Is maternal hypotension during pregnancy and/or posterior located placenta associated with increased risk of stillbirth? A case-control study

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Abstract

Title

Is maternal hypotension during pregnancy and/or posterior located placenta associated with increased risk of stillbirth?

Design

A retrospective case-controlled study comparing a group of stillbirths with a live born control group matched for maternal age, baby gender, gestational age and year of birth. The purpose of this study was to ascertain whether hypotensive women or women with a posterior located placenta are at increased risk of stillbirth.

Two Australian tertiary referral obstetric hospitals were chosen as participating hospitals for this study. All cases with a discharge diagnosis of stillbirth over a five year period at these hospitals were identified and considered as cases for inclusion in the study. An attempt was made to match each case with two controls. After exclusions there were 124 cases and 243 controls.

Blood pressure (BP) readings throughout pregnancy were extracted from the medical record of each subject, and summary 'exposure' measures were created. These included: diastolic and systolic readings as well as mean arterial pressure taken at the initial (booking BP), minimum, calculated average, and final reading prior to the birth. Placental position, as determined by midtrimester ultrasound, was also collected.

Results

This study found that low Diastolic Blood Pressure (DBP) readings (between 60-70mmHg) throughout pregnancy were associated with a statistically significant increased risk of stillbirth. This trend was seen from the initial reading at booking (OR 1.83 95% CI 1.0-3.2, p=0.03) through to the last taken before the birth (OR 1.53 95% CI 0.9-2.5, p=0.09) including the calculated average over the course of the pregnancy (OR 1.61 95% CI 1.0-2.6, p=0.05) and minimum observed during the pregnancy (OR 2.94 95% CI 0.98-

8.8, p=0.05). In addition, this study found a minimum diastolic reading of less than 60mmHg carries a significant risk of stillbirth with a crude odds ratio of 3.5 (95% CI 1.18-10.41, p=0.02).

This study did not show a statistically significant association of systolic hypotension with stillbirth. However, after combining both systolic and diastolic blood pressures to calculate the mean arterial blood pressure (MAP) the analysis did suggest that women with a minimum MAP between 73-83mmHg were at increased risk of stillbirth (OR 1.69 CI 1.02-2.81, p=0.04). Furthermore, this study found that three MAP readings of less than 83.3 during the course of the pregnancy carries almost twice the risk of stillbirth (adjusted OR 1.99) even after adjusting for race, gravidity, parity, BMI and SGA (and matching for maternal age, gestational age, gender and year of birth.)

Women who have a posterior located placenta were statistically more likely to suffer a stillbirth than women who had a placenta in any other position (crude OR 1.64) and this estimate was largely unaffected by adjustment for blood pressure and other putative risk factors (adjusted OR 1.67)

Conclusion

In conclusion, this is the first study which specifically examined a stillborn population in order to explore whether maternal hypotension and posterior located placenta impact negatively on stillbirth incidence and the results of this study suggest that both maternal hypotension and posterior located placenta are probably independent contributory risk factors for stillbirth. This means that maternity care providers should closely manage and monitor progress of women who are hypotensive during pregnancy or those whose placenta is posterior; and that effective management strategies need to be developed to care for these women.

Article by the candidate published in a peer refereed journal

Warland J and McCutcheon H *Is there an association between maternal hypotension and poor pregnancy outcome?: a review of the literature.* Australian Journal of Midwifery Vol 15 No 4 December 2002 p22 - 26

Presentations at conferences made by the candidate

Free paper 'Challenging conventional belief: Is hypotension benign in pregnancy?' International Society of Perinatal Obstetricians Meeting (Adelaide) Nov 2002. Abstract for this paper was published in the *ANZ Journal of Obstetrics and Gynaecology* Vol 43 No 2 April 2003 pp 175-187 abstract number 13.

Keynote address 'Like a Fire in your heart' and 2 workshops 'Partners in Grief' and 'Subsequent pregnancy' at the 4th SANDS New Zealand National Conference (Napier) September 2003

Invited paper 'SAD cases of stillbirth: the Epidemiology and experience of unexplained stillbirth close to term' and *Free Paper 'Unheard voices: Is there an association between maternal hypotension and poor pregnancy outcome?'* C&N project people Midwifery Expo (Adelaide) September 2004

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The University of Adelaide
Candidate's Certification

This work contains no material which has been accepted for the award of any degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available in all forms of media, now or hereafter known.

Signed…

Dated…

Glossary

Accoucher The person attending the birth who assists the mother to birth her baby.

Anencephaly A neural tube defect that causes the baby to be born with little or absent cerebrum and flat bones of the skull.

Antepartum The period before giving birth.

Antepartum haemorrhage (APH) Vaginal bleeding in excess of 15 ml after 20 weeks of pregnancy.

Apgar score: A numerical score indicating the condition of the baby after birth. The infant is given a score out of two for heart rate, respiratory effort, muscle tone, reflex response and colour.

Autopsy (Necropsy) A pathological examination of a deceased person performed to determine the cause of death.

Bicornuate Uterus A congenital developmental error causing partial or complete duplication of the uterus and two fundal 'horns'.

Body Mass Index (BMI) an index which relates a person's weight to their height to determine if they are lean, normal, overweight or obese. The index is calculated by weight in kilograms (kg) divided by height in metres (m) squared.

Caesarean Section (LSCS) an operation when the baby is delivery via an abdominal operation through the lower segment of the uterus.

Cardiotocograph (CTG) also known as electronic fetal monitoring a machine generated printout which depicts fetal heart rate in relation to uterine activity.

Caucasian: An individual of European descent.

Cervical incompetence painless dilatation of the cervix in the second trimester which may result in fetal loss.

Cholestasis of pregnancy Pregnancy related reduction of gallbladder function resulting in excessive bile acids in the blood stream and skin. The most common symptom is itchiness. This condition is responsible for sudden fetal demise.

Chorioamnionitis inflammation of the chorion and amnion (membranes).

Cordocentesis an antenatal diagnostic procedure during which a fetal blood sample is taken from the umbilical cord.

Diastolic Blood Pressure (DBP) the lower blood pressure reading produced during ventricular diastole.

Essential Hypertension Hypertension existing prior to the onset of the pregnancy.

Funisitis: infection of the umbilical cord.

Gestation: Duration of the pregnancy taken from the first day of the last normal menstrual period (usually measured in completed weeks).

Gestational diabetes mellitus: Diabetes which arises during the pregnancy and resolves after the pregnancy ends.

Gestational Hypertension: hypertension arising in pregnancy after 20 weeks gestation without any other feature of multi-system disorder (pre-eclampsia) and which resolves within 3 months postpartum.[1]

Grandmultigravida a woman who has been pregnant more than four times.

Gravidy: The number of times a woman has been pregnant.

Group B Streptococcus (GBS) a common bacteria found in the intestinal and genital tracts. It is the main causative agent of maternal infections of the genito-urinary tract and the neonate.

HELLP Syndrome An advanced and often serious form of PE characterised by hypertension as well as hemolysis, elevated liver enzymes, and low platelets.

Hypoxic insufficient oxygen levels.

Incompetent Cervix see cervical incompetence.

Intrapartum the time when the woman is labouring and giving birth

Intrauterine Growth Restriction (IUGR) The infants birth weight is below the 10th centile for that which would be expected for the gestational age.

Korotkoff Sound Named after the physician who first described them there are five Korotkoff sounds associated with the taking of blood pressure.

Lupus/Antiphospholipid syndrome A disorder of the immune system associated with excessive blood clotting.

Mean Arterial Blood Pressure (MAP) a term which describes a notional average blood pressure in an individual. It is typically calculated by using the following formula (SBP+2*DBP/3).

Meconium stained liquor (MSL) fetal faeces present in the liquor which stains it green.

Multigravida a woman who has been pregnant more than once.

Nuchal Cord: Umbilical cord around the neck of the baby.

Nulliparous a woman who has never given birth.

Orthostatic dysregulation: a 20mmHg drop in MAP and increase in pulse rate by 20 beats per minute occurring after exercise.

Orthostatic hypotension: a blood pressure drop of 10-20mmHg when a person changes position from lying to standing.

Parity: The number of times a woman has given birth at greater than 20 weeks gestation (the baby need not have been live born).

Perinatal death: a term which encompasses death around birth including stillbirth and neonatal death.

Placental Abruption the placenta partially or completely abrupts or 'tears away' from the uterine wall.

Placental Perfusion: the passage of blood and nutrients through the placenta.

Placenta praevia: the placenta reaches or covers the internal cervical os.

Placentation :the way in which the placenta is formed and attached to the uterus.

Post-prandial hypotension a drop in blood pressure following eating.

Pre-eclampsia (PE) hypertension arising after 20 weeks gestation with one or more of: proteinuria, renal insufficiency, liver disease, neurological problems, haematological disturbances, fetal growth restriction. The hypertension returns to pre-pregnancy levels within 3 months postpartum.[1]

Pregnancy Induced Hypertension (PIH) see gestational hypertension.

Preterm (Premature) an infant born prior to the 37th completed week of gestation.

Primiparous A woman who has given birth for the first time.

Pulse Pressure (PP) the difference between the systolic and diastolic blood pressure.

Septate uterus the body of the uterus is partially of completely divided by a septum.

Small for Gestational Age (SGA) a term synonymous with intrauterine growth restriction as above.

Stillbirth: "birth of a fetus at or after 20 weeks gestation and/or with a birthweight of 400 gm or more , with no signs of life at birth"[2] (p.40).

Supine hypotensive syndrome occurs when the pregnant woman lies supine and the gravid uterus occludes the inferior vena cava causing her to feel faint.

Systolic Blood Pressure (SBP) the higher blood pressure reading produced during ventricular systole.

Thrombophilia a range of diseases both inherited and acquired associated with blood clotting. The most common inherited thrombophilia affecting pregnancy outcome is Factor V Leiden.

Trisomy three copies of a chromosome rather than the usual two. Common trisomies are 18 and 21.

Umbilical artery doppler velocimetry measuring the speed at which blood travels through the umbilical arteries.

Unexplained stillbirth Birth of an infant who shows no signs of life (as in stillbirth definition above) whose death was unexpected by history, and after an autopsy of the baby together with gross and histologic examination of the umbilical cord, placenta and membranes no antecedent cause of death was demonstrated.

Unicornuate Uterus A congenital developmental error causing an abnormally thin uterus.

Velamentous umbilical cord insertion cord inserted into the membranes causing the fetal blood vessels to run between the membranes and the placenta.

Dedication

To a beautiful daughter
Emma Louise Warland
Stillborn 22/4/93

and

To a wonderful father and friend
William 'Brian' Kelley
19/4/28 - 26/10/94

To mourn too long
For those we love
Is self indulgent-
But to honour their memory
With a promise
To live a little better
For having known them,
Gives purpose to their life-
And some reason
For their death…

Nanushka

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Prologue

The dying

All stories, if continued far enough, end in death and he is no true storyteller who would keep that from you

Ernest Hemingway

The woman flops down onto her bed, it has been a long day and she feels tired. She almost immediately drifts off to sleep but just before she does her unborn baby starts to kick. "Fair enough," the woman thinks, as she gently rubs her pregnant abdomen, "I've probably not given my baby a chance to sleep all day today and now it’s returning the favour!" In spite of her baby's vigorous kicks the woman falls asleep with a smile on her lips… even though it's near the end of her fourth pregnancy she will never lose the wonderment at feeling her unborn baby move inside her… she loves being pregnant.

A few hours later…

The birth suite room is dimly lit notwithstanding it is the middle of the day. The woman has now been labouring since early morning and is lying on the bed obviously in the final stages of labour.

As each contraction overpowers her, she takes deep breaths of nitrous oxide and moans restlessly. The midwives in the room make eye contact; nothing needs to be said, they can tell by the sounds she is making and her behaviour that she will begin pushing soon. It’s the woman's fourth baby so the birth will probably be quick.

Sure enough with the next contraction the woman lets out a primeval scream and grunts loudly. The midwives can immediately see some of the head and one of them dons a pair of gloves ready to assist with the birth. The other speaks softly and reassuringly to the woman.

