)
Overweight	1.34 (1.07–1.67)	1.29 (1.03–1.61)
Maternal age (per 5 y increase)	1.44 (1.29–1.60)	1.44 (1.29–1.60)
Maternal height (per 1 cm decrease)	1.08 (1.06–1.09)	1.08 (1.06–1.09)
Gestational hypertension	1.50 (1.05–2.15)	1.49 (1.04–2.13)
Induction of labor	1.63 (1.32–2.01)	1.63 (1.32–2.01)
Final gestation at delivery (per 1 wk increase)	1.27 (1.16–1.38)	1.27 (1.16–1.38)
Large-for-gestational-age neonate	2.80 (2.05–3.83)	2.81 (2.06–3.83)
Cesarean delivery in first stage of labor		
Obesity	2.89 (2.19–3.80)	2.94 (2.23–3.87)
Overweight	1.39 (1.09–1.79)	1.40 (1.09–1.80)
Maternal age (per 5 y increase)	1.31 (1.17–1.48)	1.31 (1.17–1.47)
Maternal height (per 1 cm decrease)	1.08 (1.01–1.064)	1.09 (1.07–1.10)
Gestational hypertension	1.63 (1.12–2.36)	1.61 (1.11–2.33)
Preeclampsia	1.67 (1.03–2.70)	1.63 (1.00–2.64)
Induction of labor	1.77 (1.41–2.22)	1.76 (1.41–2.21)
Final gestation at delivery (per 1 wk increase)	1.25 (1.14–1.37)	1.25 (1.14–1.37)
Large-for-gestational-age neonate	3.09 (2.23–4.28)	3.10 (2.24–4.29)

Data are adjusted odds ratio (95% confidence interval).
Referent group is vaginal birth at term. Logistic regression analyses are adjusted for maternal age, height, socioeconomic index, smoking, assisted reproductive technology, gestational hypertension, preeclampsia, induction of labor, gestational diabetes, gestation at delivery, small for gestational age, large for gestational age, and type of obstetric care.

Table 6-3 Independent Risk Factors for Caesarean Delivery in Labour at Term

In a secondary analysis, women who had labor induced were excluded (n=797). Independent risk factors for cesarean delivery amongst women who went into spontaneous labor (n=1832), were the same, with a similar magnitude of effect, except gestational hypertension which was not significant (*Table 6.4*).

Because there was no significant difference in the rates of second stage cesarean delivery between BMI groups, no multivariable analysis was performed. A subgroup analysis was performed to compare birth outcomes by BMI groups in women who reached the second stage of labor (*Table 6.5*). Of note, obese women who reached second stage had a higher rate of spontaneous vaginal birth than did those women in the control population with normal BMI's.

Risk Factor	Ethnicity-Specific Body Mass Index	World Health Organization Body Mass Index
Obesity	2.27 (1.62–3.17)	2.32 (1.66–3.24)
Overweight	1.51 (1.14–2.00)	1.40 (1.06–1.86)
Maternal age (per 5 y increase)	1.39 (1.21–1.60)	1.39 (1.21–1.60)
Maternal height (per 1 cm decrease)	1.08 (1.06–1.10)	1.08 (1.06–1.10)
Final gestation at delivery (per 1 wk increase)	1.28 (1.14–1.44)	1.27 (1.13–1.43)
Large-for-gestational-age neonate	3.18 (2.18–4.65)	3.12 (2.18–4.64)

Data are adjusted odds ratio (95% confidence interval).
Referent group is vaginal birth at term. Logistic regression analyses are adjusted for maternal age, height, socioeconomic index, smoking, assisted reproductive technology, gestational hypertension, preeclampsia, gestational diabetes, gestation at delivery, small for gestational age, large for gestational age, and type of obstetric care.

Table 6-4 Independent Risk Factors for Caesarean delivery in Spontaneous Labour at Term

Outcome	Body Mass Index (kg/m²) Normal (n=1,235)	Overweight (n=624)	Obese (n=303)	*P*
Vaginal birth				
Spontaneous (n=1,405)	795 (64)	394 (63)	216 (71)	<.001
Operative (n=613)	364 (29.5)	185 (29.6)	64 (21.1)	.04
Cesarean delivery in second stage (n=144)	76 (6.2)	45 (7.2)	23 (7.6)	.87

Data are n (%) unless otherwise specifed.
P values are for comparisons among all body mass index groups.

Table 6-5 Delivery Outcomes in Women who reached the Second Stage of Labour

Discussion

We have demonstrated that nulliparous women in labor at term who were overweight or obese, by either WHO or ethnic specific BMI criteria, had an increased risk of cesarean independent of other

recognized risk factors for cesarean delivery. The novel and clinically important finding is that this elevated risk of cesarean delivery in labor among overweight and obese women was confined to first stage.

Our findings are consistent with previous publications reporting increased risk of cesarean delivery in labor among nulliparous women with increased BMIs (Bhattacharya, et al., 2007; Cnattingius, Cnattingius, & Notzon, 1998; Usha Kiran, et al., 2005). However, few previous reports have prospectively studied low risk nulliparous women in labor at term (Bergholt, et al., 2007; Vahratian, et al., 2005) or presented findings regarding timing of cesarean delivery (Vahratian, et al., 2005). Bergholt reported that overall most cesareans were performed in the first stage of labor (82%), but did not analyze the risk by BMI group. A smaller study reporting a tendency to increased risk of cesarean delivery in the first and second stage in obese women compared to those with normal BMI, only analyzed the risk for cesarean in the first stage of labor. Our findings suggest that labor dysfunction in overweight and obese women predominantly occurs in the first stage.

Among women who reached the second stage of labor, obese women had a higher rate of spontaneous vaginal birth and fewer operative vaginal births compared to women with normal BMI. The relevance to clinical care is that once obese nulliparous women progress to the second stage of labor they are just as likely to birth vaginally as women with normal BMIs.

The implications of our findings, regarding the elevated risk for cesarean in the first stage of labor in overweight and obese women, are that obstetricians need to plan in advance for these more complicated and high risk procedures. With the burgeoning epidemic of obesity, maternity units need to implement their own obesity birthing protocols, including specialised equipment, and the presence of senior obstetrical, surgical and anesthetic staff. Importantly, if obese women reach the second stage, the increased anticipation and planning required for potentially challenging high risk cesarean surgery, particularly for morbidly obese women, can be down scaled and a spontaneous vaginal birth can be anticipated as the most likely outcome. The underlying mechanisms for increased cesarean delivery rates among obese women are currently unknown but there are data suggesting a dose dependent reduction in uterine contractility occurs, at least in vitro, with increased BMI (Zhang, et al., 2007). If this is so, the effect of impaired contractility on the first stage of labor may be so profound that full dilation is not achieved, presenting as dystocia in the first stage of labour. Maternal expulsive effort is unlikely to be compromised in obese women as second stage intrauterine pressure during active pushing has been reported to be equivalent between BMI groups (Buhimschi, Buhimschi, Malinow, & Weiner, 2004). There is a possibility that practitioner decision making with regard to timing of cesarean delivery in obese women influenced our findings. However, it has been reported that practitioners wait longer in overweight and obese women than normal weight women before performing a cesarean for labor dystocia, so this is unlikely to have a major influence on our findings (Vahratian, et al., 2004).

A novel aspect of our study was the use of ethnicity specific BMI categories in our multiethnic study population. Our cohort included women of Maori or Pacific and Asian descent who have lower and

higher percentages of body fat, respectively, than European women at an equivalent BMI, resulting in recommendations for increased and decreased BMI thresholds for definitions of overweight and obesity (Rush et al., 2004; Swinburn, et al., 1999; World Health Organization, 2004). Use of ethnicity specific criteria to classify BMI confirmed the increased risk of cesarean birth among obese women similar to that seen when WHO criteria were applied.

We found no difference in gestation at delivery or post term delivery in overweight and obese women. Earlier studies have reported an inconsistent relationship between postdates pregnancy and maternal BMI (Sarkar, et al., 2007; Stotland, Washington, & Caughey, 2007). Few previous studies have defined how the estimated date of delivery was calculated, raising questions about the reliability of measures of gestation at delivery in some of these earlier studies (Caughey, Stotland, Washington, & Escobar, 2009; Stotland, et al., 2007).

Strengths of our study include the prospective study design which included only nulliparous women at term and the application of predetermined definitions for active labor, prelabor elective and prelabor emergency cesarean delivery. This approach ensured that our final study population only included women in established labor. Our estimation of BMI was accurate as maternal height and weight was measured in early pregnancy, rather than using less reliable self-reported measures (Bergholt, et al., 2007; Weiss et al., 2004). Normal BMI was our referent group. In contrast, several previous studies used or included low BMI or overweight as the referent group potentially resulting in either over or under estimation of risk for cesarean delivery, respectively (Cnattingius, et al., 1998; Usha Kiran, et al., 2005).

Because we did not have information about augmentation of labor or epidural use, a potential limitation is we were unable to include these in our model. Although early augmentation of spontaneous labor with amniotomy and oxytocin to either prevent delay in labor progression or treat mild delay has been associated with a modest reduction in cesarean delivery rates compared to standard care (Wei et al., 2009), no effect was found in a systematic review when augmentation was implemented for established delay in active labor (Wei, et al., 2009). There are conflicting data from randomized controlled trials regarding association between use of epidural analgesia and increased rate of cesarean delivery (Bofill, et al., 1997; Ramin et al., 1995). Recent systematic reviews again suggest that epidural use does not independently affect the rate of cesarean delivery (Anim-Somuah, 2005; Leighton & Halpern, 2002; Liu & Sia, 2004).

Epidural use is associated with longer duration of second stage and increased rates of operative vaginal delivery (Anim-Somuah, 2005; Liu & Sia, 2004). We cannot exclude the possibility that differing rates of epidural analgesia use among women of differing BMI may have confounded our finding of reduced duration of second stage of labor and reduced operative vaginal delivery rates in obese women. We were unable to control for any possible effect of weight gain in pregnancy in our model as these data were not available.

Future research is needed to investigate the mechanisms underlying the association between increased BMI and cesarean delivery, and in particular why obese women fail to progress in the first stage of labor leading to increased cesarean delivery. If others confirm that the increased cesarean rate in overweight and obese women is confined to the first stage, then clinical trials can be designed to optimize first stage management for this rapidly expanding group of pregnant women.

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Chapter 7. Obesity, cholesterol and Caesarean section

This chapter presents results on the association between obesity, maternal lipids in early pregnancy and risk of intrapartum caesarean in overweight and obese nulliparous women

***Full title*:**

Elevated maternal lipids in early pregnancy are not associated with risk of intrapartum caesarean in overweight and obese nulliparous women.

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Authors:

Elaine M FYFE, Karen S RIVERS, Dr John MD THOMPSON, Dr Kamala PL THIYAGARAJAN, Dr Katie M GROOM**,** Professor Gustaaf A DEKKER**,** Professor Lesley ME MCCOWAN

Contributions:

EF conceived of the study and participated in its design, performed the statistical analysis, interpreted the data and drafted and revised the manuscript.

KR assisted in collecting the data and helped to draft and revise the manuscript.

JT assisted with statistical analysis, interpreted the data, and helped to draft and revise the manuscript.

KT assisted in collecting the data and helped to draft and revise the manuscript.

KG helped to draft and revise the manuscript

GD helped to draft and revise the manuscript

LMcC conceived of the study and participated in its design, interpreted the data and helped to draft and revise the manuscript.

Abstract

Background

Maternal overweight and obesity are associated with slower labour progress and increased caesarean delivery for failure to progress. Obesity is also associated with hyperlipidaemia and cholesterol inhibits myometrial contractility in vitro. Our aim was, among overweight and obese nulliparous women, to investigate 1. the role of early pregnancy serum cholesterol and 2. clinical risk factors associated with first stage caesarean for failure to progress at term.

Methods

Secondary data analysis from a prospective cohort of overweight/obese New Zealand and Australian nullipara recruited to the SCOPE study. Women who laboured at term and delivered vaginally (n=840) or required first stage caesarean for failure to progress (n=196) were included. Maternal characteristics and serum cholesterol at 14-16 weeks' of gestation were compared according to delivery mode in univariable and multivariable analyses (adjusted for BMI, maternal age and height, obstetric care type, induction of labour and gestation at delivery ≥41 weeks).

Results

Total cholesterol at 14-16 weeks was not higher among women requiring first stage caesarean for failure to progress compared to those with vaginal delivery (5.55 ± 0.92 versus 5.67 ± 0.85 mmol/L, *p*= 0.10 respectively). Antenatal risk factors for first stage caesarean for failure to progress in overweight and obese women were BMI (adjusted odds ratio [aOR (95% CI)] 1.15 (1.07-1.22) per 5 unit increase, maternal age 1.37 (1.17-1.61) per 5 year increase, height 1.09 (1.06-1.12) per 1cm reduction), induction of labour 1.94 (1.38-2.73) and prolonged pregnancy ≥41 weeks 1.64 (1.14-2.35).

Conclusions

Elevated maternal cholesterol in early pregnancy is not a risk factor for first stage caesarean for failure to progress in overweight/obese women. Other clinically relevant risk factors have been identified.

Paper III

Elevated maternal lipids in early pregnancy are not associated with risk of intrapartum caesarean in overweight and obese nulliparous women.

Background

Caesarean delivery in overweight and obese women is associated with increased morbidity and mortality, along with increased utilisation of health care resources (Heslehurst, et al., 2008). Increasing maternal body mass index (BMI) is associated with a dose dependent elevated risk of emergency caesarean section in labour, which is largely due to failure to progress (Bergholt, et al., 2007; Ehrenberg, et al., 2004; Fyfe, et al., 2011; Heslehurst, et al., 2008; Zhang, et al., 2007). We have previously demonstrated that this elevated risk is confined to the first stage of labour, and rates of caesarean in the second stage of labour do not differ according to BMI (Fyfe, et al., 2011).

Factors that differentiate overweight and obese women who deliver vaginally from those who require intrapartum caesarean have not previously been reported. The ability to identify those overweight and obese women in early pregnancy who are at higher risk for caesarean in labour at term might assist with delivery planning and counselling.

The underlying reason for failure to progress is thought to be reduced uterine contractility (Zhang, et al., 2007). Reduced contractility in term myometrial biopsies has been reported in specimens from overweight and obese women compared with those from women of normal weight (Zhang, et al., 2007). In addition the rate of cervical dilation in labour is slower in overweight and obese women (Kominiarek, et al., 2011). However, the mechanisms underlying the association between elevated BMI and caesarean section for failure to progress in overweight and obese women are not understood. The relative hyperlipidaemia of normal pregnancy is exaggerated in obese women and it has been speculated that obesity related dyslipidaemia may contribute to altered myometrial cell signalling, dysfunctional labour and increased caesarean delivery for failure to progress (Noble, et al., 2006).

Among overweight and obese women, the level of serum cholesterol may differentiate those who display impaired myometrial function and require caesarean section in labour from those who progress to a vaginal birth. This association has not previously been investigated.

We aimed to investigate the relationship between maternal characteristics, including serum cholesterol, and the risk of caesarean for failure to progress in the first stage of labour among overweight and obese women. We hypothesised that overweight and obese nulliparous women at term who required a caesarean in the first stage of labour for failure to progress would have higher serum cholesterol levels at 14-16 weeks' of gestation compared with those who had a vaginal delivery.

Methods

Participants were healthy, nulliparous women recruited to the Screening for Pregnancy Endpoints Study (SCOPE) from Auckland, New Zealand and Adelaide, Australia. The SCOPE study is a multicentre prospective cohort study, with the primary aim of developing screening tests for prediction of preeclampsia, spontaneous preterm birth and small for gestational age babies. Ethical approval was obtained from local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008) and all women provided written informed consent. The population for the current study comprised overweight and obese women who laboured at term (*Figure 7.1.*) and either delivered vaginally (spontaneous or operative) or had a caesarean in the first stage of labour for failure to progress. Women who had a caesarean in the first stage of labour for any reason other than failure to progress or had a caesarean in the second stage of labour were excluded.