Another contraction seizes the woman, this time the scream is blood curdling and she pushes again… the head 'crowns' and then is born. The midwife eases the umbilical cord over the baby's head as the woman, her whole face etched with effort, her eyes tightly closed, gives one final push to birth the rest of her baby and the midwife gently lifts the newborn infant onto the mother's chest.

The woman opens her eyes to inspect her new arrival. She is a perfectly formed baby. Her hair is blond with auburn highlights… just like her mother's. She has a sweet little nose and a wide intelligent forehead, just like her father. She is perfect in every way but one… she is not crying. This perfectly formed, term infant is lifeless.

The mother and midwife both examine the placenta… it seems healthy. The cord is very long and very thin but there is no knot or any other evidence of trauma. There does not seem to be any obvious reason for the baby's death.

I ask, "Why did my baby die?" and my midwife colleague just sadly shakes her head.

Our baby 'Emma's death was then, and remains to this day, unexplained.

The birthing

You would know the secret of death. But how shall you find it unless you seek it in the heart of life.

Kahlil Gibran

Several years later…

The midwife sitting at the desk in labour ward has had a long night. A young woman having her first baby has just been admitted to the birthing rooms in early labour. During her pregnancy the woman tested positive for Group B Streptococcus so the midwife has organised for her to have intravenous access via an intravenous cannula and has given her a dose of prophylactic antibiotics. She has taken a set of baseline observations and noted that the woman has a blood pressure of 105/65 … "Nice and low," she says to the woman.

The midwife has placed a Cardiotocograph (CTG) on the woman as part of the hospital's normal admission procedure. She has ensured that the woman is comfortably positioned on her side and has left the room to attend to some paper work which still needs to be done from an earlier birth. She leaves the CTG running loudly enough for her to hear the fetal heart rate from outside the room. She sits down and sips her cup of coffee and begins to write. After several minutes, she becomes aware of the fetal heart rate echoing out from the room… it must have dropped to half the usual rate. She rises quickly and races into the room. She sees the woman lying on her back fast asleep. She rouses her whilst she presses the 'nurse assist' bell to call for help, places an oxygen mask on the

woman's face and quickly takes her blood pressure (90/50). The fetal heart is still sickeningly slow. She raises the foot of the bed and asks the midwife who answered the call bell to commence an intravenous infusion. Slowly but surely, the fetal heart rate recovers.

Shortly after this occurrence, the shift ends but on the way home the midwife reflects on the night's events. She is an expert birth suite midwife who has many times experienced the kind of incident that just occurred with the unborn baby. The difference between this time and every other time is that this time the woman did not have an epidural in situ, this time the woman's blood pressure had dropped not in response to epidural drugs but apparently because her blood pressure had fallen whilst she was asleep.

I wondered how often this could happen to pregnant women who were asleep and what would occur if what had just transpired in the controlled, monitored environment of a labour ward had instead happened at home. Would the fetal bradycardia have continued and got worse? Is it possible that the baby could have died if the monitoring and resuscitative efforts were not available because the woman had simply fallen asleep and dropped her blood pressure like that at home?

Could this be what happened to Emma?

A few weeks later…

It's my day off and I switch on the Internet and surf to the bulletin board, S*tillbirth Support.* One of the regular visitors has just posted a message asking, “Has anyone here had an unexplained stillbirth? If you have, you might like to contact Dr. Jason Collins (an American Obstetrician / Gynaecologist) he has an interesting theory.”

I note this doctor's contact details and send him an email saying, “I’m from Australia and I had an unexplained stillbirth.” The next day there is an email in my inbox, Dr Collins is asking for my telephone number. I replied, giving him my home number and told him again that it was an Australian number and that he might like to “talk” to me via email. Imagine my surprise when the following afternoon I received a phone call at work.

> “Is that Jane Warland?" a voice with an American accent asked - "Yes," I replied.
>
> “It’s Dr Jason Collins here.” - “Good heavens!" I exclaimed incredulously.
>
> I told him that I had had an unexplained stillbirth and said that I had heard that he might have a theory to share with me. He said that he would like to ask me some questions first and then he would tell me his theory.
>
> He asked:
>
> “Did your baby die over night?” - My reply, “Yes.”
>
> “Did she have the umbilical cord around her neck?”- Again “yes” is my answer.
>
> “Was there something unusual about the cord? For example was it long and/or thin?” - “Yes both, the midwife and I thought it was the longest, thinnest cord we had ever seen.”
>
> “Was the placenta sited posterior on the 20 week ultrasound scan?” - “I don’t know but when I get home I can check the records and get back to you on that one”
>
> “Do you suffer from hypotension?” - “Yes”

By this stage I had goosebumps and the hairs on the back of my neck were standing straight up. How could it be that this man, who lived half way across the world from me, was asking me these questions about my baby's pregnancy and stillbirth, and the answer to all of them was yes?

I asked him about his theory. He explained that a woman who has a posterior located placenta, with a baby whose cord is unusually long and thin as well as around the neck,

who suffers from hypotension may become excessively hypotensive whilst sleeping. The mother may lie for a short time on her back, her baby may be affected by her low blood pressure and supine position, and either faint or become bradycardic or both. The baby may then slump onto its posterior-located placenta resting on its long thin cord which is looped close to its body due to the presence of the nuchal cord, thus causing blood supply and therefore oxygen supply to be cut off, resulting in the baby's death. This made perfect sense to me. Both my personal and professional experience told me that this was a theory that was worth considering.

When I got home from work I tore in through the door and pelted down the passageway to the study not saying a word to anyone. I ripped open the filing cabinet door and rustled through the files until I got to Emma's 20 week ultrasound report. I opened it and the words "posterior placenta" leapt out at me from the page. I then found all of our other children's reports: Greg "anterior" - Peter "anterior" - Cate "anterior" - Sarah "anterior". Emma's pregnancy had been my only pregnancy with a posterior placenta. Jason Collins' theory seemed to apply one hundred percent to me and made me wonder if it were too much to be a coincidence. Furthermore, if there was something in this theory, then it needed to be validated by research.

The journey

The greatest pleasure in life is doing what people say you cannot do.

Walter Bagehot

As a practicing midwife with no research qualifications, the ability to verify Dr Collins' theory seemed to be well outside my own capabilities. However, this thesis represents the culmination of a ten-year journey from my own unexplained stillbirth into PhD candidature. The burning passion driving me over the many obstacles along the way … to find out the reason for Emma's death and thereby maybe… just maybe… to change the way the story ends for someone else…

Chapter 1 - Background

Introduction

In this chapter, a general summary of current knowledge about risk factors for fetal death is outlined. Reasons for the choice of maternal hypotension and posterior placental position as the research variables are explained. Finally, the study research questions and purpose of the study is presented.

Risk factors for poor pregnancy outcome

There is much research activity focussing on possible reasons for poor pregnancy outcome. These outcomes include babies who are born small for gestational age (SGA), preterm, or those succumbing to perinatal death. Findings of research examining poor pregnancy outcomes highlight a plethora of causative and contributing factors, which may create a 'web' of risk factors for these outcomes.

The vulnerable baby caught in this web may be susceptible to one or all of the surrounding strands and become trapped, overwhelmed and succumb. This is depicted visually in figure 1.1. Some of the stands of this web are not known or fully understood, however, known strands of the web or risk factors can be divided into four main groups, namely: maternal, socioeconomic, fetal and environmental. Each of these is discussed in this chapter.

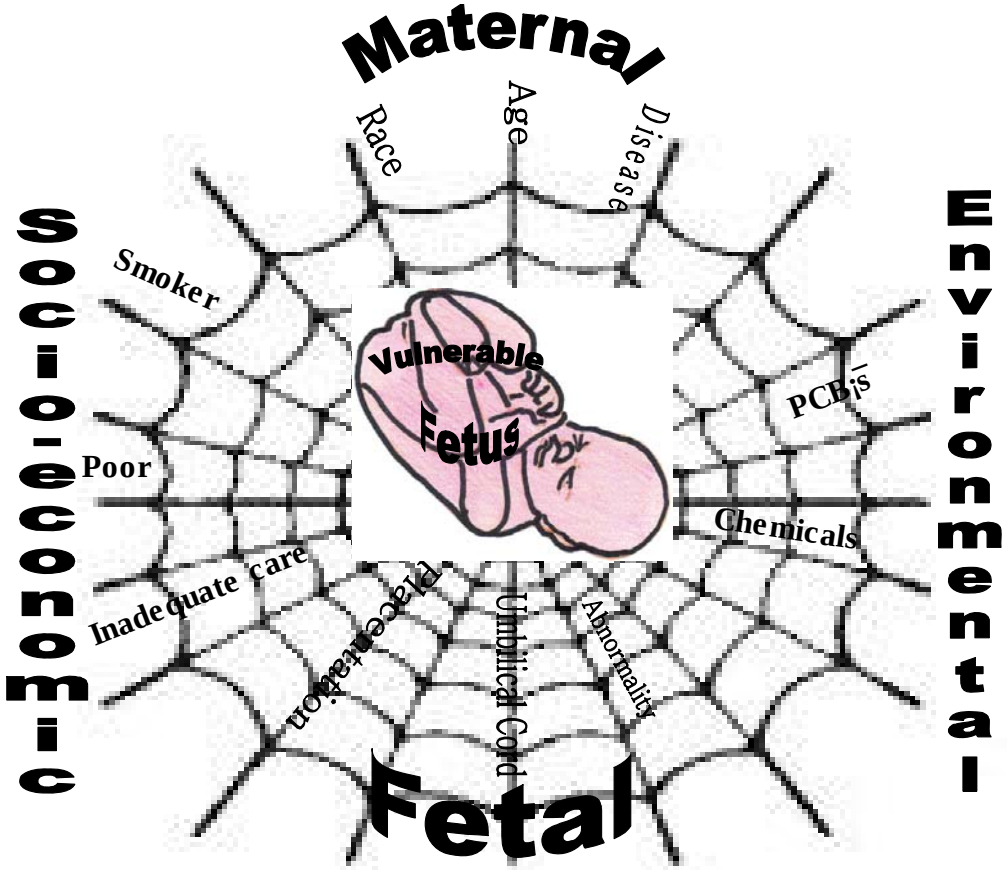

Figure 1.1 Web of causation

Maternal factors

There are a large number of reported studies examining maternal health and life-style and associated increased risk of perinatal death. The most commonly cited of these are extremes of age,[3,4] tobacco smoking,[5] non-caucasian race[6] and nulliparity.[7] Less commonly cited are maternal haemoglobin concentration (less than 115g/dL and greater than 146 g/dL increases the stillbirth risk),[8] maternal body mass index (BMI) with overweight and obese women being at increased risk of fetal loss[9] and illicit substance abuse e.g. the cocaine abuser is at substantial increased risk of stillbirth.[10] Mental illness, specifically Schizophrenia, has also been implicated in poor pregnancy outcome.[11] Even excess coffee consumption has been put forward as a risk factor for fetal death.[12]

Maternal reproductive system structural defects

The pregnant woman may also suffer structural defects of her reproductive system e.g. bicornuate uterus or incompetent cervix. An incompetent cervix can put her at risk of extreme preterm birth which may result in an early neonatal death. Women with an abnormally shaped uterus such as bicornuate, unicornuate, and septate uteri are also at increased risk of early pregnancy loss.[13] Such structural defects may not always be congenital, for example, if the woman has a scarred uterus from a previous caesarean section then she is at increased risk of uterine rupture and subsequent fetal demise as a result of fetal hypoxia.[14]

Maternal medical problems

Medical problems such as thyroid diseases,[15] inherited abnormalities of blood clotting (thrombophilias)[16] Lupus/Antiphospholipid syndrome[17] and Cholestasis of pregnancy.[18] may have a negative effect on pregnancy outcome. Also, pregnancy may induce or worsen some medical disorders such as gestational diabetes mellitus[19] and maternal hypertensive disorders.

Maternal hypertensive disorders

It is well recognised that both essential (pre-existing) and/or pregnancy induced hypertension (PIH) are less than desirable maternal states. There have been several thousand publications, in both peer reviewed professional journals and text books, dating back many decades which have investigated the negative impact hypertension has on both the fetus and the mother. In spite of this there is often confusion regarding the definition of hypertension in pregnancy as well as terminology used. All definitions of the different hypertensive states that are used in this thesis are given in the glossary and

are those suggested by the Australasian society for the study of hypertension in pregnancy.[1]

Maternal injury

Another cause of fetal death is maternal injury. It has been estimated that approximately one percent of Australian pregnant women sustain some kind of trauma during pregnancy[20] and this may be either from an accidental or non-accidental cause. Pregnant women are at particular risk of blunt injury trauma because the pregnant uterus becomes progressively larger as the pregnancy progresses and this enlargement effectively thins both the abdominal wall and uterine wall. Such an injury may be sustained through motor vehicle accident, falls or domestic abuse and assault. It has been estimated that as many as five percent of these injuries result in fetal loss.[21]

Socio-economic factors

Socio-economic factors include inadequate perinatal care[22] and low socio-economic status.[23] The reasons why women who come from a disadvantaged socio-economic group are at increased risk of stillbirth are surprisingly unclear. Whilst one might surmise that women from this group are more likely to smoke tobacco and be prone to infections such as bacterial vaginosis[24] as well as less likely to seek early antenatal care, studies which allow for some of these common confounders still find a significant risk for stillbirth in this group which appears to be independent of these factors.[25] Such results show just how difficult it is to tease out risk factors for stillbirth from the web of causative and contributing elements of fetal death.

Fetal factors

The human fetus is vulnerable to a variety of influences both from within the uterus and external to it. Within the uterus, the fetus is reliant on both placental supply and umbilical cord flow for survival. Potential placental and umbilical cord problems which may threaten fetal well-being are presented here.

Placenta and umbilical cord problems

The placenta is the fetus' only means of sustenance. The placenta enables exchange of nutrients and gases between the maternal and fetal circulatory systems. This exchange can fail in one of two ways: either placental perfusion is insufficient or the placentation is defective. In order to understand how placental perfusion can fail, some basic placental anatomy and physiology should be explained.

Placental anatomy and physiology

Fetal blood reaches the placenta via the umbilical arteries. The two umbilical arteries each supply approximately half of the placenta. Once the umbilical cord reaches the insertion point on the placental surface the two arteries divide to form capillaries which run through the chorionic villi. On the maternal side of the placenta, blood enters the intervillous space via the spiral arteries and leaves via the endometrial veins. In the uteroplacental vessels, the spiral arteries increase in diameter as they approach the intervillous space. This enables the largest possible surface area for maternal blood to wash through or perfuse the fetal placental tissue and allows exchange of nutrients and gases for fetal 'waste'.[26] When there is constriction of maternal blood vessels this reduces the pool of blood available for placental perfusion. This description of placental physiology is depicted graphically in figure 1.2.

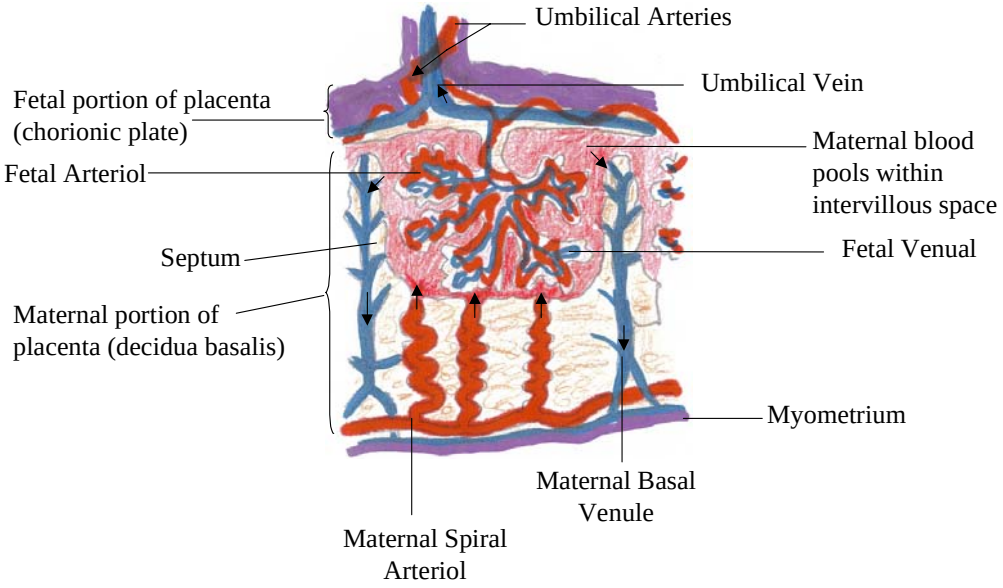

Figure 1.2 Placental vascular structure based on diagram in Coad and Dunstall[26] (p.169)

Placentation

The most common and well know example of a cause of vasoconstriction resulting in reduced placental perfusion is gestational hypertension. However, the way in which the placenta is formed or attached, 'placentation' may also be defective. Two examples of this are placenta praevia and vasa praevia. Placenta praevia is an abnormally implanted placenta that occurs when the placenta forms in the lower uterine segment and the edge of the placenta reaches or covers the internal cervical os.[26] Vasa Praevia is also a rare placentation defect[27] occurring when fetal blood vessels run through the amnion making them vulnerable to rupture and fetal death by exsanguination.

Another commonly known, although rare, placentation defect occurs in twin-to-twin transfusion. This occurs when monozygotic, monochorionic twins share a common circulation via a shared placental cotyledon. This can result in discordant growth and in around 10 % of cases the death of one or both twins.[28]

Occasionally both placentation and perfusion will be inadequate; placental abruption is one example of this. When placental abruption occurs the placenta separates from the uterus before the infant's birth thus, partially or completely, disrupting the fetus' blood supply.

Another consequence of placental abruption can be fetomaternal haemorrhage. This occurs when there is a transplacental passage of fetal red blood cells into the maternal circulation. This leakage is as a result of disruption of the fetoplacental interface which occurs following placental abruption, blunt trauma, cordocentesis, bleeding placenta praevia and the like. Complications of fetomaternal haemorrhage for the fetus include anaemia, tachycardia and fetal death.[20] After a fetomaternal haemorrhage the mother may become isoimmunised.

Rhesus (Rh.) isoimmunisation is the most common form of alloimmune disease in pregnancy with other less common forms being ABO and Kell incompatibility, as well as alloimmune thrombocytopaenia. Rhesus isoimmunisation occurs when a Rhesus negative mother is pregnant with a Rhesus positive fetus and co-mingling of blood occurs, often due to fetomaternal haemorrhage. This causes the mother's immune system to begin producing antibodies (anti-D) to the red blood cells of her fetus. Once the mother has developed these anti-D antibodies, they cross the placenta and attach to fetal red blood cells causing them to haemolyse. After the woman has been sensitised her immune response becomes successively worse each time she carries a fetus who has an incompatible Rh. factor. Approximately 15% of all pregnant women are Rh. negative[29] and it has been estimated that 17% of these will become isoimmunised during an incompatible pregnancy without prophylaxis.[30] Before the advent of Anti-D immune globulin administration in the 1970's maternal isoimmunisation caused perinatal

mortality and morbidity affecting as many as four per thousand births. Nowadays this figure has dropped to five in 10,000.[31] Whilst it is now rare, Rh. isoimmunisation is still a cause of fetal death particularly for women who have declined to accept prophylaxis for religious reasons. Also some women fail to adequately respond to the single-dose antigen, or the sensitising event may have occurred during the pregnancy prior to the routine administration of the anti-D immune globulin. Rhesus alloimmune disease is an example of the placenta being both the source of sustenance as well as potential danger to the developing fetus.

Umbilical cord physiology

Just as the placenta provides the fetus with all its nutritional needs, likewise the umbilical cord is also the developing baby's lifeline for the duration of the pregnancy. This lifeline may be jeopardised by either inadequate blood flow or cessation of blood flow at any stage of the pregnancy, labour or birth.[32] Such an interruption to blood flow may be because of a true knot, entanglement of the cord around a part of the baby's anatomy e.g. nuchal cord, or cord prolapse. Velamentous umbilical cord insertion has also been found to be associated with poor pregnancy outcome, although the mechanism for this remains somewhat unclear[33] it may be to do with decreased blood flow to the fetus.

Reduced flow can now be detected. Umbilical artery doppler velocimetry has become a routine method for fetal surveillance especially in high-risk pregnancy. Colour doppler images of the blood flow in the middle cerebral artery used in conjunction with an umbilical artery resistance index particularly in the absence of fetal umbilical artery end-diastolic velocity is a reliable predictor of adverse perinatal outcome.[34] Recently a 'placental score' has been developed which simplifies evaluation of uteroplacental and

fetoplacental doppler velocimetry enabling maternity care providers to better assess fetal risk.[35]

Congenital abnormality

Congenital abnormality is another fetal factor strongly associated with stillbirth risk. These abnormalities may affect the structure and/or function of an organ or body system, or the abnormality may be chromosomal. Congenital abnormalities can be associated with one single body system such as the cardiovascular system e.g. hypoplasic left heart. The abnormality may be mainly associated with one body system but cause an abnormality in another, such as renal agenesis which leads to minimal liquor production resulting in fetal pulmonary hypoplasia. Congenital abnormalities can also be associated with a number of body systems such as VATER syndrome. (Vertebral/Vascular anomalies, Anal atresia, Tracheo-esophageal fistula, Oesophageal atresia, Renal anomaly /Radial dysplasia) A congenitally abnormal baby may not be able to survive pregnancy; this is particularly true of those babies with a gross central nervous system abnormality such as anencephaly or an extreme chromosomal abnormality like Trisomy 13.

Small for gestational age (SGA)

Babies weighing less than the tenth percentile for their gestational age may be classified as being small for gestational age (SGA).[36] Intrauterine growth restriction (IUGR) and fetal growth restriction (FGR) are terms which are commonly used interchangeably with SGA. Fetus' who are SGA are at increased risk of stillbirth. Ogunyemi, Jackson, Buyske and Risk, found the stillborn babies in their study were six times more likely to be SGA.[37] It is unclear if being small *per se* is a risk factor for perinatal death or if other factors which impact on fetal growth are the antecedents for the fetal demise such as maternal tobacco smoking [38] and maternal hypertension.[39] This again highlights the

notion that perinatal death has a web of causation from which it is frequently hard to definitively determine individual risk factors.

Intrauterine infection

Intrauterine infection may also be an important factor in some perinatal losses. Such an infection can be either chronic or acute. Chronic infections are often caused by toxoplasmosis, rubella, cytomegalovirus and herpes, these being referred to as the TORCH organisms. Parvovirus 19 and Listeria monocytogenes also may be associated with increased risk of stillbirth.[40] Another common causative organism for devastating intrauterine infection is the Group B streptococcus. This organism has many times been found to be the primary infective agent causing rampant intrauterine infection in the placentas, fetal membranes, fetal lung tissues and fetal gastric contents of stillborn infants.[41]

Other fetal factors

Other fetal factors negatively affecting pregnancy include multiple pregnancy,[42] spontaneous preterm labour or rupture of membranes, and antepartum haemorrhage.[43] Some of these fetal factors are inter-linked within the web of causation e.g. pre-term labour, birth is frequently associated with a multiple pregnancy, and infection is one cause of preterm premature rupture of membranes.[44]

Environmental factors

Some known environmental risk factors thought to be associated with poor pregnancy outcome have not yet been thoroughly explored. These include the impact of environmental factors such as exposure to ionizing radiation, contact with various environmental contaminants in the work place, as well as polychlorinated biphenyl

(PCB's) and other pesticides. Even contaminants in drinking water have come under scrutiny as contributing factors in adverse pregnancy outcome.[45,46] Thorough exploration of exposure to environmental contaminants is often not possible in humans because randomised controlled trials (RCT's) are not feasible due to ethical considerations. In spite of this, many studies show an increased risk of poor pregnancy outcome for women working in occupations which have heavy chemical and other environmental exposures.[47,48]

Risk factors for stillbirth

This summary of current knowledge about risk factors for perinatal death indicates that many obstetric antecedents for stillbirth are known, however, unexplained stillbirth remains one of the largest categories (18.8%) within perinatal mortality figures (figure 1.3).