Detailed data collected from all participants during interview with a research midwife, at 14-16 weeks gestation, have previously been described in detail (North, et al., 2011) and included demographic information, smoking, family, medical and gynaecological history. Maternal measurements recorded at 14-16 weeks of gestation included blood pressure, height and weight. Non-fasting serum cholesterol was measured from bloods drawn at the time of interview. Maternal BMI was calculated using maternal height and weight, measured to the nearest centimetre and kilogram respectively. Overweight and obesity were defined according to conventional WHO criteria as BMI 25-29.99 and ≥ 30 kg/m^2 respectively (World Health Organization, 2006).

Outcome measures and exposures

The primary outcome measure was mode of delivery classified as vaginal [spontaneous or operative (forceps or ventouse)] or caesarean in first stage of labour for failure to progress. The exposure was non-fasting serum cholesterol level measured at 14-16 weeks of gestation. Cholesterol measurements (mmol/L) included total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and total cholesterol: HDL-cholesterol ratio.

Definitions

Estimated date of delivery was calculated from a certain last menstrual period date and only adjusted if either an ultrasound scan at less than 16 weeks' gestation found a difference of seven or more days between the scan gestation and that calculated by the last menstrual period, or at a 20 week scan a difference of 10 or more days was found between the scan gestation and that calculated from the last menstrual period. If the last menstrual period date was uncertain, scan dates were used to calculate the estimated date of delivery (Australian New Zealand Clinical Trials Registry, 2007). Socioeconomic index was a measure of socioeconomic status derived from maternal occupation (Galbraith, et al., 1996). Private obstetric care was that provided by a private obstetrician and the comparison group

included care that was hospital based, or provided by an independent midwife or a general practitioner. Definitions for gestational hypertension and preeclampsia have previously been described in detail (North, et al., 2011). Term delivery was delivery at 37^0 or greater weeks of gestation. Active labour was defined as regular, painful uterine contractions with progressive cervical effacement and dilation and cervical dilatation ≥3cms (Chamberlain, 1995). Emergency caesarean in labour was delivery required because of an emergency situation in active labour (e.g. failure to progress, fetal distress) when the caesarean was performed having not been previously considered necessary (National Centre for Classification in Health (Sydney), 2004).

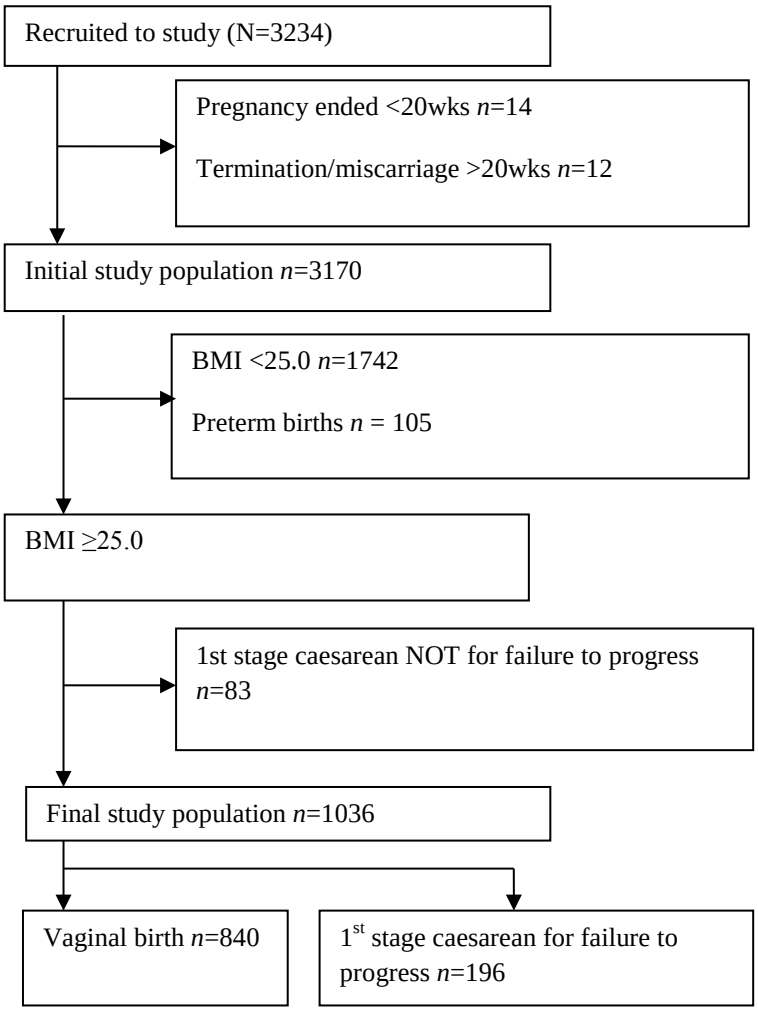

Figure 7-1 Participant Flow Chart

Indication for caesarean stated on the delivery summary by the attending doctor was used to determine whether caesarean in first stage was performed for failure to progress or another indication. If there were combined indications which included failure to progress, then the indication was recorded as failure to progress. Gestational Diabetes Mellitus was defined in accordance with The Australian Diabetes in Pregnancy Society (Hoffman, Nolan, Wilson, Oats, & Simmons, 1998). Small for gestational age (SGA) and large for gestational age (LGA) were infants with birthweight

<10th customised centile and >90th customised centile respectively, adjusted for infant sex, gestation at delivery and maternal characteristics: parity, ethnicity, height and booking weight (McCowan, et al., 2004).

Statistical analysis

Data were entered into an internet accessed, auditable database *(Medscinet AB, Sweden). Data* analysis was performed using the statistical software package SAS© version 9.2. (SAS Institute Inc., Cary, NC). Univariable analysis was performed to compare maternal characteristics and birth outcomes between women who had a vaginal delivery (spontaneous or operative) and women who had a first stage caesarean for failure to progress. Vaginal birth was the referent group. The chi square test was used for analysis of categorical variables, and a Student's *t*-test was used to compare continuous variables. There were no missing data for any variables used in this analysis. Adjusted odds ratios were calculated using multiple regression analyses, controlling for all variables with P<0.1 in univariable analyses, and all maternal cholesterol measures as a priori variables. With our sample size (N=1036, 840 vaginal and 196 caesarean births) we are able to detect a difference of 0.2mmol/L in total cholesterol between the groups (alpha of 0.05 and power 80%) and therefore our study has sufficient power to detect clinically meaningful differences in total cholesterol.

Results

Between November 2004 and Oct 2008, 3234 women were recruited to the SCOPE study in Auckland and Adelaide and follow up was complete in 3195 (99%) participants (*Figure 7.1*). The initial study population (*n*=3170) included 1742 (55.0%) women with BMI <25 who were excluded from this study. Of the final eligible study population of 1036 nulliparous overweight and obese women who laboured at term, 840 (81.1%) had a vaginal delivery and 196 (18.9%) had a first stage caesarean for failure to progress.

Maternal characteristics and antenatal outcomes

Women who had a first stage caesarean for failure to progress were older, shorter, and had a higher BMI compared to those who delivered vaginally (*Table 7.1*). There were no differences in ethnicity, socioeconomic index, smoking, marital status or rates of gestational diabetes or hypertensive pregnancy disorders according to mode of delivery.

Serum cholesterol levels at 14-16 weeks of gestation were not higher among overweight and obese women who had a first stage caesarean for failure to progress compared with overweight and obese women who delivered vaginally (*Table 7.1*). There were also no differences in other lipid parameters.

Labour and delivery outcomes

Of 1036 overweight and obese women at term, 677 (65%) laboured spontaneously, and 359 (35%) had labour induced. The rate of first stage caesarean for failure to progress following induction of labour was twice as high as that following spontaneous onset of labour (28% v 14%, *p*=<0. 001). Although women who had a first stage caesarean for failure to progress had an increased final gestation at delivery, the difference of only two days was not clinically significant (*Table 7.1*). Those with caesarean for failure to progress in the first stage of labour were more likely to have a prolonged pregnancy (≥ 41^0 weeks) compared to those who delivered vaginally. The mean customised birthweight centile and the rate of LGA infants was higher among women who had a first stage caesarean for failure to progress, and the rate of SGA infants was lower (*Table 7.1*).

	Vaginal delivery N = 840 (81%)	1st stage caesarean for failure to progress N = 196 (19%)	*P*
Maternal characteristic			
Body mass index (kg/m^2)	29.4 ± 4.4	30.9 ± 5.5	<0.001
Age (years)	27.1 ± 5.6	28.9 ± 5.9	<0.001
Ethnicity			0.18
European	732 (87)	179 (91)	
Socioeconomic index	38 ± 16	39 ± 15	0.35
Smoking at 14-16 weeks	103 (12)	22 (11)	0.69
Unmarried	77 (9)	13 (7)	0.26
Maternal height (cm)	166 ± 6.4	163 ± 5.8	<0.001
Private obstetric care	83 (10)	28 (14)	0.07
Pregnancy complications			
Gestational diabetes*	26 (3)	12 (6)	0.11
Gestational hypertension	85 (10)	25 (13)	0.28
Preeclampsia	46 (5)	16 (8)	0.15
Serum lipids			
Triglycerides	1.55 ± 0.63	1.62 ± 0.63	0.16
Total Cholesterol†	5.55 ± 0.92	5.67 ± 0.85	0.10
LDL‡- Cholesterol†	3.10 ± 0.82	3.18 ± 0.75	0.20
HDL§- Cholesterol†	1.75 ± 0.36	1.75 ± 0.34	0.87
Total Cholesterol:HDL ratio	3.29 ± 0.80	3.34 ± 0.76	0.42
Labor and delivery			
Induction of labour	259 (31)	100 (51)	<0.001
Gestation at delivery (weeks)	39.6 ± 1.2	39.9 ± 1.2	0.002
Gestation at delivery ≥ 41 weeks	205 (24)	71 (36)	0.002
Neonatal outcomes			
Birthweight (g)	3500 ± 445	3734 ± 484	<0.001
Customised birthweight centile	44 ± 28	57 ± 29	<0.001
Small for gestational age‖	91 (11)	12 (6)	0.05
Large for gestational age‖	56 (7)	32 (16)	<0.001

Data are n (%) or mean ± standard deviation

* Unknown n=40
† mmol/L
‡ low density lipoprotein
§ high density lipoprotein
‖By customised birthweight centiles

Table 7-1 Maternal characteristics, pregnancy and neonatal outcomes for overweight and obese nulliparous women according to mode of delivery.

Following adjustment for all variables in univariable analysis with *P* value <0.1, maternal total cholesterol, LDL, HDL and total LDL: HDL ratios were not independently associated with risk of first stage caesarean for failure to progress. The following variables were identified as independent antenatal risk factors for first stage caesarean for failure to progress: decreasing maternal height, increasing maternal age, increasing BMI, induction of labour and gestation at delivery greater than or equal to 41 weeks (*Table 7.2)*.

Antenatal factor	Adjusted Odds Ratio (95% confidence interval)
BMI* (per 5 units ↑)	1.40 (1.18-1.66)
Maternal age (per 5yr ↑)	1.37 (1.17-1.61)
Maternal height (per 1cm ↓)	1.09 (1.06-1.12)
Induction of labour	1.94 (1.38-2.73)
Gestation at delivery ≥ 41wks	1.64 (1.14-2.35)

* kg/ m^2

Table 7-2 Antenatal risk factors for 1st stage caesarean for failure to progress among overweight and obese nullipara

As birthweight is not an antenatal risk factor, we did not include it as a variable in the final multivariable model. However, when a secondary analysis was undertaken that included birthweight, the risk for caesarean doubled for every 500g increase in birthweight (aOR 2.19, 95% CI 1.78-2.69) and gestation at delivery ≥41 weeks was no longer significant (aOR 0.92, 95% CI 0.62-1.37). Hence, in our multivariable model of antenatal risk factors for caesarean, prolonged pregnancy (≥41 weeks) likely acts as a surrogate for increasing birthweight (*Table 7.2*).

Discussion

In this cohort of overweight and obese nulliparous women who laboured at term we have demonstrated, contrary to our hypothesis, that those requiring first stage caesarean for failure to progress are not more likely to have higher serum cholesterol levels at 14-16 weeks of gestation compared with overweight and obese women who deliver vaginally. We have identified clinically relevant antenatal risk factors among overweight and obese women for first stage caesarean for failure to progress at term.

Our findings are novel as the relationship between maternal serum cholesterol and caesarean for failure to progress in overweight and obese women has not previously been described. We have previously demonstrated that overweight and obesity in nulliparous women confers an independent risk for caesarean only in the first stage and not in the second stage of labour (Fyfe, et al., 2011). In vitro studies using term myometrial biopsies from women undergoing intrapartum caesarean have demonstrated inhibited contractile amplitude following addition of cholesterol to the medium, leading to the postulation that higher serum cholesterol levels may contribute to sub-optimal myometrial

contractility (Zhang, et al., 2007). Oxytocin and oestrogen receptor function is modulated by the amount of cholesterol in the uterine myometrial plasma membranes and extraction of cholesterol from myometrial plasma membranes in vivo has been demonstrated to greatly enhance spontaneous contractions (Smith, et al., 2005). Although we did not find a difference in cholesterol levels in early pregnancy by mode of delivery, as cholesterol levels continue to increase with advancing gestation (Lippi et al., 2007), it is possible that either late pregnancy cholesterol levels or the magnitude of increase might influence the risk of caesarean for failure to progress. It was not possible to explore this relationship in the current study as we did not collect late pregnancy samples in the SCOPE study where the focus was early pregnancy risk prediction. We used non fasting lipids for our study, however lipid profiles change minimally in response to food intake (Langsted, Freiberg, & Nordestgaard, 2008), and a very large recent study showed that fasting times showed little association with lipid subclass levels in a community-based population, suggesting that fasting for routine lipid levels is largely unnecessary (Sidhu & Naugler, 2012). Non fasting lipid profiles may be used as standard (Nordestgaard & Benn, 2009).

Our findings of several simple antenatal risk factors associated with caesarean for failure to progress specifically among overweight and obese nulliparous women are novel and clinically relevant. Although many studies have identified risk factors associated with caesarean for failure to progress in a general obstetric population of mixed BMI (Kominiarek et al., 2010), and identified obesity as a risk factor, no studies have specifically investigated risk factors among overweight and obese women only. Two studies with populations of mixed BMI have performed subgroup analyses of obese women and reported a two to three fold increase in the rate of caesarean among obese women with short stature (Cnattingius, et al., 1998; Dempsey, et al., 2005) but a third study reporting interventions during labour in relation to height in obese women did not support this association (Jensen, Agger, & Rasmussen, 2000).

In summary, we have identified the following antenatal risk factors for first stage caesarean for failure to progress among overweight and obese nulliparous women at term: increasing maternal age, increasing BMI, reducing height, induction of labour and prolonged pregnancy. These factors can be incorporated into risk assessment when planning for delivery in overweight and obese women. Early pregnancy cholesterol measures are not useful as part of this risk assessment.

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Chapter 8. Obesity and postpartum haemorrhage

This chapter presents results on the association between obesity and postpartum haemorrhage.

Title:

Maternal obesity and postpartum haemorrhage after vaginal and caesarean delivery among nulliparous women at term: a retrospective cohort study

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Authors:

Elaine M FYFE**,** John MD THOMPSON, Ngaire H ANDERSON, Katie M GROOM, Lesley ME MCCOWAN

Contribution:

EF participated in the conception and design of the study, carried out the data collection, conducted statistical analysis of the data, interpreted the data and drafted the manuscript.

JT assisted with statistical analysis and interpretation of the data and helped to edit the manuscript.

NA assisted with interpretation of the data and helped to draft and revise the manuscript

KG assisted with interpretation of the data and helped to edit the manuscript.

LM participated in the conception and design of the study, assisted with interpretation of the data and helped to draft the manuscript.

Abstract

Background

Increasing rates of postpartum haemorrhage rates in developed countries over the past two decades are not explained by corresponding changes in risk factors and conjecture has been raised that maternal obesity may be responsible. Few studies investigating risk factors for PPH have included BMI or investigated PPH risk among nulliparous women. The aim of this study was to determine in a cohort of nulliparous women delivering at term whether overweight and obesity are independent risk factors for major postpartum haemorrhage (PPH ≥1000ml) after vaginal and caesarean section delivery.

Methods

The study population was nulliparous singleton pregnancies delivered at term at National Women's Hospital, Auckland, New Zealand from 2006 to 2009 (N=11,363). Multivariable logistic regression was adjusted for risk factors for major PPH.

Results

There were 7238 (63.7%) women of normal BMI, 2631 (23.2%) overweight and 1494 (13.1%) obese. Overall, PPH rates were increased in overweight and obese compared with normal-weight women (n=255 [9.7%], n=233 [15.6%]), n=524 [7.2%], p <.001) respectively. There was an approximate twofold increase in risk in obese nulliparous women that was independent of confounders, adjusted odds ratio [aOR (95% CI)] for all deliveries 1.86 (1.51-2.28). Being obese was a risk factor for major PPH following both caesarean 1.73 (1.32-2.28) and vaginal delivery 2.11 (1.54-2.89) and the latter risk was similar after exclusion of women with major perineal trauma and retained placentae. Three additional factors were consistently associated with risk for major PPH regardless of mode of delivery: increasing infant birthweight, antepartum haemorrhage and Asian ethnicity.

Conclusion

Nulliparous obese women have a twofold increase in risk of major PPH compared to women with normal BMI regardless of mode of delivery. Higher rates of PPH among obese women are not attributable to their higher rates of caesarean delivery. Obesity is an important high risk factor for PPH, and the risk following vaginal delivery is emphasised. We recommend in addition to standard practice of active management of third stage of labour, there should be increased vigilance and preparation for PPH management in obese women.

Paper IV

Maternal obesity and postpartum haemorrhage after vaginal and caesarean delivery among nulliparous women at term

Background

The incidence of postpartum haemorrhage (PPH) has been increasing in several developed countries over the past two decades, with rates rising by over one third (Callaghan, et al., 2010; Knight, et al., 2009; Rossen, et al., 2010). This disturbing rise, with its associated maternal morbidity and mortality, (Centre for Maternal and Child Enquiries, 2010) is not explained by corresponding changes in risk factors such as increased rates of caesarean section and induction of labour (Ford, et al., 2007; Joseph, et al., 2007). A contemporaneous rise in global obesity has raised conjecture that maternal obesity may be responsible for this increase in PPH rates (Knight, et al., 2009). Associations between obesity and PPH have been reported in several studies investigating the relationship between increased BMI and birth outcomes in a general obstetric population (Heslehurst, et al., 2008; Sebire, et al., 2001). Studies investigating specific risk factors for PPH have demonstrated that nulliparous women have elevated rates of PPH compared to those who are multiparous (Combs, et al., 1991b; Driessen, et al., 2011; Magann, et al., 2008). Nulliparous women comprise a large sub-group of the birthing population especially in Western countries. Amongst studies specifically investigating a variety of risk factors for PPH, maternal BMI is rarely considered as a potential risk factor. In these few studies results are inconsistent with one showing no association between BMI and PPH (Driessen, et al., 2011), but others showing a positive association (Naef 3rd, et al., 1994; Stones, et al., 1993). One study has directly investigated maternal BMI and risk of PPH, and in this group of women of mixed parity, increasing BMI was associated with increased risk of PPH (Blomberg, 2011).

Maternal obesity is associated with an elevated risk of intrapartum caesarean section, predominantly for failure to progress, (Bergholt, et al., 2007; Fyfe, et al., 2011; Zhang, et al., 2007) the mechanism of which is suggested to be due to reduced uterine contractility (Zhang, et al., 2007). Among nulliparous women in labour at term, we have previously shown that the elevated risk of intrapartum caesarean is confined to the first stage of labour, as obese women who progress to the second stage of labour are just as likely to deliver vaginally as women with normal BMI (Fyfe, et al., 2011). We speculate therefore that obese women who give birth vaginally may have normal myometrial contractility. Uterine atony, the leading cause of PPH, has been associated with slow progress in labour, a surrogate for impaired intrapartum myometrial contractility (Driessen, et al., 2011). This has led us to hypothesise in this retrospective cohort study of nulliparous women who delivered at term, that 1. overweight and obese women who delivered vaginally would not have increased rates of major PPH (≥1000mls) compared to women with normal BMI, and 2. overweight and obesity would be independent risk factors for major PPH (≥1000mls) in women who had a caesarean section.

Methods

The National Women's Health (NWH) clinical database of births from Jan 2006 to Dec 2009 was used for this retrospective cohort study. NWH is a tertiary referral hospital in Auckland, New Zealand with a diverse ethnic population and approximately 7500 deliveries per year. The NWH database of births consists of de-identified, prospectively collected maternity data for all births occurring at greater than or equal to 20 weeks of gestation, which includes demographic data, antenatal complications, and detailed delivery and newborn data. Data are routinely checked for completeness, out of range values and inconsistency (National Women's, 2009). Ethical approval for this study was gained from the Northern X Regional Ethics Committee (NTX/09/179/EXP). The final study population included nulliparous women with a singleton pregnancy who delivered a live infant at term (*Figure 8.1*).

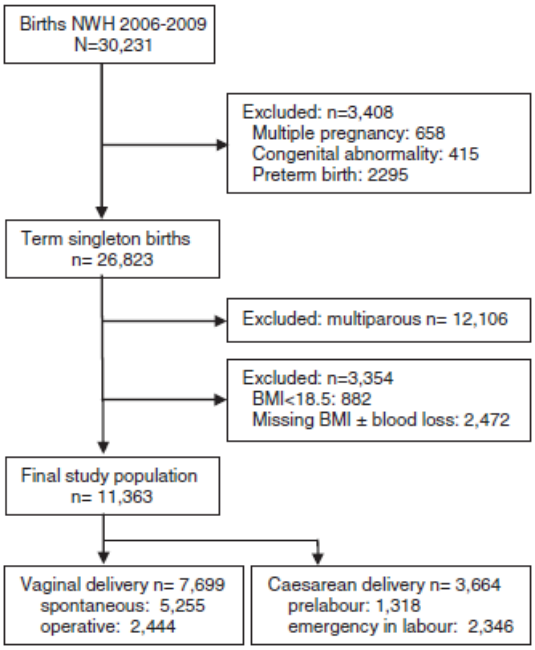

Figure 8-1 Recruitment flow chart

Maternal body mass index (BMI) (kg/m^2) was calculated using maternal height and weight measured to the nearest centimetre and kilogram respectively at the first antenatal booking visit, and was available for 91.2% of the term study population. As the focus of the current study was overweight and obesity, underweight women (BMI less than 18.5), who comprised a small proportion of this population (6.0%), were excluded. Women were classified into normal, overweight and obese groups according to conventional World Health Organization (WHO) BMI criteria: normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2) (World Health Organization, 2006). Normal BMI was the referent group. The primary outcome measure was major primary postpartum haemorrhage defined as blood loss equal to or greater than 1000mls (Women's Hospitals Australasia, 2007) within

24hrs of delivery as recorded on the delivery summary by the attending midwife or doctor. Standard practice for estimation of blood loss is a combination of visualisation and measurement by weight. This clinically relevant amount was selected as a lesser blood loss of between 500mls and 1000mls is not uncommon and is not associated with adverse outcomes in the majority of healthy women (Drife, 1997; Gilstrap & Ramin, 1994). Active management of the third stage of labour, 10IU of intramuscular oxytocin at the time of delivery of the anterior shoulder, is recommended standard practice within our unit. Estimated date of delivery (EDD) was calculated from a certain last menstrual period date or by ultrasound scan aas per the Australasian Society for Ultrasound in Medicine guidelines (Australasian Society for Ultrasound in Medicine, 2001-2007a, 2001-2007b). Ethnicity was self-determined and prioritised as per New Zealand Ministry of Health guidelines (Ministry of Health, 2004). Antepartum haemorrhage (APH) was defined as vaginal bleeding from any cause at or beyond 20 weeks of gestation after excluding placenta praevia (National Women's, 2009). Gestational hypertension and preeclampsia were defined as per International Society for the Study of Hypertension in Pregnancy criteria (Brown et al., 2000). Gestational Diabetes Mellitus (GDM) was defined in accordance with The Australian Diabetes in Pregnancy Society (Hoffman, et al., 1998).

Term delivery was delivery at a gestation of 37 weeks and 0 days or greater. Active labour was defined as regular, painful uterine contractions with progressive cervical effacement and dilation and cervical dilatation ≥3cm (Chamberlain, 1995). Prelabour elective caesarean section delivery was a planned procedure before or following the onset of labour, when the decision for caesarean section was made before labour (National Centre for Classification in Health (Sydney), 2004). Prelabour emergency caesarean section delivery was a delivery required because of an emergency situation (e.g. fetal distress) before the onset of active labour when the caesarean section was performed having not been previously considered necessary. Emergency caesarean section in labour was delivery required because of an emergency situation in active labour (e.g. failure to progress, obstructed labour, fetal distress) when the caesarean section was performed having not been previously considered necessary (National Centre for Classification in Health (Sydney), 2004). Perineal tears were defined as per Royal College of Obstetricians and Gynaecologists (Fernando, Williams, & Adams, 2007). Retained placenta was failure of placental delivery within 60 minutes after delivery of the fetus (Auckland District Health Board). Small for gestational age (SGA) and large for gestational age (LGA) were defined as infant birthweight $<10^{th}$ and $>90^{th}$ customised centile respectively (McCowan, et al., 2004).

Statistical analysis

Univariable logistic regression was performed to compare maternal characteristics and antenatal, birth and neonatal outcomes for women who had major PPH compared with those who did not. This analysis was undertaken for all births and then repeated for vaginal and caesarean deliveries separately. Multivariable logistic regression for major PPH was performed adjusting for potential confounders identified after an extensive literature review. The following variables of hypothesised interest or potential confounders were hence included in the model: BMI, maternal age; ethnicity; smoking; maternity care provider; antepartum haemorrhage; diabetes; hypertension; induction of

labour; epidural anesthesia; duration of first, second and third stages of labour; mode of delivery; perineal trauma; retained placenta and birthweight (Al-Zirqi, et al., 2008; Bateman, et al., 2010; Blomberg, 2011; Rossen, et al., 2010; Sebire, et al., 2001). As all of the characteristics and outcomes in univariable analyses were potential confounders, all covariates were included in the multivariable models. Data analyses were performed using SAS© version 9.2. (SAS Institute Inc., Cary, NC).

Results

Of 30,231 births at National Women's Hospital, Auckland, between January 2006 and December 2009, 12,407 (41%) were in nulliparous women, of whom 11,363 (92%) met the entry criteria for this study. Vaginal delivery occurred in 7699 (67.8%), and caesarean section in 3664 (32.2%) women (*Figure 8.1).* Prevalence of major postpartum haemorrhage (PPH) overall was 8.9%, [vaginal delivery (5.4%); caesarean section (16.2%)]. Among the whole population, being overweight or obese was associated with an increased risk for PPH (OR1.38, 95% CI 1.18-1.61 and 2.37, 95% CI 2.01-2.79 respectively). Other risk factors for PPH among all deliveries in univariable analysis were Pacific Island or Asian ethnicity, a history of antepartum haemorrhage (APH) or hypertensive disorders, induction of labour and retained placenta (*Table 8.1*). Compared to spontaneous vaginal delivery, forceps and caesarean section were associated with a two to threefold increase in risk of major PPH respectively. Increasing infant birthweight also increased risk of major PPH.

After adjustment for confounding factors, there was a dose dependent relationship between BMI and risk of major PPH, which was more common among women who were overweight 255 (9.7%) or obese 233 (15.6%) compared with those with normal BMI 524 (7.2%), (aOR 1.20, 95% CI 1.01-1.42 and 1.86, 95% CI 1.51-2.28 respectively) (*Figure 8.2*). Other results were similar following adjustment for confounding factors.

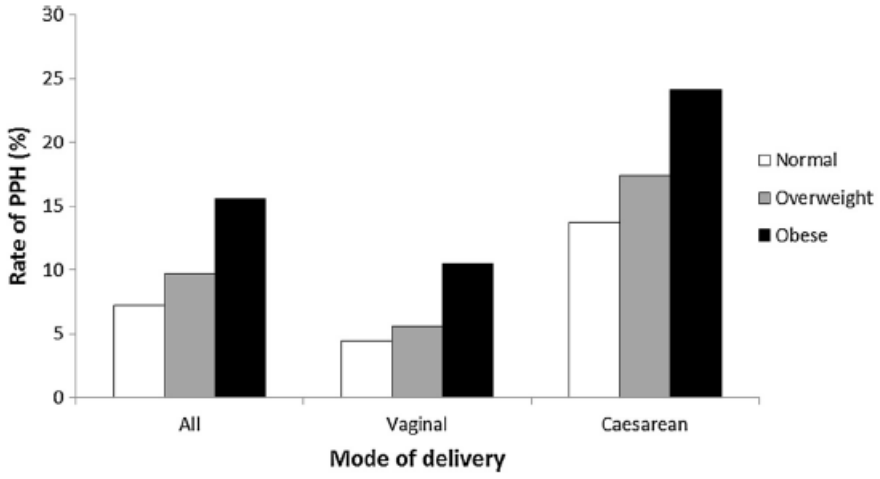

Figure 8-2 Rate of major postpartum haemorrhage (≥1000mls) by maternal BMI according to mode of delivery