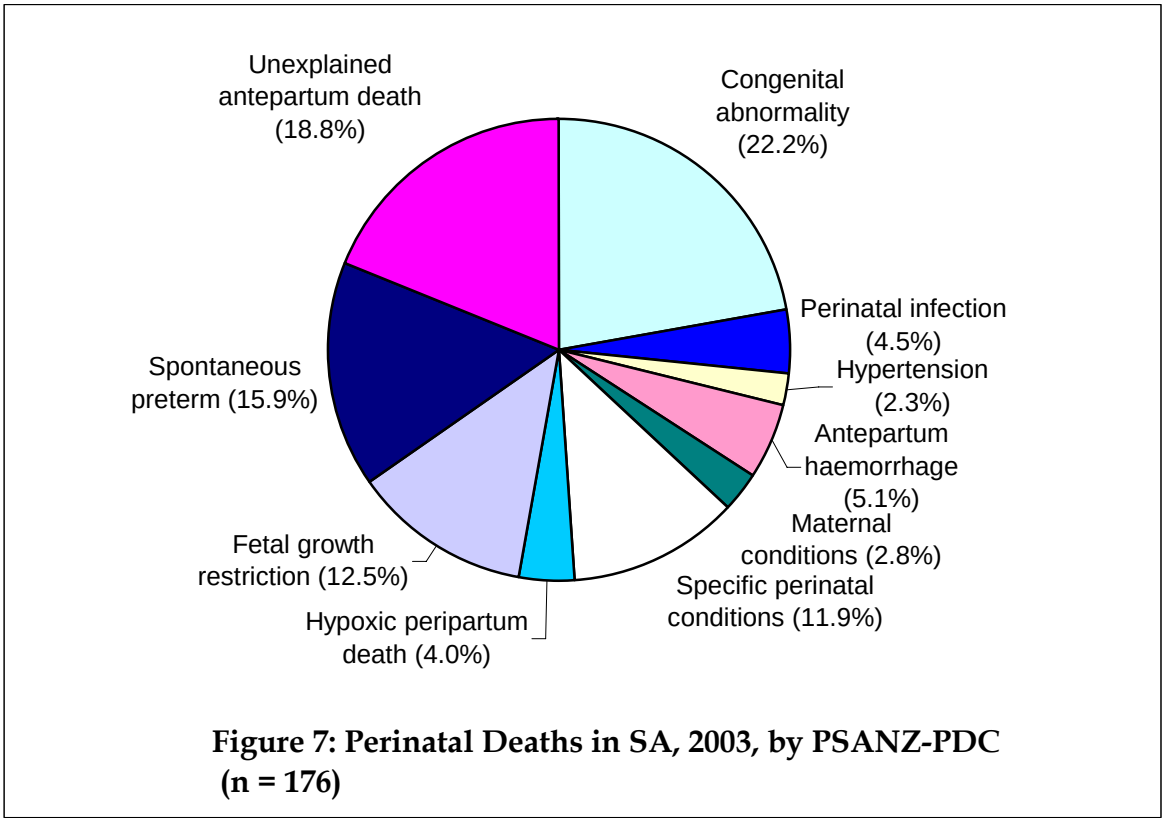

Figure 1.3 Perinatal deaths in South Australia, 2003, by PSANNZ-PDC[43]

Whilst evidence gained from research has been applied to antenatal care in order to reduce the incidence of this tragedy, further research needs to be undertaken to identify whether there are more strands on the web of causation associated with adverse perinatal outcome. Two more strands on this web, as suggested in the prologue, may be placental position and maternal hypotension. Reasons why these may be potential risk factors for stillbirth are further discussed here.

Choice of study variables

When planning this research initially all of the variables suggested by Doctor Jason Collins were considered as study variables. However, whilst time of death and nuchal cord, as well as umbilical cord length and thickness were all taken into account as possible study variables, these variables are rarely recorded in case notes. Furthermore, it seemed likely that maternal hypotension and posterior located placenta were the two main causative variables in his theory. Therefore, these two were chosen as the study variables.

Hypotension and pregnancy outcome

There has been little research undertaken on persistent maternal hypotension during pregnancy particularly any associated risk of fetal death. Conventional medical belief is that hypotension throughout adult life is acceptable, even good. Maternity care providers are often intent on avoiding the devastating consequences of pregnancy induced hypertension and so they are generally pleased to see a pregnant woman with hypotension. This is in spite of the fact that an acute maternal hypotensive episode has a well known harmful affect on the unborn baby. Adverse events may result from an episode of maternal orthostatic hypotension, post-prandial hypotension, supine hypotensive syndrome, trauma, or medically induced hypotension. Each of these forms of

hypotension are further described here along with a short explanation of how they are known to impact on pregnancy.

Orthostatic Hypotension

Ejaz, Haley, Wasiluk, Meschia and Fitzpatrick define orthostatic hypotension as an overall blood pressure drop of 10-20mmHg when a person changes position from lying to standing.[49] This blood pressure drop can cause temporary dizziness or faintness and is usually both transient and benign. Orthostatic hypotension is widespread in the general population.[49] The effect of orthostatic hypotension on pregnancy is poorly understood and has not been widely investigated however, one study estimated that 73% of pregnant women in late pregnancy (third trimester) suffered from orthostatic hypotension.[50] Another showed that orthostatic dysregulation (20mmHg drop in MAP and increase in pulse rate by 20 beats per minute) occurred in around 77% of hypotensive pregnant women following a "load stress test" compared with only seven percent of normotensive women.[51] The results of these studies suggest that orthostatic hypotension may have a negative influence on pregnancy outcome particularly for women who are already hypotensive.

Postprandial hypotension

Another time when blood pressure can drop is after eating, this is called postprandial hypotension. Although it is not commonly known, one study examining an elderly population found that 83% of patients with orthostatic hypotension also suffered postprandial hypotension.[49] Ejaz et.al. also suggest that autonomic dysregulation may be the root cause of both orthostatic hypotension and postprandial hypotension and that such dysregulation may explain why their elderly population were likely to be suffering from

both forms of hypotension. There has not been a study of pregnant women to determine if they are also affected by this syndrome.

Supine hypotension

Supine hypotensive syndrome occurs when the pregnant woman lies supine and experiences a sudden drop in blood pressure as a result of the gravid uterus occluding the inferior vena cava. This occlusion causes a reduction in venous return to the heart and consequent reduction in maternal blood supply to the fetus. Such a decrease can cause a negative affect on the fetus by depriving it of oxygen as well as impairing placental perfusion.[52] Holmes explains what happens to the placental circulation when a pregnant mother suffers an episode of maternal supine hypotension,

> "Whenever grave maternal (supine) hypotension occurs the well-being of the baby is in question. Furthermore, the engorgement of the uterine veins which will result from compression of the inferior vena cava may be an additional factor in the impairment of placental circulation"[53] (p.306).

Whilst the effects of a supine hypotensive episode are usually transitory this syndrome has been implicated as a factor in the aetiology of placental abruption[54] and therefore needs to be managed and where possible, avoided due to the potential for harm to both mother and fetus.[55] Maternal supine hypotension can be simply relieved by tilting the mother laterally by 45 degrees.

Acute traumatic hypotension

Another means of acute hypotension negatively affecting the pregnancy is through trauma.

An acute episode of hypotension as a result of haemorrhage has long been known to cause both bradycardia and hypoxia in the fetus.[56] Other acute causes of hypotension

have also been implicated in case studies examining poor pregnancy outcome. For example, a study by Ali, Yeo, Gana and McLellan, showed that acute maternal hypotension in the emergency room, post trauma, tended to be associated with fetal demise.[57] A case study by Suri, Salfield and Baxter reported an episode of acute hypotension in pregnancy resulting from anaphylaxis caused congenital paraplegia[58] and a case of arthrogryposis (congenital persistent joint flexion) was also ascribed to a prolonged acute episode of maternal hypotension in pregnancy.[59] Therefore, hypotension resulting from a traumatic event has been known to negatively alter fetal well-being.

Epidural/Spinal anaesthesia hypotension

Perhaps the most common acute hypotensive episode, which has an adverse affect on both mother and unborn baby, is that which occurs as a common side effect of administration of an epidural/spinal anaesthetic in labour or before operative delivery. There has been extensive research reporting this phenomenon beginning from the early days of epidural administration[60] and continuing through to today.[61] The principle focus of these papers was on minimising or reducing the impact of hypotension on labour because of the poor fetal response caused by this event. In fact, the negative affect on the fetus is so well know and so concerning that ways of preventing hypotension resulting from spinal anaesthesia administration have been extensively evaluated via Cochrane review[62] and many hospitals require women with epidural analgesia to be continuously monitored via Cardiotocograph (CTG) once an epidural is inserted during labour.[63]

Figure 1.4 shows an example of a CTG taken from the episode mentioned in the prologue. It depicts fetal bradycardia, of less than 100 beats per minute (BPM), persisting for 5 minutes (paper speed 1cm/min). This episode was apparently due to a maternal blood pressure of 90/50mmHg, which was not epidural related.

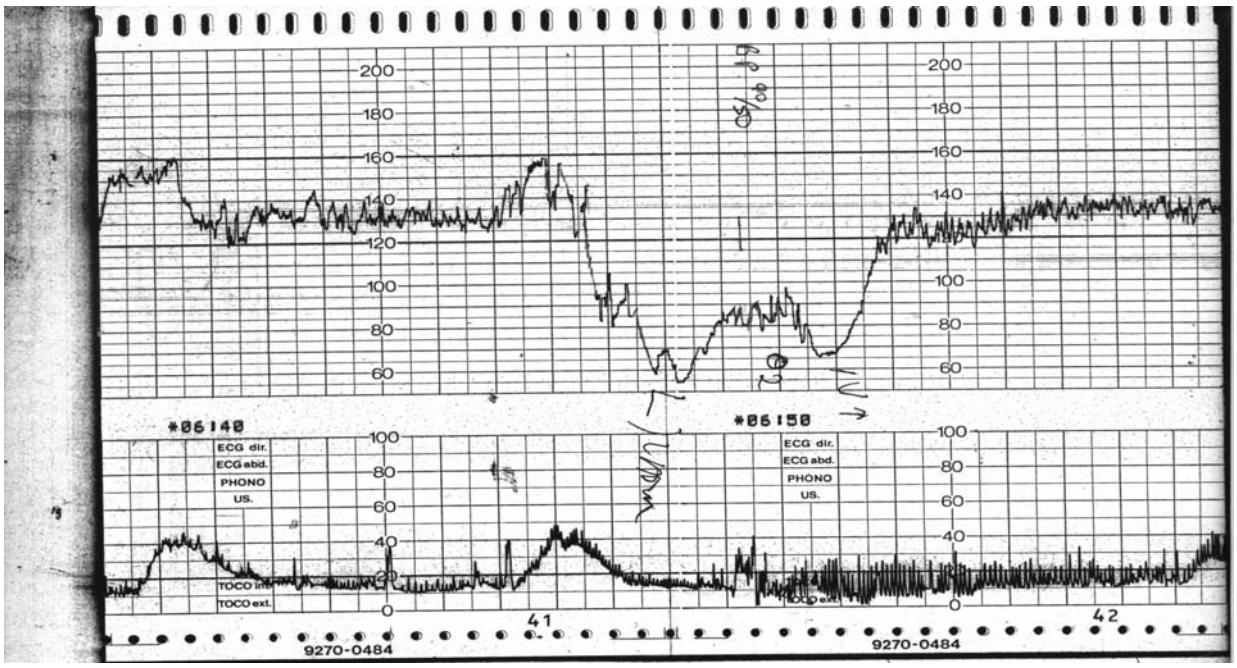

Figure 1.4 CTG showing episode of fetal bradycardia

This occurrence led to the postulation that maternal hypotension may stress the fetus not only as a result of epidural administration during labour but also during pregnancy, perhaps especially during maternal sleep.