	No PPH n= 10351 (91.1%)	PPH n= 1012 (8.9%)	Unadjusted OR's	Adjusted OR's*
Maternal characteristic				
BMI†				
18.5-24.9	6714 (64.9)	524 (51.8)	1.00	1.00
25.0-29.9	2376 (22.9)	255 (25.2)	1.38 (1.18-1.61)	**1.20 (1.01-1.42)**
≥ 30.0	1261 (12.2)	233 (23.0)	2.37 (2.01-2.79)	**1.86 (1.51-2.28)**
Age (y)				
Less than 20	551 (5.3)	38 (3.8)	0.70 (0.49-0.98)	0.77 (0.53-1.12)
20-29	4078 (39.4)	405 (40.0)	1.00	1.00
30-34	3553 (34.3)	336 (33.2)	0.95 (0.82-1.11)	0.94 (0.79-1.11)
≥ 35	2169 (21.0)	233 (23.0)	1.08 (0.91-1.28)	0.93 (0.77-1.14)
Ethnicity				
European	5573 (53.9)	491 (48.5)	1.00	1.00
Maori	765 (7.4)	78 (7.7)	1.16 (0.90-1.49)	1.27 (0.95-1.69)
Pacific island	881 (8.5)	136 (13.5)	1.75 (1.43-2.15)	**1.60 (1.25-2.06)**
Asian	2052 (19.8)	227 (22.4)	1.26 (1.06-1.48)	**1.61 (1.34-1.94)**
Indian	766 (7.4)	64 (6.3)	0.95 (0.72-1.24)	1.20 (0.89-1.61)
Other	314 (3.0)	16 (1.6)	0.58 (0.35-0.96)	0.68 (0.40-1.15)
Smoking (at booking)				
No	9086 (87.8)	908 (89.7)	1.00	1.00
Yes	778 (7.5)	69 (6.8)	0.89 (0.69-1.15)	0.86 (0.65-1.14)
Unknown	487 (4.7)	35 (3.5)	0.72 (0.51-1.02)	**0.67 (0.47-0.97)**
Maternity care				
Private	2556 (24.7)	231 (22.8)	1.00	1.00
Public	7795 (75.3)	781 (77.2)	1.11 (0.95-1.29)	**0.83 (0.69-0.99)**
Pregnancy complications				
Antepartum haemorrhage‡				
No	9899 (95.6)	924 (91.3)	1.00	1.00
Yes‡	378 (3.7)	60 (5.9)	1.70 (1.28-2.25)	**1.76 (1.31-2.36)**
Placenta praevia	74 (0.7)	28 (2.8)	4.06 (2.61-6.30)	**4.00 (2.48-6.47)**
Diabetes				
Nil	7651 (73.9)	733 (72.4)	1.00	1.00
Type 1 or Type 2	64 (0.6)	8 (0.8)	1.31 (0.62-2.73)	0.82 (0.38-1.80)
Gestational	463 (4.5)	52 (5.2)	1.17 (0.87-1.58)	0.92 (0.66-1.29)
Unknown	2173 (21.0)	219 (21.6)	1.05 (0.90-1.23)	1.06 (0.90-1.26)
Hypertension				
Nil	9332 (90.2)	878 (86.8)	1.00	1.00
Chronic	143 (1.4)	26 (2.6)	1.93 (1.27-2.95)	**1.78 (1.13-2.80)**
Gestational	523 (5.0)	56 (5.5)	1.14 (0.86-1.51)	0.98 (0.72-1.33)
Preeclampsia	353 (3.4)	52 (5.1)	1.57 (1.16-2.11)	1.33 (0.95-1.85)
Induction of labour	3187 (30.8)	397 (39.2)	1.45 (1.27-1.66)	**1.20 (1.03-1.40)**
Delivery outcomes				
Mode of delivery				
Vaginal				
Spontaneous	5010 (48.4)	245 (24.2)	1.00	1.00

Ventouse	1561 (15.1)	102 (10.1)	1.34 (1.05-1.70)	**1.40 (1.09-1.79)**
Forceps	711 (6.9)	70 (6.9)	2.01 (1.53-2.66)	**1.98 (1.49-2.65)**
Caesarean				
Prelabour	1165 (11.2)	153 (15.1)	2.69 (2.17-3.32)	**2.99 (2.33-3.83)**
Emergency in labour	1904 (18.4)	442 (43.7)	4.75 (4.03-5.60)	**4.47 (3.74-5.35)**
Retained placenta	109 (1.1)	38 (3.8)	3.67 (2.52-5.33)	**6.60 (4.42-9.85)**
Neonatal outcomes				
Gestation at delivery (days)	278.7 ± 8.6	279.8 ± 8.6	1.11 (1.05-1.17) per ↑1wk	0.96 (0.90-1.03) per ↑1wk
Birthweight (g)	3416 ± 462	3621 ± 511	1.58 (1.47-1.69) per ↑500g	**1.49 (1.38-1.62) per ↑500g**
Small for gestational age	1205 (11.6)	84 (8.3)	0.69 (0.55-0.87)	§
Large for gestational age	848 (8.2)	178 (17.6)	2.39 (2.01-2.85)	§

Data are n (%) or mean ± standard deviation.
Significant adjusted OR's are bolded.
* Adjusted for all variables in table.
†Body Mass Index.
‡from any cause excluding placenta praevia >20wk gestation.
§ SGA/LGA not included in multivariable model.

Table 8-1 Risk and protective factors for major postpartum haemorrhage (≥1000mls) for term nulliparous women – all deliveries.

Among women who delivered vaginally, independent risk factors were similar to those for the whole population (*Table 8.2*). Higher BMI was associated with an increased risk of major PPH (normal BMI 223 [4.4%], overweight 96 [5.6%], and obese 98 [10.5%]). After adjustment for covariates, obese women had a twofold increase in for major PPH compared to women with normal BMI aOR 2.11, 95% CI 1.54-2.89). Other independent risk factors for major PPH in women with vaginal birth are shown in Table 10. In subgroup analyses, women with risk factors associated with non-atonic PPH, namely episiotomy, third/fourth degree perineal lacerations (n=230) or retained placenta (n=147) were excluded. The resulting independent risk factors were the same with a similar magnitude of effect (data not shown), demonstrating that the association between obesity and PPH was not attributable to perineal trauma or retained placenta.

Risk factor	Adjusted OR's*
BMI ≥ 30.0	2.11 (1.54-2.89)
Ethnicity	
Pacific island	2.30 (1.62-3.27)
Asian	1.64 (1.22-2.20)
Antepartum haemorrhage†	1.91 (1.25-2.91)
Pre-eclampsia	1.97 (1.22-3.19)
Induction of labour	1.46 (1.15-1.86)
Third stage of labour > 15min‡	1.62 (1.18-2.22)
Retained placenta	4.88 (3.08-7.73)
Episiotomy	1.94 (1.19-3.19)
3rd or 4th degree tear	5.09 (2.91-8.89)
Birthweight (g) ↑ 500g	1.39 (1.22-1.59)

Data are adjusted odds ratio (95% confidence interval).
* Adjusted for all variables in Table 1 plus duration of 1st, 2nd and 3rd stages of labour and perineal trauma (including graze, second degree tear).
†from any cause excluding placenta praevia >20wk gestation.
‡ compared with third stage 5–10 minutes.

Table 8-2 Independent risk factors for major postpartum haemorrhage (≥1000mls) after vaginal delivery in term nulliparous women

Emergency caesarean section in labour was associated with a higher risk for major PPH compared with prelabour caesarean section (aOR 4.47, 95% CI 3.74-5.35 versus aOR 2.99, 95% CI 2.33-3.83) (*Table 8.1*). However, there was no significant difference in magnitude of effect related to any of the risk factors for major PPH between prelabour and emergency intrapartum caesarean section (data not shown). This demonstrated that the increase in risk with emergency intrapartum caesarean was not explained by any of the variables included in this study. Therefore, all caesarean sections were combined and analysed as a single entity (*Table 8.3*). Among women with caesarean sections, those who were obese a near twofold increase in the rate of major PPH compared to women with normal BMI (normal [13.7%], overweight [17.4%], obese [24.2%]) (*Figure 8.2*). This increase in risk associated with obesity was very similar following adjustment for covariates (aOR 1.73, 95% CI 1.32-2.28), consistent with our findings after vaginal delivery (*Table 8.3*). Other independent risk factors for major PPH after caesarean section are shown in Table 8.3.

Risk factor	Adjusted OR's*
BMI ≥30.0	1.73 (1.32-2.28)
Asian ethnicity	1.57 (1.23-2.01)
Public obstetric care	1.39 (1.11-1.74)
Antepartum haemorrhage†	1.65 (1.08-2.52)
Placenta praevia	3.08 (1.91-4.98)
Chronic hypertension	1.90 (1.08-3.35)
Birthweight (g) ↑ 500g	1.48 (1.34-1.64)

Data are adjusted odds ratio (95% confidence interval).
* Adjusted for all variables in Table 1.
†from any cause excluding placenta praevia >20wk gestation.

Table 8-3 Independent risk factors for major postpartum haemorrhage (≥1000mls) after caesarean delivery in term nulliparous women

Obesity was one of four factors (along with Asian ethnicity, antepartum haemorrhage and increasing infant birthweight) consistently associated with risk for major PPH regardless of mode of delivery. When we investigated the relationship between birthweight by z-scores (thus accounting for gestational age) and major PPH, we demonstrated a linear relationship between birthweight z-scores and adjusted odds ratios of major PPH (data not shown).

Discussion

We have demonstrated that obese nulliparous women delivering a singleton infant at term have a twofold increase in risk of major PPH, regardless of mode of delivery, and that this risk is independent of many other recognised risk factors for major PPH. Contrary to our hypothesis we have found that obese nulliparous women who give birth vaginally have a twofold increase in risk of major PPH,

similar in magnitude to those delivering by caesarean section. Previous studies have suggested that the increase in risk of PPH in obese women was largely explained by a concurrent increased caesarean section rate (Bhattacharya, et al., 2007; Mantakas & Farrell, 2010). Our findings identifying elevated risk for major PPH in obese women after vaginal birth are an important alert for clinicians. Active management of third stage is already recommended as standard practice for all women (World Health Organization, 2012). We would recommend in this group of women who are obese, additional vigilance is required to prevent and manage PPH. No other studies have primarily investigated the role of maternal obesity on risk of major PPH among nulliparous women. The rate of major PPH (greater than or equal to1000mls) in this nulliparous cohort was 8.9%, (vaginal delivery [5.4%]; caesarean section [16.2%]). This is higher than the rate reported in a previous study in women of mixed parity (5.3%) where a higher threshold was used for major PPH, namely blood loss greater than 1000mls (Blomberg, 2011). If this same definition is applied to our population (i.e. >1000mls), the rates of major PPH are almost identical (5.1% in our cohort). Among the few previous publications reporting maternal obesity and general birth outcomes in nulliparous women, comparisons are difficult due to absent or differing definitions of PPH and none have assessed the risk of PPH after vaginal delivery and caesarean section separately. Our findings are consistent with the only study of nulliparous women that adjusted for confounding factors, and reported a two fold increase in risk of major PPH in obese women (Bhattacharya, et al., 2007). However, in that study vaginal and caesarean births were not analysed separately, and no adjustment was made for perineal trauma or birthweight which are consistently reported as risk factors for PPH (Al-Zirqi, et al., 2008). Two other studies in nulliparous women have reported no association between obesity and major PPH but these studies were underpowered (Athukorala, et al., 2010; Haeri, et al., 2009). In a further study, increased rates of PPH (blood loss greater than 500mls) were reported after vaginal birth in nulliparous obese women compared to those with a BMI of 20-30, but the magnitude of risk was not quantified (Usha Kiran, et al., 2005).

Only one other study has primarily investigated the relationship between maternal obesity and PPH (defined as haemorrhage >1000mls) (Blomberg, 2011). Blomberg reported a small increased risk among obese women following vaginal delivery, but PPH risk was variable according to class of obesity following caesarean section. This study population was of mixed parity, and adjustment was only possible for very limited confounders (year of infant birth, maternal age, parity and smoking). Blomberg reported an increased rate of PPH in obese women predominantly associated with uterine atony, but also due to soft tissue trauma. No association was reported between obesity and PPH due to retained placenta. Although we did not have data available to identify the primary cause of PPH, when we performed a subgroup analysis amongst women who delivered vaginally excluding those with major perineal trauma (episiotomy or third/fourth degree laceration), and/or retained placenta, there was no significant difference in effect. We therefore demonstrated that the higher rates of PPH in obese women in our study were not attributable to either major perineal trauma or retained placenta and hence were most likely due to uterine atony. Other risk factors we found for major PPH after vaginal birth were similar to those previously identified, as seen in Table 8.2.

It is well established that obese women have higher rates of caesarean section, especially emergency intrapartum caesarean section, (Fyfe, et al., 2011) and we confirmed that this mode of delivery was associated with the highest rates of PPH among the whole study population. We found that obese women who had a caesarean section had a 70% increase in risk for PPH. Challenging surgery in obese patients is associated with prolonged operative time, and consequently with increased blood loss (Doherty, et al., 2008). Other risk factors that we identified for PPH after caesarean section are consistent with previous studies (Bateman, et al., 2010; Doherty, et al., 2008; Ford, et al., 2007; Magann et al., 2005; Sheiner, et al., 2005).

Obesity was one of four factors we identified that independently increased risk for PPH after both vaginal and caesarean deliveries among nulliparous women (along with increasing birthweight, APH and Asian ethnicity). The relevance of our finding that increasing birthweight is associated with risk of PPH is that we have shown that the relationship is dose dependent and that there is not a cut off at which increased risk occurs, for example with macrosomic or large for gestational age infants, which has been reported previously (Bais, et al., 2004; Magann, et al., 2005). Contextualising this finding to the clinical setting, there is a 40% increase in risk for PPH with every 500g increase in birthweight in term infants.

Our novel finding that the independent risk for PPH was increased in women with a history of APH from any cause exclusive of placenta praevia is clinically significant as APH (predominantly of unknown origin) occurred in 5.2% of our nulliparous cohort. An association between PPH and Asian ethnicity has been reported previously (Al-Zirqi, et al., 2008; Combs, et al., 1991a; Magann, et al., 2005).

A strength of our study was the ability to adjust for many known risk factors for PPH to better determine the independent effect of obesity for vaginal and caesarean delivery discretely. In keeping with other clinical studies, visual estimation was usual practice to estimate blood loss in our study (Al-Zirqi, et al., 2008). Visual estimation has been reported to underestimate higher volumes of blood loss, (Duthie, et al., 1990) it is therefore unlikely that we overestimated major PPH prevalence. We did not have data to further assess PPH defined by peripartum reduction in haemoglobin or requirement for blood transfusion.

Conclusions

We advocate the inclusion of obesity in future research investigating risk factors for major PPH as recommended by the International Postpartum Hemorrhage Collaborative Group (Knight, et al., 2009). Nulliparous obese women should be regarded as high risk for PPH, with a twofold increase in risk of major PPH (≥1000mls) compared to normal weight women regardless of mode of delivery. Therefore we recommend in addition to standard practice of active management of third stage of labour, there should be increased vigilance and preparation for PPH management in obese women.

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Chapter 9. Obesity and pre-eclampsia

This chapter presents results on the association between obesity and pre-eclampsia

Title:

Early pregnancy risk factors for pre-eclampsia among obese nulliparous women

Journal:

Awaiting submission[2]

Authors:

Elaine M FYFE**,** John MD THOMPSON, Lucilla POSTON; Louise KENNY; Gus DEKKER; Phil BAKER; James WALKER; Lesley McCOWAN.

Contribution:

EF participated in the conception and design of the study, carried out the data collection, conducted statistical analysis of the data, interpreted the data and drafted the manuscript.

JT assisted with statistical analysis and interpretation of the data and helped to edit the manuscript.

LP helped edit the manuscript

LK helped to edit the manuscript.

GD helped to edit the manuscript.

PB helped to edit the manuscript.

JW helped to edit the manuscript

LM participated in the conception and design of the study, assisted with interpretation of the data and helped to edit the manuscript.

[2] This paper will be submitted subsequent to publication of a primary pre-eclampsia paper by the SCOPE consortium, predicted to be early 2013.

Abstract

We aimed to identify risk factors present at 14-16 weeks of gestation among obese nulliparous women that were associated with development of pre-eclampsia.We hypothesised that obese women who developed pre-eclampsia would have higher rates of dyslipidaemia and central adiposity compared to obese women who did not.

Study Design

Participants were obese nullipara recruited to the multicentre prospective SCOPE study (n=835). Univariable analysis compared maternal characteristics and known risk factors for pre-eclampsia between obese women who developed pre-eclampsia and those who did not. Two multivariable regression models were created, one using the whole cohort (n=835) and a second using the subgroup with lipid measurements at 14-16 weeks (n=577).

Results

78 of 835 (9.3%) obese nulliparous women developed pre-eclampsia. Four factors were independently associated with pre-eclampsia: increasing BMI [OR1.44 (1.14-1.82) per 5 unit increase], family history of stroke [OR2.93 (1.34-6.39)], family history of pre-eclampsia [OR2.14 (1.14-4.04)] and shorter time to conceive [OR1.21 (1.05-1.41) per 3mth decrease]. In the multivariable model which incorporated serum lipids, results were very similar but decreasing high density lipoprotein cholesterol was also associated with a higher risk of pre-eclampsia [OR1.52 (1.00-2.32) per 0.5mmol/L decrease]. Increased waist circumference was associated with later pre-eclampsia in univariable analysis, but did not add additional discriminatory information beyond that of BMI in the multivariable model.

Conclusion

Risk factors for pre-eclampsia identified among obese nullipara share similarities with those implicated in cardiovascular disease and may in part explain the linkage between pre-eclampsia and later cardiovascular disease. The role of HDL as a risk factor for pre-eclampsia requires further confirmation in other studies.

Paper I

Early pregnancy risk factors for pre-eclampsia among obese nulliparous women

Background

The global obesity epidemic, affecting women of all ages, is having a significant impact on rates of pregnancy complications including pre-eclampsia (Duckitt & Harrington, 2005; Gaillard, et al., 2011). A two to four fold increase in risk for pre-eclampsia has been consistently reported in obese women after adjustment for confounding factors (Anderson, McCowan, et al., 2012; Bodnar, et al., 2005; Sohlberg, et al., 2012). Compared to a five percent rate of pre-eclampsia amongst all nulliparous women, pre-eclampsia complicates eight to twelve percent of pregnancies in obese nullipara (Bhattacharya, et al., 2007; North, et al., 2011). Whilst the rate of pre-eclampsia among nulliparous women is elevated, it is not generally considered high enough to warrant specialist care nor to justify prophylactic treatment with low dose aspirin given the large numbers needed to treat to prevent one case (Cnossen et al., 2007; Milne, et al., 2005). Development of a risk stratification method that identified the subgroup of obese nulliparous women at even higher risk for pre-eclampsia could contribute to improved management of care.

Few studies have attempted to identify those obese women who are at greatest risk of pre-eclampsia. There is a dose dependent relationship between increasing body mass index and pre-eclampsia, with morbidly obese women being at greatest risk (Bodnar, et al., 2005). In a recent prospective cohort study of clinical risk factors that predict pre-eclampsia in nulliparous women, BMI was included in the algorithm, together with other well recognised (blood pressure, family history of pre-eclampsia) and less established factors (prolonged vaginal bleeding and low maternal birth weight) (North, et al., 2011). Furthermore, in that study, North et al found the combination of obesity with other clinical characteristics, such as a raised blood pressure in early pregnancy and a family history of pre-eclampsia was associated with an increase in the rate of pre-eclampsia to 16-18 percent, compared to 10 percent when using obesity singularly as a risk factor.

Individual features of the metabolic syndrome have been associated with an increased risk of pre-eclampsia (Dane, Dane, Kiray, Koldas, & Cetin, 2009). The physiological dyslipidaemia of normal pregnancy is exaggerated in both obesity and pre-eclampsia (Belo, et al., 2002; Lain & Catalano, 2007). Prospective studies have established that dyslipidaemia, (particularly hypertriglyceridemia) in early pregnancy is a risk factor for pre-eclampsia (Belo, et al., 2002; Demirci, et al., 2011; Enquobahrie, et al., 2004; Ray, et al., 2006). Increased central adiposity in early pregnancy in populations of women with mixed BMI has also been reported to be associated with adverse pregnancy outcomes including pre-eclampsia (Sattar, et al., 2001; Wendland, et al., 2007). It would follow that obese women who share features of the metabolic syndrome, notably dyslipdaemia and increased central adiposity, may be at greater risk of pre-eclampsia. To date no studies in otherwise healthy obese women have investigated whether known risk factors for pre-eclampsia, other than increasing BMI, would assist in discriminating between those obese women who develop pre-eclampsia and those who do not. One study reported an association between hypertriglyceridaemia

and development of pre-eclampsia in obese nullipara, but this cohort included a large subgroup of women with hypertension and diabetes (Rajasingam, et al., 2009).

In this prospective study of obese nulliparous women, we aimed to identify risk factors present at 14-16 weeks of gestation that were associated with development of pre-eclampsia. We hypothesized that obese nulliparous women who developed pre-eclampsia would have higher rates of dyslipidaemia and central adiposity (estimated by waist circumference) than obese women who did not develop pre-eclampsia.

Methods

Participants were healthy, nulliparous women recruited to the Screening for Pregnancy Endpoints Study (SCOPE) from Auckland, New Zealand and Adelaide, Australia, London and Manchester, UK and Cork, Ireland between November 2004 and February 2011. The SCOPE study is a multicentre prospective cohort study, with the primary aim of developing screening tests for prediction of pre-eclampsia, spontaneous preterm birth and small for gestational age babies (SGA). Ethical approval was obtained from local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London and Manchester 06/MRE01/98, and Cork ECM5 (10) 05/02/08) and all women provided written informed consent. Women were excluded if they had underlying medical conditions which increased their risk for pre-eclampsia, small for gestational age (SGA) or preterm birth, such as chronic hypertension, diabetes, renal disease, antiphospholipid syndrome or systemic lupus erythematosus. Detailed data collected from all participants during interview with a research midwife at 14-16 weeks gestation, have previously been described in detail and included demographic information, smoking, family, medical and gynecological history (North, et al., 2011). Maternal measurements recorded at 14-16 weeks of gestation included height and weight, waist circumference and two consecutive manual blood pressure measurements (mercury or aneroid sphygmomanometer, with a large cuff if the arm circumference was ≥33 cm and Korotkoff V for diastolic blood pressure) were recorded. Non-fasting random whole blood glucose and serum lipid concentrations (triglycerides, total cholesterol (TC), high density lipoprotein cholesterol (HDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol), total cholesterol:high density lipoprotein cholesterol ratio (total HDL ratio)) were measured from non-fasting bloods drawn at the time of interview in the first 3530 women recruited to the SCOPE study. Maternal BMI was calculated as kg/m^2. Women were classified into underweight, normal, overweight and obese groups according to conventional WHO criteria (World Health Organization, 2006) : <18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal), 25-29.9 kg/m^2 (overweight) and ≥ 30 kg/ m^2 (obese). The final study population comprised obese women (*Figure 9.1*).

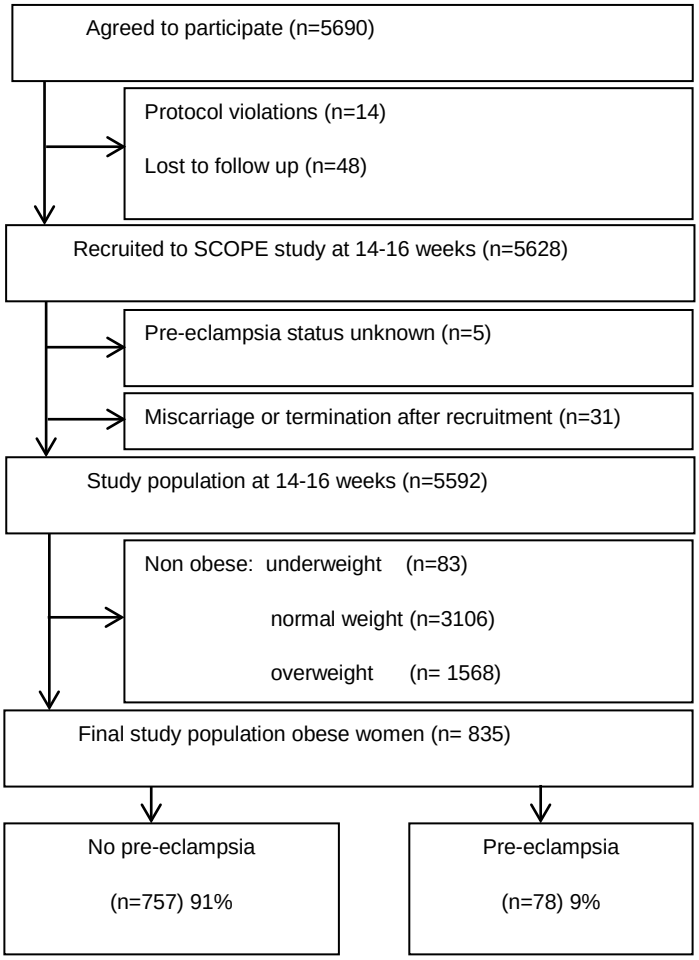

Figure 9-1 Recruitment flow chart

Primary outcome

The primary outcome was pre-eclampsia, defined as systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90 mmHg, or both, on at least two occasions four hours apart after 20 weeks' gestation but before the onset of labor, or postpartum, with either proteinuria (24 hour urinary protein ≥ 300mg or spot urine protein: creatinine ratio ≥30mg/mmol creatinine or urine dipstick protein ≥++ in a midstream urine specimen) or any multisystem complication of pre-eclampsia (Australian New Zealand Clinical Trials Registry, 2007; Brown, et al., 2000). Multisystem complications included any of acute renal insufficiency defined as a new increase in serum creatinine concentration ≥100 μmol/L antepartum or >130 μmol/L postpartum; effects on liver, defined as raised aspartate transaminase or alanine transaminase concentration, or both, >45 IU/L and/or severe right upper quadrant or epigastric pain or liver rupture; neurological effects included eclampsia, imminent eclampsia (severe headache with hyper-reflexia and persistent visual disturbance), or cerebral haemorrhage; and haematological effects included thrombocytopenia (platelets $<100\times10^9$/L), disseminated intravascular coagulation, or haemolysis (North, et al., 2011). The reference group was obese women who did not develop pre-eclampsia.

Other definitions

Detailed methodology and definitions have previously been described in detail (North, et al., 2011). Small for gestational age (SGA) and large for gestational age (LGA) were defined as infant birthweight <10th and >90th customised centile respectively (McCowan, et al., 2004).

Statistical methods

Univariable analysis was performed using the statistical software package SAS© version 9.1. (SAS Institute Inc., Cary, NC) to compare maternal characteristics recorded at 14-16 weeks of gestation and pregnancy and birth outcomes between obese women who did and did not develop pre-eclampsia. Factors which have been previously been consistently associated with risk of pre-eclampsia were included: BMI; maternal age; smoking status; previous pregnancy with either the same or a different partner from the one who fathered the current pregnancy; months to conceive; participant birthweight; high fruit intake (≥3 pieces per day); waist circumference; mean arterial blood pressure; family history (mother or father) of type 2 diabetes, chronic hypertension, coronary artery disease or stroke and family history (mother or sister) of pre-eclampsia (Cnossen et al., 2008; Conde-Agudelo, Althabe, Belizan, & Kafury-Goeta, 1999; Dempsey, Williams, Luthy, Emanuel, & Shy, 2003; Kho, et al., 2009; North, et al., 2011; O'Brien, et al., 2003; Qiu et al., 2003; Rigo Jr et al., 2006; Saftlas et al., 2003; Sattar, et al., 2001; Skjaerven et al., 2005). In univariable analyses, chi square test was used for analysis of categorical variables, and a Student's *t*-test to compare continuous variables. Variables with a p value of <0.1 were included in the multivariable model. Multivariable analysis was performed using backward regression in the whole cohort of 835 obese women to generate model 1, retaining variables that were significant at the 5% level. We then created a second model (model 2) using risk factors from model 1 and including lipid variables which had been shown to be significant in univariable analysis (triglycerides and HDL-cholesterol) in the 577 obese women who had lipids measured at 14-16 weeks of gestation.

Results

Between November 2004 and Feb 2011, 5628 women were recruited to the SCOPE study at 14-16 weeks of gestation and follow up was complete in 5592 (99%) of participants. Women who were underweight 83 (1%), of normal weight 3106 (56%) or overweight 1568 (28%) were excluded from the current study, resulting in a final study population of 835 (15%) obese women of whom 78 (9.3%) developed pre-eclampsia (Figure 9.1). Of the 78 women with pre-eclampsia, 71 had proteinuria and in seven the diagnosis of pre-eclampsia was based on gestational hypertension with multisystem complications. Table 9.1 shows the background characteristics, maternal and infant outcomes in obese women according to pre-eclampsia status. BMI was higher in women who developed pre-eclampsia, p =0.004. Rates of pre-eclampsia were 9%, 7%, 14% and 32% among BMI categories 30-34.9, 35-39.9, 40-44.9 and ≥45kg/m2 respectively. Central adiposity (as estimated by waist circumference) was increased; HDL-cholesterol lower and there was a trend to higher triglycerides among obese women who developed pre-eclampsia compared to those who did not. Mothers who

developed pre-eclampsia had babies with a lower mean birthweight, a twofold increase in the rate of small for gestational age infants and more than a threefold increase in the rate of preterm birth (*Table 9.1*).

	No pre-eclampsia n=757 (91%)	Pre-eclampsia n=78 (9%)	P value
Maternal characteristics at 14-16 weeks			
BMI (kg/m^2)			
30-34.9	517 (68%)	49 (63%)	0.004
35 – 39.9	172 (23%)	13 (17%)	
40 -45	51 (7%)	8 (10%)	
>=45	17 (3%)	8 (10%)	
Maternal age (yrs)	28.0 (5.6)	27.2 (5.7)	0.24
Caucasian ethnicity	692 (91%)	70 (90%)	0.62
Married/defacto	663 (88%)	71 (91%)	0.37
Socioeconomic index	37 (15)	34 (16)	0.14
<12yrs schooling	325 (43%)	39 (50%)	0.23
Full/part time work	615 (81%)	63 (81%)	0.92
Primigravida	565 (75%)	54 (69%)	0.30
Current smoker	118 (16%)	9 (12%)	0.34
Blood pressure (mean arterial)	84 (8)	86 (9)	0.10
Waist circumference (cms)	102 (10)	105 (13)	0.03
Serum lipids mmol/L (n=577)	n=518	n=59	
Total cholesterol	5.63 (0.88)	5.68 (1.04)	0.71
LDL-cholesterol	3.17 (0.79)	3.26 (0.99)	0.50
HDL-cholesterol	1.69 (0.35)	1.57 (0.36)	0.02
Total cholesterol:HDL ratio	3.47 (0.88)	3.78 (1.00)	0.01
Triglycerides	1.71 (0.72)	1.88 (0.64)	0.09
Fetal outcomes			
Gestational age at delivery	39.7 (2.1)	38.2 (2.7)	<0.0001
Birthweight (g)	3504 (593)	3169 (856)	0.001
Preterm birth (<37 weeks)	42 (6%)	16 (21%)	<.0001
- spontaneous	34 (4%)	1 (1%)	
- iatrogenic	8 (1%)	15 (19%)	
SGA	97 (13%)	22 (28%)	0.0002
LGA	64 (8%)	9 (12%)	0.36

data are n (%) or mean (SD)

Table 9-1 Characteristics of all participants by pre-eclampsia status.

Four factors were independently associated with pre-eclampsia among obese nulliparous women (*Table 9.2).* For every 5 unit increase in BMI above 30, there was an approximate 50% increase in risk of pre-eclampsia. A family history of pre-eclampsia and of stroke was associated with a twofold and threefold increase respectively. For every 3 month decrease in time taken to conceive, risk of pre-eclampsia increased by 16%. Following addition of maternal lipid variables for model 2 (n=577), the above adjusted odds ratios were very similar to those calculated without the lipid variables in model 1 (n=835) (*Table 9.3*). For every 0.5mmol/L decrease in HDL-cholesterol, there was a 52% increase in risk of pre-eclampsia (OR 0.52, 95% CI 1.00-2.32).