Maternal hypotension during sleep

A study by Seligman[64] using automatic blood pressure recordings over a 24-hour period showed there was much variation in a pregnant woman's blood pressure over the course of a day. He found the mean waking blood pressure reading in 10 normotensive patients to be 124/68mmHg However, this mean fell during sleep to 78/40mmHg Some previous studies have examined maternal and fetal heart rate circadian rhythms. To date none of these studies have including measuring maternal blood pressure. For example, Lunshof monitored 26 normal singleton pregnancies between 26-38 weeks via continuous fetal and maternal heart rate and three hourly blood oestriol levels. He found that the "fetus does not passively follow the diurnal rhythm of the mother" (p.251) but that they are "in phase" with each other.[65] Another study by Hoppenbrouwers, Combs, Ugartechea,

Hodgman, Sterman, and Harper[66] virtually wired 16 pregnant women for sound! They attached a fetal heart rate monitor, maternal pulse oximeter, electroencephalograph (EEG) and goggles to detect rapid eye movement (REM) during sleep. Their aim was to establish "normative sleep parameters" as well as to observe what happens to the fetal heart rate during maternal sleep. They reported that "maternal sleep stages do not predictably influence fetal heart rate variability" (p.307). However, they noted an "intriguing" transient but marked increase in fetal heart rate around the time of sleep onset and "tentatively attributed" this to "fetal response to decline in maternal blood pressure" (p.308). This is indeed an intriguing finding. However, the rationale for this conclusion is unclear since they did not measure blood pressure at all in their study.

Similar studies have not been performed on women known to be hypotensive. However, if a normotensive woman's blood pressure falls to such a degree it seems possible that a hypotensive woman's blood pressure might fall at least to the same degree. If that were the case and the mother was at home and asleep and the fetus became bradycardic as a response to this very low blood pressure and no resuscitation occurred, because everyone including the mother was unaware of her baby's situation, could it be possible that the baby might die in utero?

If persistent maternal hypotension is a problem during pregnancy poor placental perfusion may be the mechanism.

Placentation and pregnancy outcome

Research has shown that maternal hypertension affects placental perfusion, placing the fetus in jeopardy.[67] Fetal well being is, of course, reliant on adequate placental perfusion. A study by Scheler and Woraschk[68] reported that hypotension may also negatively

influence placental perfusion. They found that women with hypotension had low placental perfusion concluding that hypotension in pregnancy is a "high risk" for which we “have to observe carefully.”(p.16) Scheler and Woraschk came to this conclusion in 1993 and yet there have been few studies done to support or refute this finding.

Placental location and placental perfusion

Placental location may also affect placental perfusion. As suggested in the prologue, posterior location of the placenta within the uterus may be more of a problem for the baby than one located elsewhere within the uterus. One reported study supports the notion that fetal distress during labour occurs more often in a pregnancy with a posterior located placenta.[69]

Placental perfusion and posterior located placenta

It may be that placental perfusion is less efficient with a posterior located placenta. If maternal hypotension negatively impacts on placental perfusion and the posterior position of the placenta within the uterus also negatively influences placental supply; it may be possible that a fetus with both of these factors present may suffer such a lack of blood flow that he or she is at increased risk of fetal death. Is it possible then that a pregnant hypotensive mother with a posterior located placenta is more at risk of stillbirth?

The study questions

These questions informed and focussed the research questions for this study namely:

- Does posterior placental position negatively impact on the incidence of stillbirth?

- Does the presence of maternal hypotension in pregnancy negatively influence the incidence of stillbirth?

- Does the presence of both posterior placental position and maternal hypotension influence the incidence of stillbirth?

Purpose of the study

The purpose of this study was to determine if there was an association between hypotension and stillbirth, posterior location of placenta and intrauterine fetal death, and a combined effect of association between hypotension, placenta location and fetal death. Therefore, the aims of this study were to:

- Determine if there is a relationship between maternal hypotension and stillbirth.

- Determine if there is a relationship between the posterior location of the placenta and stillbirth

- Assess if any relationship is compounded when the two variables are both present.

The first step in establishing whether maternal hypotension and/or posterior located placenta do affect pregnancy outcome is to assess what is currently known via a literature review. In the next chapter the literature supporting the notion that hypotension and/or placental location may be risk factors for stillbirth is reviewed and critiqued. In the following chapters the study design is outlined, and then the data analyses and results are discussed. Subsequently, recommendations for future research are made and methods for dissemination of results suggested. Finally the study is summarised and conclusions given.

Chapter 2 – Literature Review

Introduction

In this chapter the literature specifically related to maternal hypotension and location of the placenta is presented. Initially the search method is outlined. Then the literature concerning maternal hypotension is summarised. A detailed review of each of these papers follows which includes both critique and discussion. Then the literature reporting association between placental position and poor pregnancy outcome is reviewed and critiqued. Finally the gaps in the literature identified through this process are established.

Literature search method

A literature search of CINAHL, Medline, and the Cochrane data bases was made by searching in both the title and text using combinations of the MeSh terms; "pregnancy", "stillbirth", "hypotension", ("orthostatic", "persistent", "chronic" and "arterial") "pregnancy-complications" and "perinatal outcome". A separate search was made using MeSh terms, "pregnancy" "posterior" "placenta" "location" "position" and "site". The citations of all identified studies were searched for additional references. The results of these searches were few. Furthermore, the result of the hypotension in pregnancy search mainly consisting of papers published in German. Advice was sought from a researcher at The Joanna Briggs Institute in Adelaide, skilled in literature searches, who confirmed that the keywords used were both adequate and appropriate and that the scant results were indicative of little published literature in this area, not of poor search technique. The results of the literature are a mixture of prospective cohort, case-control, case-study or literature review articles and reports. Papers implicating persistent maternal hypotension and poor perinatal outcome referred to in this chapter are summarised in table 2.1

Table 2.1 Summary of all hypotension and stillbirth studies. (SBP systolic blood pressure DBP Diastolic blood pressure all BP's in mmHg) (Antenatal visits AN) (H hypotensive group) (N normotensive group)

Author/Year	Method	Population	Definition of Hypotension	Statistically Significant results
McClure Browne 1961	Prospective	7,344 Primigravid	< 105 SBP < 60 DBP	Increased risk of perinatal death if either initial or maximal SBP<105 or DBP <60
Friedman & Neff 1979	Data bank analysis	38,636 singleton first visit before 28 wks. >4 AN	Maximum DBP < 65	Three fold risk for fetal death if maximum DBP< 65
Goeschen et.al. 1982	Prospective Cohort	289(H) 289(N) 3 AN prior to 28 weeks	SBP Severe <100. Light 101-110 **N** 111-140 with DBP <90	H group more pregnancy / labour complications including: SGA, & Perinatal mortality
Harsanyi & Kiss 1985	Prospective Cohort	596(H) 596(N) 5 AN prior to 28 weeks	SBP Severe <100. Light 101-110 **N** 111-140 with DBP< 90	H group increased risk of miscarriage, TPL Premature birth, Anaemia SGA, Perinatal mortality
Wolff, Bauer, & Bolte. 1990	Prospective Cohort	70 (H) 770 (N) 5 AN after 20 weeks	SBP <100	H group increased risk of premature birth, pathological CTG, PPH.
Hohmann & Kuenzel. 1990	Retrospective comparison	423 (H) 667 (N) Hospital cohort	SBP<110 in the 28th week	No significant differences between the groups for Premature, IUGR
Ng & Walters 1992	Case-Control Retrospective	134 (H) 134 (N) Singleton, First visit < 20 wks. > 3 AN	Blood pressure at or below 110/70 at all AN visits	Increased risk of preterm birth, LBW. MSL during labour and PPH
Zhang & Klebanoff 2001	Data bank analysis.	28,095 singleton First visit < 25 wks. > 3 AN	Total baseline DBP<80	The lower the baseline the higher the incidence of preterm birth, IUGR.
Steer, et.al. (2004)	Prospective data base	210,814 First Singleton	Highest DBP. BP <70	Low SBP and DBP associated with increased perinatal mortality and SGA

Some papers reporting association between maternal hypotension and poor perinatal outcome were translated from German to English. Other German papers consist of either literature review or small case studies looking at treatment of hypotension and perinatal outcome, have not been fully translated but have been read to the researcher by a person whose first language is German and are briefly referred to here. Papers summarised in table 2.1 are discussed more fully next.

Hypotension research

Early hypotension research

In June 1960, the seventh international conference of the International Society of Geographical Pathology took place in London. At this meeting J.C Mc Clure Browne, an English obstetrician, presented a paper titled "Survey of eclampsia - Clinical Aspects."[70] In it, he described a prospective study involving 7,344 pregnancies, all primigravid women. He included women who received their first antenatal visit prior to the end of the 13th week of pregnancy in order to establish an initial blood pressure reading. The purpose of this study was to establish if initial readings correlated to an episode of eclampsia or pre-eclampsia in the third trimester, which might negatively influence the outcome of the pregnancy. He reported "clear" evidence that an initial SBP greater than 140mmHg resulted in a rise in perinatal mortality. However, he also "noticed a curious fact - that the very low systolic pressure (less than 105mmHg) showed a definite increase in perinatal mortality and abruptio placentae. The same is true of the very low initial diastolic pressures." He continues ... "What the significance of this is I do not know, but the point is worthy of further and more detailed examination at another time" (p. 547).

Some eighteen years after McClure Browne's study an American pair Friedman and Neff[71] also set out to investigate the role of hypertension in pregnancy. They undertook an extensive study using data from a large multi-centered collaborative study of 58,000 women. Those with viable pregnancies who attended an antenatal clinic and had at least four antepartum examinations (38,636) were selected to study the relationship between high blood pressure, proteinuria, and fetal outcome. Like McClure Browne before them, these researchers were surprised to find a correlation between hypotension and fetal

death. They reported that diastolic hypotension, with levels less than 65mmHg in the last trimester yielded a threefold risk for fetal death.

Whilst Friedman and Neff seemed unaware of Browne's earlier study, they refer to their discovery as "new" and do not cite him, graphs from these two studies show remarkable similarities. Both depict a "J" shaped curve, which suggests that maternal hypotension, is as much a risk factor for perinatal mortality as moderate levels of hypertension (see figures 2.1 and 2.2).

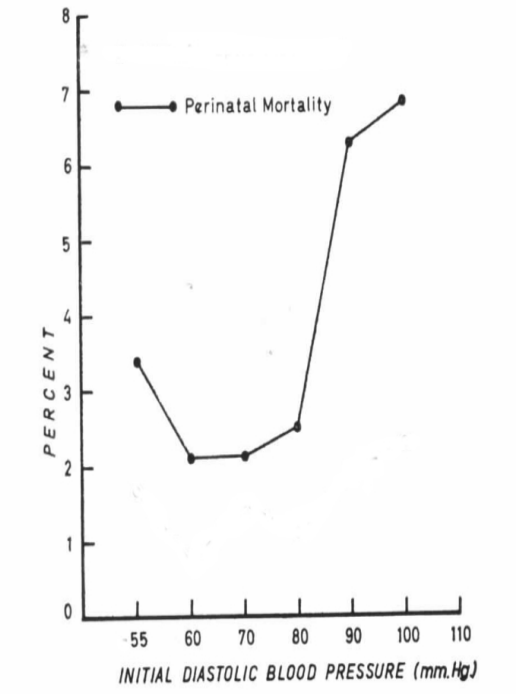

Figure 2.1 McClure Browne[70] (p.547).

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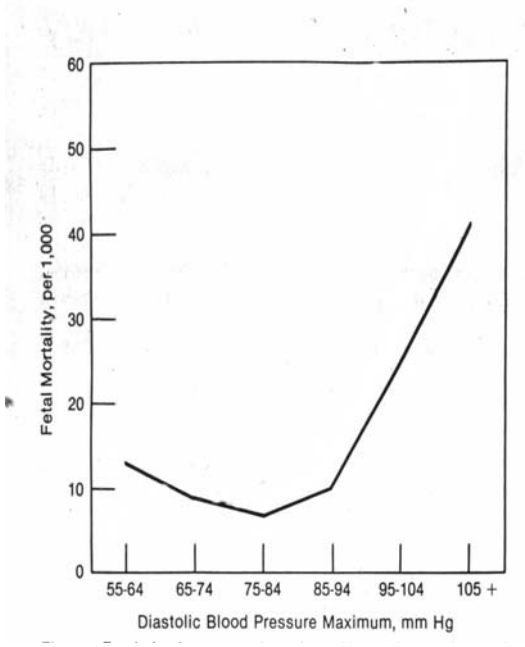

Figure 2.2 Friedman & Neff[71] (p.2250)

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Whilst there has been very little response to these findings published in English, a number of German researchers have examined this discovery more closely.

German hypotension studies

Two German studies by Goeschen, Pluta, Meyer-Wilmes and Saling[72] as well as Harsanyi and Kiss[73] reported a negative outcome associated with maternal hypotension throughout all stages of pregnancy and birth. However, other studies by Wolff, Bauer and Bolte[74] as well as Hohmann and Kuenzel[50] do not wholeheartedly agree with the negative findings of these two studies. They are all presented and critiqued here.

The first German study by Goeschen et.al.[72] identified 289 hypotensive women from a cohort of 2582 singleton vertex livebirths. Women were classified as hypotensive if they had a maximum SBP of less than or equal to 110mmHg over the course of at least three antenatal clinic visits before the 28th week of pregnancy. A normotensive control group was also identified with normotension defined as SBP 110-140mmHg along with a DBP not exceeding 90mmHg They further divided their hypotensive group into a "light" group consisting of 235 women whose SBP was between 101-110mmHg and a "severe" group including 54 women whose SBP was less than 100mmHg.

They followed this cohort through their pregnancies. The hypotensive women were more likely to have problems throughout their pregnancy and birth. These problems included threatened premature labour, suspicion of fetal growth restriction, more frequent signs of fetal distress in labour (CTG and pH-Values). The study showed there was a statistically significant increased risk of Caesarean birth (LSCS), and perinatal mortality in the hypotensive groups especially the ‘light’ hypotensive group as shown in table 2.2. However, it is important to note that the numbers in each of these categories are small.

Table 2.2 Risk of Caesarean birth and perinatal mortality associated with maternal hypotension (translated by Sandstrom)[72] (Significance = p < 0.05)

	LSCS n %	**Perinatal Mortality** n %
Normotensive (n=289)	7 2.5	1 0.4
Hypotensive (n=289)	26 9 p < 0.0007	8 2.8 p < 0.02
Light (n=235)	20 8.5 p < 0.0002	7 3 p < 0.01
Severe (n=54)	6 11.1 p < 0.0002	1 1.94 p < 0.2

The second study was by Harsanyi and Kiss.[73] They identified 596 hypotensive women attending an antenatal clinic. Inclusion criteria for their study were the same as Goeschen's except they required five antenatal visits prior to the 28th week. These authors also prospectively followed this identified cohort throughout their pregnancies. Their hypotensive group was also more likely to have problems throughout their pregnancy and birth. These problems included preterm birth, intrauterine growth restriction, preterm rupture of membranes, meconium stained liquor, low birth weight, low Apgar score as well as increased risk of perinatal mortality. (Significant results from this study are presented in table 2.3).

Table 2.3 Poor perinatal outcomes associated with maternal hypotension (translated by Sandstrom) [73] (Length of birth and birth weight presented as mean ± standard deviation.) (Significance = p < 0.05)

	Premature Birth n %	**Length of Birth** (Minutes)	**Birth Weight** (Grams)	**Perinatal Mortality** n %
Control (n=596)	49 8.3	408.6 ±193.6	3253.8 ± 556.7	10 16.7
Hypotensive (n=596)	95 15.9 p < 0.01	460.5 ± 191.4 p < 0.01	2896.1 ± 615.6 p< 0.01	22 36.9 p < 0.05
Light (n=418)	52 12.4 p < 0.05	449.9 ± 194.0 p < 0.01	2950.0 ± 600.3 p<0.01	14 33.5 n.s.
Severe (n=178)	43 24.2 p< 0.01	485.3 ± 183.2 p<0.01	2769.4 ± 634.0 p<0.01	8 44.9 n.s.

The study by Wolff, Bauer and Bolte[74] was a prospective investigation with a sample size of 770 subjects. The cohort comprised of a group of 700 normotensive (SBP max. 130mmHg and DBP max. 90mmHg) women and 70 hypotensive women. Their method of determining hypotension was somewhat different from the earlier studies namely; three of six SBP's less than 100mmHg taken in differing positions (lying, sitting ,standing, on left and right arm) at five antenatal visits after the 20th week. All measurements were taken by the same investigator to minimise measuring errors. Whilst they report a statistically significant increase in frequency of premature birth in the hypotensive group, (6.0 % compared with 0.5 % for the normotensive ($p = 0.001$)) as well as increased risk of post partum haemorrhage (5.7 % of the hypotensive women as opposed to 1.7 % of the normotensive ($p = 0.001$)). These researchers did not find the same correlation as Goeschen and Harsanyi did for other poor pregnancy outcomes. The reasons for this difference are not readily apparent as all three studies appear to be similar in their methodological approach and rigor.

Finally, a study by Hohmann and Kuenzel[50] reported examining 667 pregnant normotensive women and 423 hypotensive women. They designated their participants as hypotensive if they had one SBP reading before the 28th week of pregnancy of less than 110mmHg They state that they were surprised to find no association between maternal hypotension and premature birth, IUGR or operative delivery. They concluded that one SBP reading at the beginning of the third trimester was not enough to recognise clinically overt symptoms of maternal hypotension.

Reasons why the studies by Hohmann and Kuenzel[50] as well as Wolff, Bauer and Bolte[74] did not find the same degree of association between poor pregnancy outcome and maternal hypotension as the earlier studies may lie in the method of determining and

defining the hypotensive women within these studies. Wolff defined hypotension as systolic less than 100mmHg and included other "light" hypotensive women in their normotensive group whereas the other two studies identified this group and analysed their outcomes separately. Also both Wolff, Bauer and Bolte[74] as well as Hohmann and Kuenzel[50] only used a low systolic blood pressure whereas the other two studies used a combination of SBP and DBP. Furthermore, the four studies may have been powered differently with the first two having 289 and 596 hypotensive participants respectively whereas Wolff only had 70 as they employed a 10:1 normotensive: hypotensive ratio and Hohmann and Kuenzel[50] did not describe how they arrived at examining 667 pregnant normotensive women and 423 pregnant hypotensive women. It is difficult to determine the affect that these differences may have made to these studies as power calculations are not discussed in any of these papers perhaps because the studies are old and these techniques did not become standard until later.

Later hypotension studies

Studies examining maternal hypotension published in English have largely ignored perinatal mortality and instead focussed on the effect of hypotension on pre-term birth and SGA babies. For example, an Australian study by Ng and Walters[75] investigated the effect of chronic hypotension during pregnancy. In a retrospective case-controlled trial, they studied 268 pregnant women throughout their pregnancy. One hundred and thirty four women with hypotension were placed in the study group and a further 134 women were identified as a control group. They found that the women with hypotension were more likely to birth before the 38th week, had SGA babies and were more likely to suffer from postpartum complications. They also noted in the study group a tendency towards meconium-stained liquor, severe decelerations of the fetal heart during labour and premature birth. There were four perinatal deaths in the group of women with

hypotension and three in the normotensive group. Whilst this was not a statistically significant finding, it is a finding of interest from the point of view of this current study.

Another American pair Zhang and Klebanoff[76] using the same data-base as Friedman and Neff, set out to establish whether low blood pressure by itself resulted in premature birth and SGA babies or if Friedman and Neff's study was "confounded" by known risk factors. Their research showed a crude relationship between low baseline DBP and incidence of both preterm and SGA babies. However, they considered that factors such as maternal height, weight and socioeconomic group may be confounding any 'negative' affect of low blood pressure on poor pregnancy outcome as once they had adjusted for these factors in their study the risk of these poor pregnancy outcomes was no longer statistically significant.

The use of this old database may have been problematic for Zhang and Klebanoff. Whilst they correctly maintain that blood pressure measurement has not changed substantially in the last 40 years they did not take into account some of the more obvious data collection problems with the earlier study on which their data relied. For example the data base population was nearly 50/50% Caucasian / African American.[77] This is a high percentage of non-caucasians in today's terms and could have accounted for the differences in height and weight and socioeconomic group which this study found. Furthermore, the older study's data collection rigor could be called into question. One problem which Niswander reported concerning this database[77] occurred when a head nurse responsible for patient selection deliberately chose women with less voluminous notes to lessen her workload! This would have skewed the sample in her hospital towards single young primiparous women with uncomplicated pregnancies. The report states this "situation was corrected" but does not say how.

Although they studied more than 58,000 pregnancies Zhang and Klebanoff did not investigate any relationship between hypotension and stillbirth in their study. However, they do allude to the notion that there may be a difference between maternal response to physiological 'chronic' hypotension as opposed to 'acute' hypotension. They assert that if the hypotension is physiological then both the pregnant woman and her baby may be better able to be adjusted to its affects than individuals who have compromised plasma volume expansion, pathological homeostasis or women with many risk factors for having a SGA baby already.

Hohmann et.al.[78] agree with Zhang and Klebanoff by suggesting that some women may be more susceptible than others to their hypotensive state. They examined the effect of orthostatic changes in pregnancy on a group of antenatal attendees at their hospital. They specifically observed differences in lying and standing blood pressures and initially found that an analysis of the birth weight of newborns from women with and without subjective symptoms produced no significant differences. However, after analyzing only those women who showed a reduction in their standing blood pressure during late pregnancy, they found a significant number of SGA babies.[78] This finding implied that women who were more prone to difficulties in maintaining their blood pressure regulation were also women who tended towards poor pregnancy outcome.

A study published well after the commencement of this PhD[79] conclusively supports Browne's earlier hypothesis that initial low DBP less than 70mmHg is associated with increased perinatal mortality. In a substantial study conducted in Britain, over 210,000 nulliparous women with singleton pregnancies were prospectively followed throughout their pregnancy. After the baby's birth, the attending midwives entered the initial DBP as well as highest DBP recorded during pregnancy into a database. They found that

“perinatal mortality was lowest when the highest diastolic maternal blood pressure during pregnancy is between 70-90mmHg” (p. 5).

Steer's cohort of women suffered over 1300 perinatal deaths. After calculating the expected number of perinatal deaths against actual numbers, they established a "linear quadratic fit" (p.1312). A figure from this study (figure 2.3) demonstrating the relationship between perinatal death and highest DBP shows similarity to those depicted earlier (figures 2.1 and 2.2).

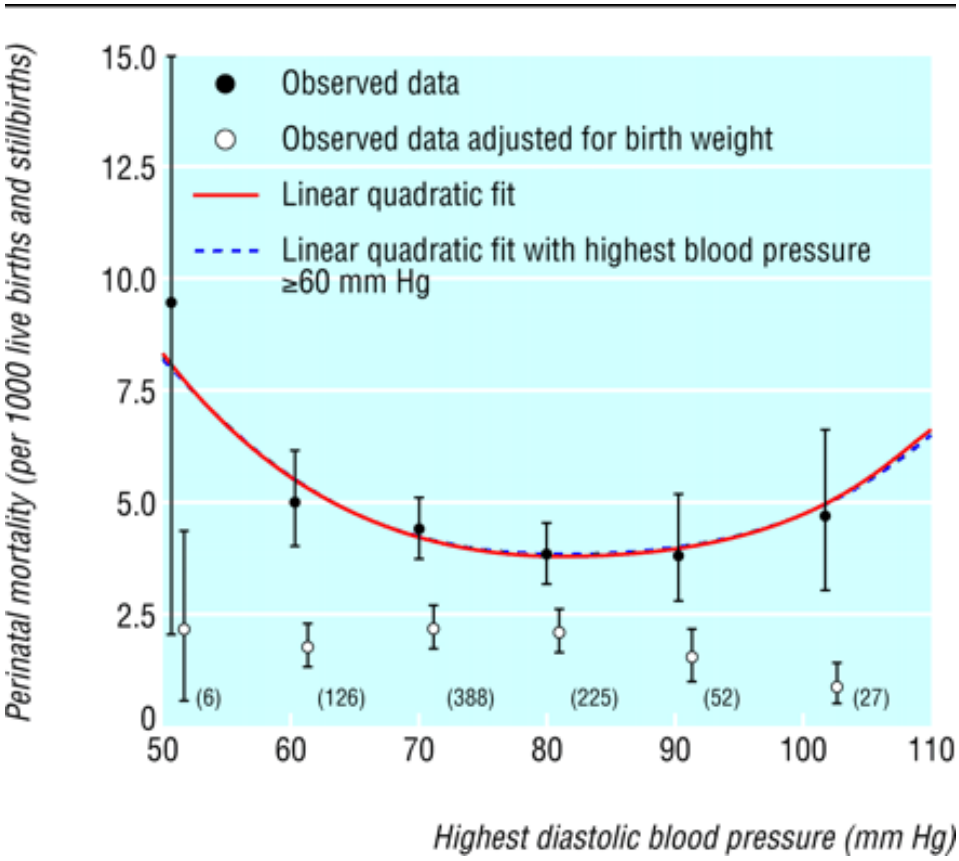


Figure 2.3 Relationship between DBP and perinatal mortality risk .Reproduced from Steer[79] (p. 1312) with permission from the BMJ Publishing group.