	No pre-eclampsia (n=757)	Pre-eclampsia (n=78)	Unadjusted OR (95%CI)	Model 1 Adjusted OR (95%CI) (n=835)
Risk factors				
BMI (per 5 units ↑)	34.3 (4.1)	35.7 (5.6)	1.37 (1.09-1.72)	1.44 (1.14-1.82)
Family history of stroke	32 (4%)	10 (13%)	3.33 (1.57-7.09)	2.93 (1.34-6.39)
Family history of pre-eclampsia	77 (10%)	15 (19%)	2.10 (1.14-3.87)	2.14 (1.14-4.04)
Months to conceive (per 3mths ↓)	8.8 (17.2)	3.8 (5.7)	1.15 (1.03-1.29)	1.16 (1.04-1.30)

Table 9-2 Independent clinical risk factors at 14-16 weeks gestation for pre-eclampsia for obese nulliparous women

	No pre-eclampsia (n=518)	Pre-eclampsia (n=59)	Unadjusted OR (95%CI)	Model 2 Adjusted OR (95%CI) (n=577)
Risk factors				
BMI (per 5 unit ↑)	34.7 (4.5)	36.1 (5.9)	1.31 (1.03-1.69)	1.33 (1.02-1.74)
Family history of stroke	22 (4%)	8 (14%)	3.53 (1.50-8.33)	2.85 (1.15-7.08)
Family history of pre-eclampsia	59 (11%)	12 (20%)	1.99 (1.00-3.95)	2.10 (1.01-4.36)
Months to conceive (per 3mths ↓)	8.7 (17.0)	3.5 (4.8)	1.18 (1.02-1.36)	1.21 (1.05-1.41)
HDL-cholesterol (per 0.5mmol/L ↓)	1.69 (0.35)	1.57 (0.36)	1.62 (1.08-2.43)	1.52 (1.00-2.32)

Table 9-3 Independent clinical risk factors at 14-16 weeks gestation for pre-eclampsia for obese nulliparous women in subgroup of women with lipids measured

Discussion

This is the first study to investigate risk factors for pre-eclampsia among a population of otherwise healthy obese women. One other study has investigated this risk among obese nullipara, but the study population included women with additional risk factors of hypertension and diabetes (Rajasingam, et al., 2009). Our finding that reduced levels of HDL-cholesterol were associated with increased risk of pre-eclampsia among obese women is novel. Whilst increased waist circumference was associated with later pre-eclampsia in univariable analysis, it did not add additional discriminatory information beyond that of BMI in the multivariable model. Increasing BMI, family history of stroke or pre-eclampsia and short time to conceive were also associated with increased risk, consistent with previous studies (Kho, et al., 2009; North, et al., 2011; Rigo Jr, et al., 2006).

Of the few prospective studies investigating early pregnancy lipids and risk of pre-eclampsia, hypertriglyceridemia has predominantly been associated with pre-eclampsia, after adjustment for confounders including BMI (Clausen, et al., 2001; Demirci, et al., 2011; Enquobahrie, et al., 2004; Van den Elzen, et al., 1996; Wiznitzer, et al., 2009). One study also reported an increased risk of pre-eclampsia related to increased total cholesterol levels in a population of women of advanced maternal age ≥36yrs (Van den Elzen, et al., 1996). A further study found increased levels of cholesterol, triglycerides LDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratio were positively associated with pre-eclampsia risk, after adjustment for confounders (Enquobahrie, et al., 2004). All these studies included populations of women with mixed BMI and none reported an independent association between HDL-cholesterol and pre-eclampsia. Low HDL-cholesterol is a recognised risk factor for cardiovascular disease, as is pre-eclampsia (Abbassi-Ghanavati, Greer, & Cunningham, 2009; Bellamy, Casas, Hingorani, & Williams, 2007; Vaisar et al., 2007).

Our findings regarding HDL-cholesterol need to be interpreted with caution as statistical significance was borderline, possibly due to our study size. However, the potential importance of HDL-cholesterol in the pathogenesis of pre-eclampsia are supported by findings from a recent SCOPE study investigating changes in the plasma proteome prior to pre-eclampsia (Blumenstein et al., 2009). Half of the 36 plasma proteins identified at 20 weeks' in women who subsequently developed pre-eclampsia overlapped with cargo proteins associated with HDL-cholesterol (Vaisar, et al., 2007). A number of these proteins have anti-inflammatory and anti-atherogenic properties which may contribute to the cardioprotective properties attributed to HDL-cholesterol (Vaisar, et al., 2007). The reduced levels of HDL-cholesterol we have observed in obese women who develop pre-eclampsia may be important in the modulation of these mechanisms that are also central in the pathogenesis of pre-eclampsia. Further it may in part account for the recognised predisposition to later cardiovascular disease. Further studies are needed to confirm or refute our findings for HDL-cholesterol.

In addition, we identified other risk factors associated with both pre-eclampsia and cardiovascular disease. Family history of stroke was associated with an almost threefold increase in risk of pre-eclampsia and is also a risk factor for cardiovascular disease (Rigo Jr, et al., 2006). We confirmed a dose dependent association between increasing BMI ≥30 and increasing risk of pre-eclampsia

(O'Brien, et al., 2003). A similar dose dependent relationship between BMI and risk of later cardiovascular disease has been reported (Anderson, Sadler, et al., 2012). Of interest neither a family history of coronary artery disease or chronic hypertension remained in the model.

In our study waist circumference was not significantly associated with pre-eclampsia after multivariable analyses. Although use of waist circumference is considered limited due to increasing abdominal girth particularly in later pregnancy, two prospective studies have reported an association between increased waist circumference in early pregnancy in populations of women with mixed BMI and adverse pregnancy outcomes (Sattar, et al., 2001; Wendland, et al., 2007). One study reported significantly increasing prevalence of pre-eclampsia related to waist quintile cut-off points (lowest quintile ≥75<79cms [1.5%], upper quintile ≥122cm (5.2%, p=<.05) (Wendland, et al., 2007). A second study reported a waist circumference >80cms was predictive for pre-eclampsia (aOR 2.7, 95% CI 1.1-6.8), however these data are not comparable as in our study population of obese women, mean waist circumference was 102cms (±12) (Sattar, et al., 2001). A recent related study found maternal abdominal subcutaneous fat thickness (measured by ultrasound scan at 18-22 weeks gestation) to be a better marker than BMI for obesity related adverse pregnancy outcomes (Suresh et al., 2012). Assessment of central adiposity by waist circumference may be more useful among non-obese women than in those who are already obese, in whom it appears to be less discriminatory. Further studies are required using imaging modalities and simple measures.

The multicentre prospective design and the high follow up rates are a strength of this study. Our calculation of BMI was accurate as maternal height and weight were measured in early pregnancy, rather than using less reliable self-reported measures (Craig & Adams, 2009). Strict criteria for diagnosis of hypertensive disorders of pregnancy ensured accurate selection of obese women according to pre-eclampsia status for this study. We used non-fasting lipids for our study as fasting samples were not available. Lipid profiles change minimally in response to food intake and non-fasting lipid profiles may be used as standard (Langsted, et al., 2008; Nordestgaard & Benn, 2009; Sidhu & Naugler, 2012). Lipid measures were only available for 577 of the 835 (69%) of our cohort. After the addition of the lipids to our model, there was minimal change in the adjusted odds ratios for the other variables in the model. This suggests the reduction in numbers in the lipid model is unlikely to have introduced bias.

Conclusion

We have identified risk factors for pre-eclampsia among an obese population of otherwise healthy nulliparous women, a population not previously investigated. Morbid obesity, lower HDL-cholesterol and a positive family history of stroke or pre-eclampsia were associated with an increased risk of pre-eclampsia. The role of HDL-cholesterol needs further validation. The risk factors identified have also been implicated in cardiovascular disease and may in part explain the linkage between pre-eclampsia and later cardiovascular disease.

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Variable Name	Variable type	Comments
Age	Continuous	Linear relationship with pre-eclampsia
Participant's birthweight	Continuous	Data was self reported, but women were asked to bring their 'birth record' if kept at home. Birthweight and gestational age at delivery was confirmed from this birth record.
Any previous pregnancy loss with same man who has fathered the current pregnancy	0 No 1 Yes	
Any previous pregnancy loss with a different man from one who has fathered the current pregnancy	0 No 1 Yes	
Family history of pre-eclampsia	0 No 1 Yes	Mother or sister(s) developed pre-eclampsia defined as new onset hypertension in second half of pregnancy with proteinuria or other multisystem complications (e.g., HELLP, eclampsia) If one or more family member had pre-eclampsia=Yes; no family history of pre-eclampsia or no family history available=No.
Family history of chronic hypertension	0 No 1 Yes	Self reported. Woman's father or mother has a history of hypertension or high blood pressure, usually on antihypertensive treatment. If one or more family member had chronic hypertension=Yes; no family history of chronic hypertension or no family history available=No.
Family history of coronary heart disease	0 No 1 Yes	Self reported From standard operating procedure: Woman's father or mother has had angina, a heart attack, coronary heart disease, coronary bypass or angioplasty. If one or more family member had coronary heart disease=Yes; no family history of coronary heart disease or no family history available=No.
Family history of Type 2 diabetes	0 No 1 Yes	Self reported. Woman's father or mother has type 2 diabetes. From standard operating procedure: Type 2 diabetes is usually adult onset diabetes that is controlled with diet, tablets and sometimes insulin. Age of onset is usually in adult life, but increasingly common in the young and obese. Unusual to develop Type 2 diabetes at <15 years unless very obese. If one or more family member had Type 2 diabetes =Yes; no family history of Type 2 diabetes or no family history available=No.
Months to conceive	Continuous	0.2% missing, median replaced with median
High fruit intake at 15±1 weeks	0 No 1 Yes	≥ 3 pieces of fruit per day at 15±1 weeks
Smoked at 15±1 weeks	0 No 1 Yes	Any number of cigarettes smoked at 15±1 weeks
Mean arterial blood pressure (MAP) at 15±1 weeks	Continuous	Mean arterial blood pressure calculated from second measurement of systolic (sBP) and diastolic blood pressure (dBP) as follows: MAP= dBP+[(sBP-dBP)/3]; linear relationship with rate of pre-eclampsia
Height at 15±1 weeks	Continuous	Measurement of height without shoes to the nearest cm.
Body mass index (BMI) at 15±1 weeks	Continuous	weight (kg) / height^2 (m), linear relationship with rate of pre-eclampsia
Waist circumference	Continuous	Waist circumference measured, in centimetres, next to the skin at the point half way between the top of the hip (iliac crest) and inferior margin of lowest rib. 0.4% missing, imputed; linear relationship with rate of pre-eclampsia

Table 9-4 Supplementary table describing variables included in analyses for pre-eclampsia study

Chapter 10. Discussion

10.1. Overview of discussion

This discussion provides a conclusion to the thesis. It will recap the context of the research and offer clinical implications for practice, implications for research and considerations for the future.

The first section gives a brief overview contextualising maternal obesity and the following three sections review maternal obesity and its' association with the obstetric complications investigated for this thesis, namely CS, postpartum haemorrhage and pre-eclampsia respectively. The final section will give an overall conclusion and a perspective for the future.

10.2. Maternal obesity

Internationally and in New Zealand, rates of obesity among women of reproductive age are high (Ministry of Health, 2008; Ogden, et al., 2012). One third of the women receiving obstetric care at the major tertiary obstetric unit in Auckland, National Women's Hospital, are overweight or obese (National Women's, 2011). Maternal obesity is a major obstetric problem, associated with increased risk of maternal, fetal and neonatal morbidity and mortality (Aviram, Hod, & Yogev, 2011). In the absence of a desired but unattainable ability to ensure every woman has a normal BMI pre-pregnancy, there is an urgent need to determine optimum management of obesity in all aspects of obstetric care to reduce adverse outcomes. Rates of CS, PPH and pre-eclampsia remain particularly high among obese nulliparous women (Bhattacharya, et al., 2007; Mantakas & Farrell, 2010; North, et al., 2011).

10.3. Obesity and Caesarean section

An association between obesity and increased rates of CS, particularly emergency intrapartum CS, is well established. This association has now been explored further since my publication (Chapter 6), with studies investigating the progress of labour, the timing of undertaking CS, and underlying mechanisms of dysfunctional contractility (Chin, Henry, Holmgren, Varner, & Branch, 2012; Elmes, Tan, Cheng, Wathes, & McMullen, 2011; Kominiarek, et al., 2011; Robinson et al., 2011; Syngelaki, Bredaki, Vaikousi, Maiz, & Nicolaides, 2011). A new prospective study examining the association between BMI at 11-13 weeks gestation and adverse pregnancy outcomes among a population of women of mixed parity, reported a 6% increase in risk of emergency CS for every BMI unit increase over the mean of 24 (aOR1.06, 95% CI 1.06-1.07) after adjustment for confounding factors (maternal age, ethnicity, mode of conception, smoking, chronic hypertension and diabetes) (Syngelaki, et al., 2011). However, this study has limitations in that it did not control for confounding factors such as pre-eclampsia and macrosomia, which may explain part of the increased incidence of CS in women with

high BMI. Our study has shown that whilst preeclampsia and large for gestational age also contribute to risk of CS, obesity persists as an important dose dependent independent risk factor.

10.3.1. *Obesity and timing of intrapartum Caesarean section.*

Our finding, that there is no association between overweight and obese BMI and increased risk of CS in the second stage of labour, has been corroborated in a subsequent study investigating increasing BMI and characteristics of the second stage of labour among nulliparous women who laboured spontaneously or were induced. Robinson et al (2011), investigating a comparable population of nulliparous women with a singleton pregnancy at ≥36 weeks gestation, confirmed our findings that increasing BMI is associated with increased risk for CS only in the 1st stage of labour (Robinson, et al., 2011).

10.3.2. *Obesity and uterine contractility.*

Citing our findings that the increased rate of CS among obese women appears to be confined to the first stage of labour, Chin et al (2012), retrospectively investigated the relationship between maternal obesity and contraction strength, measured using an intrauterine pressure catheter in the first stage of labour in a population of women of mixed parity (Chin, et al., 2012). After adjustment for parity and other confounding factors, they reported some findings consistent with ours, namely a dose dependent increased risk of 1st stage CS with increasing BMI. However, of interest, they reported that among women who had 1st stage CS for any reason, obese women had greater odds of adequate contraction strength (defined as mean Montevideo units of ≥200 measured by an intrauterine pressure catheter) compared to women with normal BMI after adjustment for confounding factors (including maternal age, parity, induction of labour, gestational age, admission cervical dilatation, excessive gestational weight gain, infant birthweight, and maximum oxytocin dosage in the last 2hrs of the 1st stage of labour) (aOR1.76, 95% CI 1.11-2.81). Results of a sub-analysis of women who had CS for dystocia (and hence assuming failure to progress) were similar. This study also reported no difference in time spent in labour according to BMI among women who had a CS in the 1st stage of labour, the majority of whom were nulliparous (86%). Nor was there any difference by BMI category in mean cervical dilatation at time of CS (5.5 ± 2.0cm). Another previous study reported no difference between mean Montevideo units achieved in nulliparous women of the lowest weight quartile versus the highest weight quartile. However, in this latter study, the whole study population underwent induction of labour with intravenous oxytocin, and there was no differentiation according to mode of birth, although CS was included as a confounder in multivariable analyses (Nuthalapaty, Rouse, & Owen, 2004).

These findings from Chin et al (2012), namely that women with increased BMI do not have reduced contraction strength but do have increased rates of CS for dystocia compared to women with normal BMI, are perplexing, and do not support the commonly stated hypothesis that obese women who require 1st stage CS may have impaired uterine contractility compared to women with normal BMI. There are important factors to consider in light of these new findings. Are the measures used

(Montevideo units) a sufficient reflection of uterine contractility? Measure of intrauterine pressure was first introduced in the 1950's, with creation of the Montevideo unit (MVU) to directly measure uterine contractile performance (Caldeyro-Barcia et al., 1957). Montevideo units are calculated by internally measuring uterine pressure above baseline tone and multiplying by the number of contractions in a ten minute period. Generally, above 200 MVUs is considered necessary for adequate labour during the active phase. Measurement of uterine contractility using an intrauterine pressure catheter has been reported to be comparable to external tocodynamometry, and electrical uterine myography (Haran, Elbaz, Fejgin, & Biron-Shental, 2012; Haran, Fejgin, & Biron-Shental, 2011; Playforth, Langer, Farinelli, Calderon, & David, 2009). It is therefore likely to be a valid measure to use when reporting uterine contractility.