The graph is more U-shaped than the earlier J-shaped graphs depicted by Browne and Friedman and Neff. There may be two possible reasons for this: firstly this graph depicts association between perinatal mortality and diastolic readings less than 50mmHg the earlier graphs stop at 55mmHg secondly, and probably more importantly, the number of

deaths due to hypertensive conditions in pregnancy have fallen over the years since the earlier studies perhaps due to increased monitoring and treatment of hypertension in pregnancy. Such monitoring and concern does not yet exist for the hypotensive pregnant woman. Steer et.al. also found that from 34 weeks onwards, low diastolic blood pressures in pregnant women resulted in babies who were small for gestational age. They suggest that if DBP does not rise 15-30mmHg after 34 weeks that the baby may be born SGA due to "placental function failing to keep pace with fetal growth"[79](p.4). These authors suggest that persistent low maternal blood pressure may be a problem in pregnancy due to poor placental perfusion or decreased uteroplacental blood flow. This concept is echoed in reports from other studies as indicated below.

Uteroplacental blood flow in hypotensive pregnancies

A small German study by Grunberger, Leodolter, and Parschalk[80] found that placental perfusion in pregnant hypotensive women was significantly reduced. This perfusion was measured in 28 hypotensive women using isotopes. They found that placental perfusion was reduced in hypotensive women and concluded that a maternal blood pressure below 115/70 should be considered "alarming." Whilst it would certainly be difficult to justify this alarm, especially in today's climate of concern about pregnancy induced hypertension, it would appear that there is at the very least cause to investigate further especially as a later study by Scheler and Woraschk[68] made a similar finding. They compared the umbilical blood flow of 40 pregnant women and also found a significant decreased flow in the hypotensive (less than 110/60) pregnancies compared with their normotensive control group.

Treating hypotensive women

Some of the studies conducted in Germany have focussed on treatment of hypotension to improve placental perfusion and thus perinatal outcome. Klosa, Wilhelm, Schillinger, and Hillemanns[81] treated 10 pregnant women with norfenefrine hydrochloride (also known as Norphenylephrine hydrochloride: a sympathomametic vasopressor) and found that after treatment there were no differences in poor outcomes between their study group and normal pregnancies. Likewise, Grunberger, Parschalk and Fisch[82] studied 60 hypotensive women where half were treated with a mineralcorticoid to raise their blood pressure and thus their placental perfusion, whilst the other half remained untreated and were used as controls. They also found that the treated group had better outcomes, especially with increased birth weight. This weight gain was attributed to increased placental perfusion.

Another German group Goeschen, Saling, and Wiktor[51] also treated a small group of hypotensive women. They used dihydoergotamine (DHE), an ergot derivative designed to cause vaso-constriction and thus raise blood pressure. They found an improvement in orthostatic dysregulation in their hypotensive group after treatment. However, this drug is widely rated as a category X drug meaning that it is not recommended in pregnancy due to its ability to cause uterine contractions! Goeschen and his colleagues recognised this and state that after treatment that no case of increased uterine activity or premature birth was noted.

In the same paper Goeschen, Saling and Wiktor[51] report that they aimed to determine if fetal endangerment originating from maternal hypotension could be detected during routine CTG monitoring and then treated with DHE during the course of pregnancy. They prospectively monitored 60 hypotensive and 60 normotensive women. They used the same definitions as their earlier study namely normotension between 110-140mmHg

and a DBP blood pressure not exceeding 90mmHg, "light" hypotension between 101-110mmHg systolic and "severe" SBP was less than 100mmHg.

All 120 women, whose pregnancies ranged in gestational age from 19 to 33 weeks, underwent a CTG under "load-test" exercise conditions (three lots of ten knee-bends within 20 minutes). These researchers surmised that such maternal exertion might cause a brief placental blood "through-flow inadequacy" which may affect the fetus. During the test, the woman's blood pressure and pulse were monitored. The results demonstrated 83.5% of the hypotensive women registered a deceleration in fetal heart rate, whereas only 4% of the normotensive CTGs indicated such a deceleration. This difference was highly statistically significant ($p<0.0001$).

After one week of treatment with dihydroergotamine (DHE 2 x 2.5 mg DETMS retard daily) and a repeat "load-test" there was no longer a significant difference between the two groups. This finding confirmed their hypothesis that maternal hypotension can negatively influence the fetus during pregnancy but that this can be both detected and treated. It is important to note that the DHE's action did not generally raise the woman's blood pressure to normal levels rather its action was thought to increase placental bed perfusion.

The CTG example from this paper (figure 2.4) bears a considerable similarly to the CTG obtained from the fetal response to low blood pressure during sleep (figure 1.4) namely a prolonged and deep deceleration not related to uterine activity but rather to maternal state.

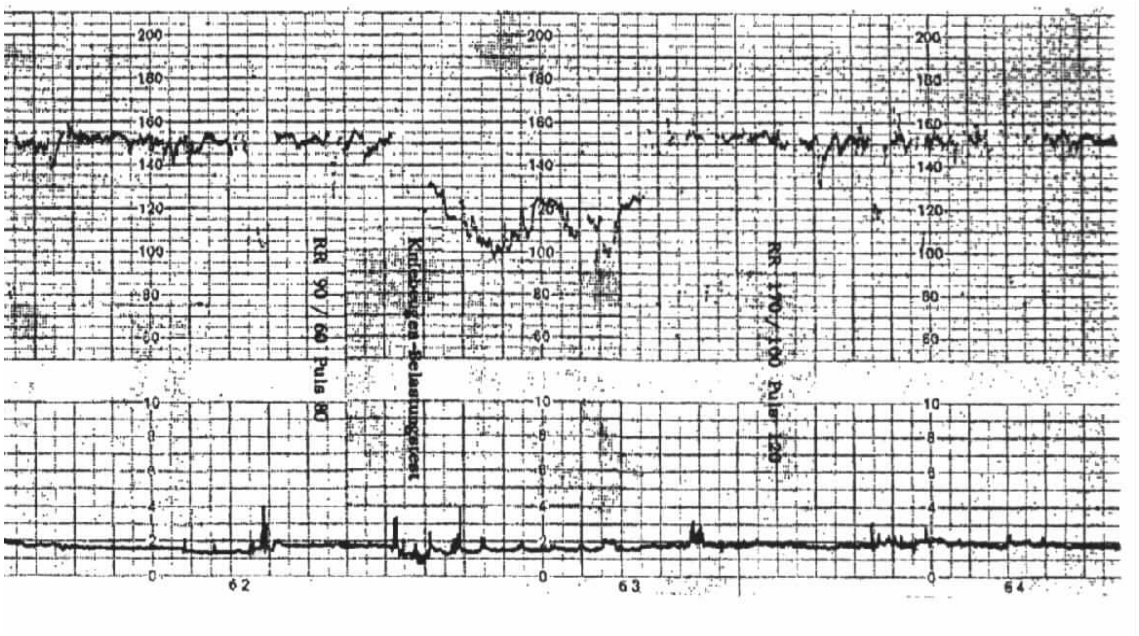


Figure 2.4 CTG during sleep from Goeschen, Saling and Wiktor[51] used with permission from Thieme publications.

Hypotension and placental site

Not only is it thought that placental perfusion may be decreased in women with hypotension during pregnancy but some research suggests that placental site may also affect the efficiency of the uterine artery blood flow. Two studies have investigated whether placental position may influence placental perfusion in turn affecting fetal well being.

A detailed study by Kofinas, Penry, Swain and Hatjis[83] examined the association between placental location and uterine artery blood flow in normotensive and hypertensive pregnancies. Flow velocity waveforms were studied via a continuous wave Doppler device. The right and left uterine artery systolic and diastolic ratios were measured. In both normotensive and hypertensive pregnancies the right and left uterine artery flow velocity waveforms demonstrated significantly different systolic/diastolic ratios when the placenta was located unilaterally. When the placenta was located centrally there was no significant difference.

The other study by Chapman, Furness, Jones and Sheat[84] found an association between "low-lying" placenta at the less than 24 week scan and SGA. They surmised that "perhaps implantation in the lower part of the uterus provides inadequate conditions for normal placental growth and perfusion" (p. 848).

These studies suggest that both lateral and low placentae may not provide adequate supply of nutrients and oxygen to the developing fetus.

Placental position research

Research, which has been undertaken on other aspects of placental position other than on low placental implantation, has been sparse. Whilst some studies have looked at how placental position impacts on pregnancy outcome no research has been undertaken on the effect of the position of the placenta and any associated increased risk of stillbirth. The small number of papers reporting any relationship between placental position and pregnancy outcome are reviewed next.

Placental location distribution

Whilst there has been extensive research on low-lying placentae especially the crucial importance of migration during pregnancy,[27,85-87] surprisingly little research has been done regarding the actual distribution of placental location.

One large study examined 2,527 women with singleton pregnancies. Following the 18-week ultrasound scan 45% of the women in their population had a posterior located placenta and 42 % had an anterior located placenta with the remaining positions being scattered through fundal, lateral and low.[88] The results of this study were used later when

making power calculations to establish a population norm for placental position distribution described later in this thesis.

Posterior located placenta and nuchal cord

Collins, Geddes, Collins and De Angelis,[69] studied 162 successive deliveries to answer their research question “How does a nuchal cord form?” They report an "incidental finding" of a statistically significant association ($p<.002$) between a posterior located placenta and nuchal cord occurrence. There were 14 nuchal cords in the 53 placentae which were posterior and only nine nuchal cords associated with the 109 placentae sited elsewhere in the uterus. They also noticed a relationship between placental location and fetal distress, increased caesarean section rates, incidence of meconium stained liquor (MSL) as well as a four-fold increase in fetal heart rate decelerations in the posterior placenta group. It was not clear from the report whether the fetal heart decelerations associated with posterior location of the placenta were affecting babies who also had the umbilical cord around their neck. It may have been that it was the presence of a nuchal cord rather than the location of the placenta that was having a negative impact on the fetus.