Intrauterine pressure measurement has also been used to determine if obesity is associated with reduced pressure in the second stage of labour. Buhimschi et al (2004) reported that there is no difference in intrauterine pressure between obese and normal weight women when pushing in the second stage of labour, which aligns with our finding that obese women who progress to the second stage of labour are just as likely to deliver vaginally as women with a normal BMI (Buhimschi, et al., 2004; Fyfe, et al., 2011).

Another factor to consider is the rate of progress of labour. It has been reported that obese women progress more slowly in the first stage of labour compared to women with normal BMI, which may suggest suboptimal uterine contractility (Kominiarek, et al., 2011; Nuthalapaty, et al., 2004; Vahratian, et al., 2004; Zhang, et al., 2007). In a study investigating duration of labour among nulliparous women according to BMI, labour progression was significantly slower before 7cms of cervical dilatation in obese women compared to normal weight women, and overall dilatation from 4 to 10cms among women who had a vaginal birth was slower among obese women compared to normal weight women (Vahratian, et al., 2004). A recent report from the Consortium on Safe Labour found that among nulliparous women, labour progressed more slowly with increasing BMI (Kominiarek, et al., 2011). Overall dilatation from 4cms to 10cms ranged from 5.4 hours for women with BMI <25 to 6.0, 6.7 and 7.7 hours for women with BMI 30<35, 35<40 and ≥40 respectively (p=<.0001). However, of note, this study used BMI measured at time of labour admission rather than a prepregnancy or early pregnancy BMI limiting comparison with other studies (Kominiarek, et al., 2011). Nuthalapaty et al (2004) reported that among nulliparous women who had labour induced, for every 10kg increase in weight, rate of cervical dilation was decreased by 0.04 cm per hour (*P*=0.05) after adjustment for known factors for CS; birth weight, maternal age and initial cervical dilation (Nuthalapaty, et al., 2004). In our study, we found no difference in duration of 1st stage of labour according to BMI, however, this was measured only among women who delivered vaginally. Robinson et al (2011) also did not report on an association between duration of 1st stage according to BMI among women who delivered vaginally (Robinson, et al., 2011).

It may be that comparing labour duration times only among those women who delivered vaginally, women who may have a contractility problem have already been excluded as they would have been delivered already by intrapartum CS. It is possible therefore that the association between slower rate

progress in labour and increasing BMI/weight reported by the aforementioned studies may not persist if their study populations were limited to women who delivered vaginally. Neither study reported this data. However, Zhang et al (2007) reported a positive association between prolongation of first stage of labour and vaginal birth in overweight and obese primiparous women compared to normal weight women. They did not report any data related to duration of second stage of labour (Zhang, et al., 2007). Current findings are not consistent with regard to progress in labour among obese women.

What still remains unexplained from the above study findings is a lack of difference in duration of the 2nd stage of labour subsequent to reduced cervical dilatation rates and increased duration of the first stage of labour (Kominiarek, et al., 2011; Vahratian, et al., 2004). Kominiarek et al (2011) suggests this reflects an association of factors other than BMI, such as birthweight. This doesn't explain why obese women should labour more slowly only in the first stage, and thus seemingly have less effective uterine contractility in the first stage of labour compared to normal weight women but then apparently have equivalent contractility in the second stage. This may lend support to theory relating to abnormal cervical function in obese women which is discussed further in a later section: underlying mechanisms of failure to progress.

If obese women do labour more slowly in the first stage of labour, are caregivers waiting an insufficient amount of time in obese women to correctly diagnose failure to progress, which could result in falsely elevated rates of CS for failure to progress? Findings from Vahratian et al (2005) suggest waiting times are adequate. Median wait times for overweight and obese women (5.2 and 4.8 hours, respectively) were markedly higher compared with normal women (2.7 hours) (Vahratian, et al., 2004). These wait times are greater than the reported difference in dilatation times for total duration of the first stage (4-10cms) among normal weight women compared to moderately obese women (5.4 hours for BMI<25 versus 6.7hrs for BMI 35<40 (p=<.0001) reported by Kominiarek et al (2011) (Kominiarek, et al., 2011). However, comparison of times must be undertaken with caution when comparing between two different study populations. Vahratian et al (2004) also reported that care providers waited longer than the 2-hour minimum for arrest of dilation before deciding to perform a caesarean section (Vahratian, et al., 2004). Other studies have reported no difference in time spent in labour according to BMI among women who had a CS in the 1st stage of labour and no association between BMI and interval to delivery (Abenhaim & Benjamin, 2011; Chin, et al., 2012; Robinson, et al., 2011). Abenhaim et al (2011) reported a shorter mean time to intervention with CS in the 2nd stage of labour among morbidly obese women compared to normal weight women, but no difference in mean time to intervention in the 1st stage of labour. However, it is important to note that this study used BMI at time of birth. Overall, these findings are reassuring that care providers are not more likely to intervene and perform CS earlier for obese women compared to women with normal BMI, which could potentially falsely elevate CS rates among obese women (Vahratian, et al., 2004).

10.3.3. *Use of BMI calculated at time of birth*

The appropriateness of using BMI measured at time of birth raises some questions and requires further consideration. Two women with the same BMI at time of birth can have very different early

pregnancy BMI's as BMI at time of birth is highly influenced by gestational weight gain. For example, a woman who had a normal BMI in early pregnancy, and gains excessive gestational weight and is classified as obese at term, and a woman who was obese in early pregnancy, had limited weight gain and whose BMI changes little by term would be considered very similarly. Evidence suggests that these two women may start pregnancy with very different pathology, and weight gain in pregnancy has been shown to be associated with numerous pregnancy outcomes such as mode of birth. A further difficulty in studies which have used BMI at time of birth relates to the rate of obesity. Proportionally, the rate of obesity will inevitably be far higher if using BMI at time of time of birth. In our study, using early pregnancy BMI, 17% of our population of nulliparous women were obese. Using BMI at time of birth, there is twofold increase in the proportion of women identified as obese women by the time of time of birth (Abenhaim & Benjamin, 2011; Kominiarek, et al., 2011).

Summary of obesity and CS

- our findings have been subsequently confirmed by others: increased risk of CS in 1st but not 2nd stage of labour among obese women
- increased rates of CS in 1st stage of labour not attributable to premature intervention for failure to progress by caregivers
- recent study reports increased risk of CS in 1st stage of labour among obese women but no difference in contraction strength according to BMI
- inconsistent findings with regard to rate of labour progression among obese women
- some reports of slow progress in 1st stage of labour but subsequent normal progress in 2nd stage of labour among obese women
- comparison between studies is made difficult by differing by times of calculation of BMI: early pregnancy or at time of delivery
- the underlying mechanism of failure to progress in obese parturients may not be related to suboptimal uterine contractility

10.3.4. *Underlying mechanisms of failure to progress*

Some of the previously described findings suggest that the underlying mechanism of labour dysfunction among obese women may not be associated with suboptimal uterine contractility. To recap: Chin et al (2012) found no difference in uterine contractile strength, measured by Montevideo units), according to BMI among women who required 1st stage CS (Chin, et al., 2012). Others have

reported slower progress in the 1st stage of labour among obese women compared to normal weight women, but no difference in subsequent progress in the 2nd stage of labour (Kominiarek, et al., 2011; Vahratian, et al., 2004). We found no difference in duration of labour among women who delivered vaginally according to BMI, and increased risk of CS among obese women only in the 1st stage of labour. Conversely, a positive association between prolongation of first stage of labour and vaginal birth in overweight and obese primiparous women compared to normal weight women has been reported (Zhang, et al., 2007).

If the underlying mechanism of labour dysfunction among obese women is associated with poor uterine contractility, it would be expected that women who progressed slowly in the 1st stage of labour might continue to progress slowly in the 2nd stage of labour. Based on the findings of our study (Chapter 6), is it reasonable to speculate that obese women did not have increased rates of 2nd stage CS because most of those with dysfunctional labour did not even reach the 2nd stage?

Are there other possible explanations for the increased rate of CS among obese women? Is the underlying mechanism related to cervical dystocia rather than suboptimal myometrial contractility? If the dysfunctional labour of obesity is related to a cervical dysfunction, it would explain why obese women may progress more slowly in the 1st stage of labour, but not in the 2nd stage of labour after the cervix is fully dilated, as reported by those studies previously discussed (Kominiarek, et al., 2011; Vahratian, et al., 2004). It has been speculated that intra pelvic fat may be explanatory (Crane, et al., 1997), but this would cause delay in descent and progress in the second stage of labour aswell as the first, so does not seem to be a likely reason. Are there pathological changes associated with obesity in cervical tissue that affect cervical remodelling in labour? Malposition of the presenting part in labour could also be associated with increased rates of CS among obese women. The fetal occipito-posterior position or a deflexed head, are associated with increased diameters of the presenting part as well as poor application of the head to the cervix and consequent increased rates of CS (Kjaergaard, Olsen, Ottesen, Nyberg, & Dykes, 2008). Deposition of pelvic fat is unconfirmed by direct evidence of increased pelvic fat deposition demonstrated on medical imaging. No studies have investigated cervical remodelling or rates of malposition according to maternal BMI.

10.3.5. *Implications for practice*

Caregivers need to be aware that obese nulliparous women are more likely to require CS in the 1st stage of labour, and accordingly have increased anticipation and advanced planning for this surgery. However, they also be need to be aware that if obese nulliparous women reach the second stage of labour, the most likely outcome is a spontaneous vaginal birth and as such, heightened anticipation and planning for increased likelihood of CS can be downgraded to the same level of risk as women with a normal BMI.

10.3.6. *Research implications*

Reports relating to the rate of progression in the 1st stage of labour according to BMI among women delivering vaginally are not consistent or conclusive. Some studies report that there is no difference in the duration of 2nd stage of labour according to BMI among women delivering vaginally. Further prospective studies investigating the duration of labour and rate of cervical dilatation according to BMI with standardised criteria defining established labour are required. Duration of both 1st and 2nd stages of labour needs to be measured, and multivariable analyses in future studies require appropriate adjustment for confounding factors such as birthweight.

Most studies to date have used pre-pregnancy or early pregnancy BMI rather than BMI at time of birth. It would be useful to compare outcomes from studies using each of these methods to determine similarities and differences in findings.

Studies investigating malposition rates (especially occipito-posterior position) in relation to BMI are required. Ideally, prospective studies need to be undertaken to specifically ensure detailed data collection of fetal position during labour, and standardised criteria for failure to progress. Assessing cervical proficiency in labour in humans is problematic. It is not ethical to use cervical biopsy samples. There have been some studies investigating activity of the cervix related to labour and use of electromyography (Rudel & Pajntar, 1999). This may be potentially useful in future research to assess cervical distensability.

10.3.7. *Obesity, lipids and myometrial contractility*

As described in Chapter 3, there is some evidence both in vitro and ex vivo, that there is an association between cholesterol and myometrial contractility (Gimpl & Fahrenholz, 2000; Smith, et al., 2005; Zhang, et al., 2007). An association between obesity and reduced myometrial contractility in vitro has been reported in myometrial strips taken from women undergoing elective CS at term (Zhang, et al., 2007). Those from obese women contracted with diminished frequency and amplitude compared to those from normal weight women. A recent paper did not confirm this relationship (Higgins et al., 2010). In both studies the myometrial samples were taken from populations of women of mixed parity undergoing elective CS at term, and some of the samples were from women who had undergone previous CS with no reason stated. It is reasonable to assume some of these CS had been performed for dystocia in the previous labour. Thus some of the samples may potentially have already been abnormal in terms of potential contractility, and this may have confounded findings.

Our study was the first to investigate whether there was an association between maternal serum lipids and CS for failure to progress. We found no association, however, our study had limitations as we only measured lipids in early pregnancy. We were unable to measure late pregnancy lipids or the increase in lipids during pregnancy. Somewhat surprisingly, to date, no other studies have subsequently investigated the relationship between maternal lipids and risk for CS.

Recently for the first time, in vivo measurement of serum lipid profiles and expression of key markers of uterine contractility have been described (Elmes, et al., 2011). Imitating increased serum lipid concentrations in obese pregnant women by feeding a high fat, high cholesterol diet to rats, the study demonstrated increased maternal plasma circulating cholesterol concentrations, however, this was not reflected in increased uterine tissue cholesterol concentration during parturition. Differences were found in expression of key contractile associated proteins, but these did not match those hypothesised to be associated with an increase or a reduction of contractility. The authors recommend a need for further research in this field.

10.3.8. *Research implications*

Effective intervention to reduce elevated CS rates among obese women for failure to progress is dependent upon an understanding of the mechanisms underlying the dysfunctional labour. Further investigation of the relationship between maternal BMI and myometrial contractility is required. To more accurately investigate an association between BMI and myometrial contractility, prospective studies obtaining myometrial samples from nulliparous women at term with a singleton pregnancy undergoing emergency intrapartum CS for failure to progress versus for reasons other than failure to progress are required.

Prospective studies measuring serum maternal lipids in both early and late pregnancy (approximately 36 weeks gestation) are required. This would enable both investigation of an association between obesity, late pregnancy lipids and risk of CS and also of the magnitude of increase of cholesterol during pregnancy and whether this impacts on risk of CS.

10.4. Obesity and Postpartum Haemorrhage

Studies have reported an association between obesity and PPH, however studies that have investigated this relationship among nulliparous women stratified by mode of birth are scarce. Our paper currently remains the only study to have primarily investigated this relationship. Our findings with regard to obesity and risk of PPH were contrary to our hypothesis. Having previously shown that obese women who progressed to the second stage of labour are just as likely to deliver vaginally as women with normal BMI, we speculated that obese women who give birth vaginally would have normal myometrial contractility. As uterine atony, the leading cause of PPH, has been associated with slow progress in labour, a surrogate for impaired intrapartum myometrial contractility, we hypothesised that obese women who give birth vaginally would not have increased rates of PPH. However, we found that obese women delivering vaginally had a twofold increase in risk of PPH after adjustment for a range of confounders. Consideration of these findings in relation to the previous section in the discussion regarding obesity and contractility is perplexing. If the underlying mechanism of dysfunctional labour among obese women is associated with suboptimal contractility, then we would have expected to have confirmed our hypothesis i.e. that obese women who deliver vaginally may not have suboptimal contractility and hence do not have higher rates of PPH. However, if the underlying mechanism of dysfunctional labour among obese women is *not* suboptimal

contractility, then again, the results from our PPH study are also not what would be expected, as PPH is predominantly due to uterine atony, secondary to reduced contractility. Again, we would have expected to confirm our hypothesis. As our study was novel, our findings need to be confirmed or refuted by others.

10.4.1. *Obesity, circulating blood volume and PPH*

Presentation of our work on PPH and obesity has prompted queries regarding circulating blood volume in obese women, and whether this may affect PPH rates. It is useful to clarify this issue. As BMI increases, total circulating blood volume (BV) increases. So does that mean women with a higher BMI are able to tolerate a higher blood loss before becoming adversely affected? The answer is no. Although total circulating BV increases with increasing BMI, it is important to understand that indexed BV measured as mL/kg total body weight, actually decreases in a non-linear manner with increasing weight (Feldschuh & Enson, 1977; Lemmens, Bernstein, & Brodsky, 2006). Therefore, proportionally, obese women do not have higher circulating blood volumes and it is incorrect to speculate that women with a higher BMI are able to tolerate a higher blood loss. Indeed, with a lower indexed blood volume, they are more likely to be affected by lower amounts of blood loss than women of a lower BMI.

10.4.2. *Risk factors for PPH*

Some recent studies have reported findings relating to risk factors for PPH that potentially link in with the association between obesity and PPH. There is some evidence that increased administered oxytocin exposure during labour is associated with increased rates of severe PPH due to uterine atony (Grotegut, Paglia, Johnson, Thames, & James, 2011). As obese women have higher rates of slow progress in labour, they are more likely to have augmentation of labour. We did not have data to investigate an association between augmentation of labour and PPH in our study. However, we were able to assess prolonged duration of 1st stage of labour, a surrogate for failure to progress. We did not find a positive association between prolonged duration of 1st stage of labour and increased BMI

A recent large retrospective cohort study (published after submission of our paper) investigated severe PPH and mode of birth. It reported findings for a subpopulation of low risk nullipara at term with delivery of a single infant (Holm & Langhoff-Roos, 2012). Severe PPH was measured by red blood cell transfusion within 7 days of delivery and low risk was defined as no pre-eclampsia, placenta praevia or placental abruption. Part of the subanalysis included calculation of odds ratios for blood transfusion according to prepregnancy BMI (adjusted for maternal age, BMI, birthweight and smoking). Normal (18.5-24.9), overweight (25-29.9) and obese (≥30) BMI were all protective against risk of transfusion compared with an underweight BMI (<18.5), and there was no difference between groups. Risk of transfusion for obese and normal BMI was identical (aOR 0.79, 95% CI 0.65-0.95). It is not possible to accurately compare our findings with this study due to differing definitions of PPH and different referent groups for BMI. However, it is interesting to note that this study found no association between obesity and severe PPH. These findings were similar to those from another

previous retrospective study investigating PPH resulting from uterine atony after vaginal birth (Driessen, et al., 2011). Measuring severe postpartum haemorrhage by a peripartum change in Hb of 4g/dL or more (considered equivalent to the loss of ≥1,000 mL), there was no reported association between BMI (at conception) and severe PPH.

10.4.3. *Obesity and risk of PPH*

It seems then that there remains some inconsistency in findings with regard to maternal BMI and risk of severe PPH. However, the majority of studies report a positive association between obesity and PPH (Heslehurst, et al., 2008). Our findings and those of the only other study to primarily investigate maternal obesity and PPH (Blomberg, 2011) also support such an association. Our findings clearly highlight that obesity is an important independent risk factor for PPH in nulliparous women, and we emphasise the risk following spontaneous vaginal birth. There has been recent suggestion that physiological management of the third stage of labour should be considered for women who labour and deliver spontaneously without complication (Dixon, et al., 2011). However, BMI data were not included in this publication and based on our findings, we recommend that BMI should be included as an important factor when investigating risk and management of the third stage of labour.

Although we have identified an independent elevated risk of PPH among obese women, the underlying mechanism is currently unknown.

Summary of obesity and PPH

- although findings are not consistent, the majority of the evidence suggests that obesity is associated an increase in risk of PPH
- our findings do not suggest a problem with suboptimal uterine contractility is responsible for the risk of PPH
- no other studies have investigated rates of PPH among nulliparous women according to mode of birth
- no studies have investigated the mechanism underlying obesity and PPH

10.4.4. *Implications for practice*

Third stage of labour should always be actively managed for obese nulliparous women even if they have no other risk factors for PPH. This management should include siting of an intravenous luer in

early labour, and patency assured throughout labour. Increased vigilance and preparation for PPH management should be undertaken.

10.4.5. *Research implications*

No other studies to date have investigated nulliparous women and risk of PPH according to both BMI and mode of birth. Our study findings need to be refuted or confirmed by others. Inconsistency in findings with regard to an association between obesity and risk of PPH also illustrate a need for further studies investigating this association. The underlying mechanism of PPH among obese women requires investigation. Our findings have shown that speculation that the increased rates of PPH among obese women are due to their higher CS rates is unfounded. If obese women deliver spontaneously and have no apparent contractility problems during labour, why do they then have a PPH rate which is twice that compared to normal weight women? There is a paucity of literature investigating the mechanism of PPH among obese women and such studies are needed.

10.5. Obesity and pre-eclampsia

In my chapter relating to obesity and pre-eclampsia (Chapter 9), the objective was to identify risk factors among obese nulliparous women present at 14-16 weeks of gestation associated with later pre-eclampsia. Obese women have a significantly elevated baseline risk and identification of subgroups at higher and lower risk might enable prudent referral for specialist care and prophylactic treatment. Individual features of the metabolic syndrome have been associated with an increased risk of pre-eclampsia and we hypothesised that obese women who had additional features of the metabolic syndrome, notably dyslipdaemia and increased central adiposity, would be at greater risk of pre-eclampsia.

10.5.1. *Risk of pre-eclampsia and association with levels of HDL*

We reported for the first time that decreased concentrations of HDL were associated with increased risk for pre-eclampsia in obese nullipara. Although others had reported an association between dyslipidaemia and risk of pre-eclampsia among nulliparous women, this had related predominantly to hyper-triglyceridaemia. However, the biological plausibility of our findings are supported by data from a recent SCOPE proteomic study (Blumenstein, et al., 2009). This study identified 36 plasma proteins expressed in women at 20 weeks gestation who subsequently developed pre-eclampsia, and reported that 18 of those proteins were identical to recently identified proteins complexed to HDL and linked to cardiovascular disease in a study by Vaisar et al (2007) (Vaisar, et al., 2007). Vaisar et al (2007) investigated the composition of HDL, a lipoprotein known to have anti-atherosclerotic properties secondary to removal of cholesterol from arterial wall macrophages. They hypothesised that HDL may have other anti-atherosclerotic properties, and compared the composition of HDL from healthy subjects with those with coronary artery disease. They identified a number of proteins not previously known to reside on HDL, and also that HDL from healthy subjects compared with HDL from individuals with coronary artery disease carried different protein cargoes. They concluded that their

observations suggested HDL is involved in regulation of both the complement system and proteolysis, and that it carries protein families that contribute to its anti-inflammatory and anti-atherogenic properties.

The overlap of the HDL linked proteins identified in Vaisar's study in individuals with coronary artery disease, with those in the SCOPE study in women with pre-eclampsia, suggests there may be similar pathology in lipid metabolism and inflammation occurring in the two conditions. Blumenstein et al (2009) speculated that as the proteins they identified may alter how HDL can protect the vessel wall, this may modulate the relationship between pre-eclampsia and later cardiovascular disease. Our findings regarding HDL and risk of later pre-eclampsia in obese nullipara need to be interpreted with caution as they were of borderline significance, possibly due to our small numbers of cases of preeclampsia. Further studies are therefore needed to confirm or refute our findings regarding HDL.

10.5.2. *Risk factors for pre-eclampsia and cardiovascular disease*

Other risk factors we found for pre-eclampsia among obese women also overlap with those for cardiovascular disease, namely increasing BMI and family history of stroke. An association between pre-eclampsia and subsequent cardiovascular disease is well established. A large retrospective cohort study reported a two fold increase in risk of cardiovascular disease in women who had a history of maternal placental syndrome in pregnancy (defined as pre-eclampsia, gestational hypertension, placental abruption or placental infarction) compared to those who did not (adj hazard ratio [HR] 2.0, 95% CI 1.7-2.2) (Ray, Vermeulen, Schull, & Redelmeier, 2005). Although in this study it was shown that the risk of cardiovascular disease associated with obesity was further increased if there was also a history of maternal placental syndrome, it is unknown whether subsequent risk of cardiovascular disease is higher among obese women who have had pre-eclampsia compared to non-obese women who have had pre-eclampsia.

Studies that have investigated risk of cardiovascular disease and a prior history of pre-eclampsia have also consistently reported a positive association (Bellamy, et al., 2007; Smith, Pell, & Walsh, 2001). If women already have features of metabolic syndrome such as dyslipidaemia, obesity or increased insulin resistance, the additional metabolic stress of pregnancy may manifest as pre-eclampsia. It has been speculated that development of pre-eclampsia exposes a pre-existing predisposition to heart disease, related to increased susceptibility to metabolic stress (Rodie, Freeman, Sattar, & Greer, 2004). An alternative view is that the effects of pre-eclampsia, such as endothelial damage, may be responsible for risk of later cardiovascular disease. Rodie et al (2004) suggest that both of these mechanisms are likely to be contributory and there may be no clear delineation (Rodie, et al., 2004). The strength of the association between pre-eclampsia and cardiovascular disease is highlighted by a recent recommendation from the American Heart Association. They now recommend that health care professionals ensure thorough screening of women for risk of cardiovascular disease by including history of pregnancy complications specifically preeclampsia, gestational diabetes mellitus, preterm birth, or birth of a small for gestational age infant (Mosca et al., 2011).

Our finding that increased time taken to conceive is positively associated with risk for preeclampsia in obese nullipara is consistent with previous reports, however no previous studies have identified this as a risk factor among obese women. Investigations from the SCOPE study have reported that length of time to conceive is associated with risk of pre-eclampsia among populations of nulliparous women of mixed BMI (Kho, et al., 2009; North, et al., 2011). Shorter duration of sperm exposure was more common in women who developed preeclampsia compared to women with uncomplicated pregnancies [≤3 months 6.9% v 2.5%, (aOR 2.32, 95% CI 1.03–5.25)] (Kho, et al., 2009). A longer time to conceive (≥12 months) has also been reported to be protective against preeclampsia [aOR 0.40, (95% CI 0.22-0.75)] (North, et al., 2011).

The challenge remains to improve prediction of pre-eclampsia among nulliparous women in the hope that a screening test can be developed that is reliable enough to introduce into clinical practice. The addition of biomarkers to clinical risk factors is likely to be helpful. In a recent study, Myatt et al (2012) investigated first trimester prediction of pre-eclampsia in a population of low risk nulliparous women of mixed BMI (Myatt, et al., 2012). This study aimed to identify both clinical characteristics and biochemical markers in first trimester samples to predict later development of pre-eclampsia. The optimal multivariable combination of clinical data (African American race, systolic blood pressure, BMI, education level) and biomarkers (ADAM-12, pregnancy-associated plasma protein-A, placental growth factor) in the first trimester did not result in a model that was reliable enough for application in clinical practice - area under the curve of 0.73. However, this study measured only a small number of biochemical markers (ADAM-12; placental protein 13; placental growth factor; soluble fms-like tyrosine kinase-1; endoglin), including one standard screening marker used for screening for Down's syndrome (pregnancy-associated plasma protein-A [PAPP-A]). Other combinations of biomarkers have been suggested for prediction of pre-eclampsia, however, none have yet achieved adequate efficiency for application to clinical practice (Dugoff et al., 2005; Levine et al., 2006; Levine et al., 2004). A prospective study aiming to develop models for prediction of pre-eclampsia in a heterogeneous population, based on a combination of maternal factors and biophysical and biochemical markers, has reported modest predictive performance (Akolekar, Syngelaki, Sarquis, Zvanca, & Nicolaides, 2011). In a population of singleton pregnancies at 11-13 weeks of gestation, models for prediction of early, intermediate or late pre-eclampsia using only maternal factors produced low estimated detection rates with area under the curve of 0.33, 0.28 and 0.25 respectively. After addition of uterine artery Dopplers and biochemical markers, estimated detection rates increased markedly with area under the curve of 0.91, 0.79 and 0.61 respectively. A recent SCOPE study report by Kenny et al (2010) using metabolomic biomarkers has also demonstrated promising results. (Metabolomic profiling investigates the metabolites [low molecular weight biochemicals such as fatty acids and amino acids]) in cells, organisms, or tissues). In one of the most detailed metabolic screens performed to date, they identified a combination of 14 metabolites which produced a predictive model for pre-eclampsia with area under the curve of 0.92 (Kenny et al., 2010). These findings require validation in a future study.

The goal of the SCOPE consortium is to develop reliable early pregnancy prediction of pre-eclampsia which can be applied in practice in healthy nulliparous women. The SCOPE consortium is currently working with a commercial partner to develop a multiplex platform to predict pre-eclampsia based on biomarkers representing the multiple pathophysiological pathways known to be involved in preeclampsia. These results will be available in 2013.

Until clinically useful models for prediction of pre-eclampsia are developed, we need to use available evidence to assess risk and plan the antenatal care for obese nulliparous women. Current guidelines should be utilised, for example Pre-eclampsia Community Guidelines (PRECOG) that recommend referral to specialist care for women with BMI ≥35 who have one or more risk factors for pre-eclampsia (Milne, et al., 2005). Other recent studies relating to obesity and pre-eclampsia also assist with clinical management. A recent large cohort study investigating maternal BMI, height and risk of pre-eclampsia among nulliparous women reported that short maternal stature (<164cms) combined with a high BMI (>30) independently increased risks of preeclampsia of all severities (Sohlberg, et al., 2012) using women with normal BMI (18.5–24.9kg/m2) and women of average height (164–171 cm) as reference. Another SCOPE publication recently reported on the impact of maternal body mass index on the phenotype of pre-eclampsia (Anderson, McCowan, et al., 2012), concluding that among women with pre-eclampsia, those who are overweight or obese in early pregnancy are not more likely to have term pre-eclampsia compared with women with a normal BMI. These findings highlight the requirement for vigilant surveillance for the development of preterm as well as term pre-eclampsia among overweight and obese women. These data are relevant to clinical practice.

Summary of obesity and pre-eclampsia

- obesity is associated with increased risk of both pre-eclampsia and cardiovascular disease
- risk factors for pre-eclampsia identified among obese nullipara share similarities with those implicated in cardiovascular disease
- there are currently no models for prediction of pre-eclampsia which are reliable enough to be implemented in clinical practice

10.5.3. *Research implications*

Further studies need to validate our findings and if confirmed to determine whether measurement of HDL may be useful in clinical practice.

Development of the SCOPE multiplex platform is awaited as well as developments from other research teams in prediction of preeclampsia using clinical and biomarker risk factors.

10.6. Summary and Conclusions

This thesis has identified novel factors that will assist with assessment, planning and clinical management of obstetric care for obese women related to risk of CS,postpartum haemorrhage and pre-eclampsia.

In summary:

- Being overweight or obese is an independent risk factor for CS in labour, but this elevated risk is confined to the first stage of labour. Obese women who progress to the second stage of labor are just as likely to birth vaginally as women with normal BMIs
- Although obesity is also associated with hyperlipidaemia and cholesterol inhibits myometrial contractility in vitro, elevated maternal serum cholesterol in early pregnancy is not a risk factor for first stage CS for failure to progress in overweight or obese women
- Nulliparous obese women have a twofold increase in risk of major postpartum haemorrhage compared to women with normal BMI regardless of mode of birth. Higher rates of postpartum haemorrhage among obese women are not attributable to their higher rates of caesarean delivery
- Risk factors present at 14-16 weeks of gestation identified among obese nullipara that were associated with development of pre-eclampsia share similarities with those implicated in cardiovascular disease and may in part explain the linkage between pre-eclampsia and later cardiovascular disease

The obesity epidemic has resulted in a massive increase in the burden of care within obstetrics. In the absence of a desired but unattainable ability to ensure every woman has a normal BMI pre-pregnancy, there is an urgent need to determine optimum management of obese pregnant women in all aspects of obstetric care to reduce adverse outcomes. My findings have provided additional understanding to assist with this challenge, and direction for future research which may further contribute to reduction of adverse pregnancy outcomes for obese women. Further research will help us to understand why not all obese women have complications that have a detrimental effect on pregnancy outcomes, and to develop a risk stratification method to identify the subgroups of obese nulliparous women at even higher risk for pregnancy complications to enable improved delivery of care.

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