A later case-study reported by Collins on his internet site <http://www.preginst.com/case_study_3.html> showed a CTG (figure 2.4) from a fetus who was being closely monitored because of the presence of a double nuchal cord (diagnosed by ultrasound antenatally). The mother’s waking blood pressure was documented as 120/70mmHg however this had fallen to 98/53mmHg while she was sleeping. At 0340, a deceleration occurred similar in appearance to both figures 1.2 and 2.3. This led Collins to conclude “The possibility exists that circadian rhythms may be detrimental to the stressed fetus. In particular, maternal sleep may be associated with

maternal hypotension and fetal hypoxia.” He therefore surmises this may be particularly true for the “cord entangled fetus.”[89]

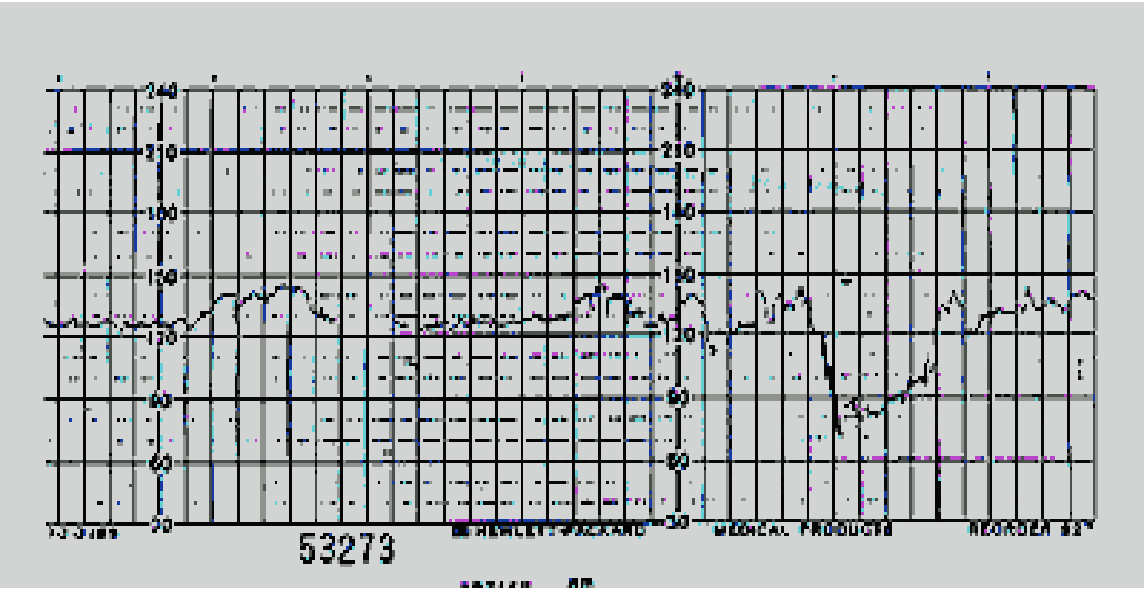


Figure 1.5 CTG fetus with double nuchal cord during maternal sleep. <http://www.preginst.com/case_study_3.html> Used with kind permission of Dr Jason Collins

Fundal placental location and pregnancy outcome

Two studies report the negative impact of a placenta located in the fundus. Davydov, Orlov, Samorodinova, and Khrustalkov,[90] investigated 2396 women examining the location of the placenta and the clinical course of labour. They described the location of the placenta as either fundal, uterine body or lower uterine segment. One of the factors they studied was the possible influence of placental location on the Apgar score. They found that there were no cases of a low Apgar score less than four in the lower uterine segment group. Whereas the higher the placenta was sited in the uterus the greater the incidence of an Apgar less than four occurring i.e. 0.6 percent in the uterine body group and 2.4 percent in the fundal group. Although this study did not distinguish between anterior or posterior located placental site it did demonstrate that a fundally located placenta could affect fetal well being.

Hadley, Main and Gabbe[91] reported from a case-control trial that women with a placenta located in the fundus carried a statistically significant increased risk of premature rupture of the membranes. They presumed that if the placenta was located fundally then this placed the weakest point of the membranes over the cervical os and predisposed women to premature rupture of the membranes with all the negative consequences that brings to poor pregnancy outcome.

The fundal placental position is also thought to delay placental separation time. Lurie, Gomel, Sadan, Ginath, Rotmensch, and Glezerman[92] evaluated the association between placental location and length of the third stage of labour. In a retrospective case-note audit they examined 200 consecutive singleton pregnancies for length of third stage. They found a significant correlation between fundal placental position and longer third stage of labour. There was no statistically significant difference between the anterior and posterior placental groups.

These studies each showed the negative impact on a pregnancy of different placental positions however, the way in which the placenta functions can also influence pregnancy outcome.

Placentation

Since the placenta is the life support system for the fetus, placentation can affect pregnancy outcome. The ability of the placenta to supply all the nutritive needs of the fetus usually exceeds fetal demand. In fact studies have shown that the placenta can have substantial reserve. Mengert, Burchell, Blumstein, and Daskal[93] found the birth of a normal infant is possible after ligating arterial blood flow to the pregnant mother's pelvis and another study by Gruenwald[94] concluded that 25-30% of the placenta may be non-

functional after abruption without fetal death. Many midwives attending births would agree that a baby can be born alive and apparently well, with a placenta that has considerable infarcted areas and/or expansive calcification. One can only wonder then about the factors that come into play when the fetus does die due to apparently inadequate placentation. Although there are only a few published studies to support this, this literature review has suggested that placental position may be one of these factors.

Summary

This literature review has identified the fact that research into the effect of maternal hypotension in pregnancy has either concentrated on an acute hypotensive episode or looked at the influence of persistent maternal hypotension on fetal growth and/or premature birth. Whilst there is some German literature that is at least ten years old, only one published English study has specifically examined the possible significance of persistent maternal hypotension during pregnancy on the risk of stillbirth. Even this study does not examine hypotension in detail as only two diastolic readings are used.

This chapter also demonstrates that published literature contains scant research examining the possible effect of placental position on pregnancy outcome. Therefore, further investigation into maternal hypotension and placental position and its specific effect on stillbirth is warranted. The next chapter outlines how this research was designed.

Chapter 3 - Study Design

Introduction

In this chapter, the study design used in the research is outlined. Epidemiology as the underpinning discipline is presented and Case-control method described in detail. This is followed by an account of how it was used in this study. The development and piloting of the data collection tool is outlined. The chapter includes some discussion about the ethical considerations and problems which needed to be addressed prior to the commencement of this study.

The epidemiological approach

The word epidemiology derives from the word epidemic, which means that epidemiology might be broadly defined as the study of epidemics. However, epidemiology is better defined as "The study of the distribution and determinants of health-related states and events in defined populations, and the application of this study to control of health problems"[95] (p.29). This definition shows that the use of an epidemiological method for this study which was examining the distribution and determinants of risk factors for stillbirth is an appropriate choice.

Furthermore, a feature of epidemiological research is its focus on groups of people, or populations, rather than individuals. Friedman states “groups must be studied in order to answer certain important questions. These questions often relate to the aetiology and prevention of disease"[96] (p.1). Epidemiological studies are employed to improve humankind's understanding of both health and disease. This study focused on a group of people i.e. pregnant women in an attempt to understand more about what causes stillbirth and therefore, fitted well into an epidemiological approach.

The discipline of epidemiology uses methods and concepts employed in studies arising from a number of different sciences including, but not limited to: ecology, immunology, toxicology, pathology, demography, social and behavioural sciences, and biostatistics. Although researchers in these fields contribute to studies other than those that are epidemiological, epidemiologists use techniques from these fields within an epidemiologic approach. Thus, a clinician and an epidemiologist describe the same disease from different viewpoints e.g. a clinician would describe pregnancy induced hypertension (PIH) in terms of its signs and symptoms whereas an epidemiologist would describe it in terms of its prevalence, or demography. Thus, this research examined stillbirth from an epidemiological rather than a clinical or experiential point of view.

Uses of epidemiology

Morris[97] (p. 262-3) identified seven uses of epidemiology. A study may be *historical* in nature which may serve to show the "rise and fall" of health and diseases over time. An epidemiological project may focus on *community diagnosis,* identifying health problems in a specific community or it might look more specifically at an *individual's chances* within that community of morbidity and mortality and the likelihood of avoiding disease. A study may investigate the *working of health services* to identify if all needed services are available, accessible and utilised appropriately. An epidemiological investigation may *complete the clinical picture* of a chronic disease by identifying previously unknown elements of the disease or it may serve to *identify a syndrome* by *lumping together or splitting apart* already known signs and symptoms to assist medical science to define new syndromes. Finally, epidemiology may be used to seek to *identify causal or risk factors* for disease. The focus of this research was on the latter.

Aims of an epidemiological study

One of the aims of this thesis was to identifying contributing factors to stillbirth. This aim is in agreement with the second of Friis'[98] identified aims of an epidemiological study as outlined below.

- To describe the health status of populations
- To explain the etiology of a disease and/or a phenomenon by discovering causal factors as well as to discover modes of transmission
- To predict the occurrence of disease to estimate the actual number of cases that will develop as well as to identify the distribution within populations
- To control the distribution of disease this involves prevention, eradication and thus prolongation of life (p.8and 9).

Friis also suggests that epidemiology has "two goals", firstly to improve "understanding of the natural history of disease" which will lead to the second goal of "intervention" and prevention. This goal is in keeping with the objective of this study, namely to improve understanding of stillbirth with a view to informing clinicians about another risk factor for stillbirth, leading to a change in practice which may in turn reduce the incidence of fetal death.

Epidemiologists have used these goals and developed epidemiological methods which have informed practice change over many hundreds of years.

A short history of epidemiology

Epidemiological thought has been in existence for many centuries dating back to Biblical times. In the book of Daniel,[99] Daniel conducts a rudimentary case-control study by asking an official of King Nebuchadnezzar's court if he and his Jewish countrymen could be given different, "non-defiling", food from the court servants, for a period of ten days prior to the steward examining them to determine if he could detect differences in their health. At the end of the ten days, they were in fact noticeably healthier than the young men who had eaten only the "royal" food.

Hippocrates too was known to be an epidemiological thinker. He shied away from prevailing beliefs that diseases were caused by the "wrath of Gods" or "bad air" and suggested that disease might be associated with his physical environment, citing water source and changes in seasons as likely origins of disease.[100]

The word epidemiology itself is thought to have been first used in the late sixteenth century by a Spanish Physician, Angelerio, who wrote about the plague in a study titled "Epidemiologia".[101]

In 1662, John Graunt, published "Natural and political observations made upon the Bills of Mortality",[102] making him the first epidemiologist to use statistical methods to describe populations.

Many epidemiologists consider John Snow to be the 'father' of modern epidemiology. This is because in 1854 he was the first to conduct an epidemiological study by collecting data about sources of drinking water and then relating these water sources to the outbreak of cholera in certain districts of London. He found that people accessing water from water companies who supplied water from pumps contaminated by sewerage were more likely to develop cholera than those whose water source was clean.[103]

One of Snow's contemporaries, William Farr, also contributed to modern epidemiology as he is considered by many to be the 'father' of modern biostatistics. In his epidemiological text Last claims that Farr "defined and clarified many basic concepts of vital statistics and epidemiology" this included "the concepts of retrospective and prospective study"[95] (p.28).

Another prominent 19th Century epidemiologist was Ignaz Semmelweiss who established that hand washing prevented puerperal fever. He noticed that women recovering from childbirth in maternity wards tended by medical students and doctors were much more likely to die from puerperal fever than women in maternity wards, who were cared for only by midwives and the incidence of puerperal fever was lowest in those women who had delivered in the street! He rejected the widely held belief that the women died because their modesty had been "offended" by birthing in the presence of men and hypothesised that doctors and medical students who attended women straight after performing autopsies without washing their hands, were transmitting "cadaverous particles" to the women, causing them to die. He tested this hypothesis by introducing the practice of enforced hand washing for all and the death rate for puerperal fever fell to unheard of low rates in his hospital.[104]

Early epidemiologists studied epidemics caused by infectious disease, however since the 20th century and the 'conquering' of infectious diseases by vaccination and antibiotics, epidemiological research has branched into all areas of human understanding of health and disease. For example, the Framingham heart study, which began in 1949, remains one of the groundbreaking works on the causes and risk factors associated with coronary heart disease.[105] Other epidemiologists such as Doll and Hill were the first to establish a causal link between smoking and lung cancer by studying the distribution of cigarette smoking between sufferers of lung cancer and people (controls) who did not suffer from this disease.[106]

Reproductive and perinatal epidemiological studies have also proliferated since the mid-19th century and span a wide area of research. Perinatal epidemiologists have studied behavioural, environmental and health care risks to reproduction for both women and

their babies. Using randomised controlled trial, investigators have established the evidence base for modern antenatal care e.g. Laurence and others suggested that folate treatment before conception prevents recurrence of neural tube defects.[107] Using case-control studies researchers have established links between such things as congenital cataract and rubella[108] and the antenatal exposure to x-rays and increased risk of malignant disease in childhood.[109] Through cohort studies epidemiologists can follow large populations over a long period of time. As already mentioned the Framingham heart study is one such enquiry, the 1958 British cohort study is another study tracking subjects born in one week in 1958 and following their physical, educational and social development over decades up to and including today.[110,111]

Whilst one single outstanding event, such as the one which lead Gregg to the discovery of a causal link between Rubella contracted by the mother during pregnancy and congenital cataracts,[108] makes the job of an epidemiologist relatively easy, more often than not there will be a web of causative and contributive factors to any given occurrence or condition making an epidemiological study a challenge for the researcher.

Epidemiology as the underpinning discipline

This study used an epidemiological paradigm because it sits well within Morris' identified uses of epidemiology and Friis' aims and goals as outlined earlier. It also fitted with how epidemiology has been historically used to identify previously unknown causative factors of disease as many of the determinants of stillbirth are yet to be clearly understood and the distribution of maternal hypotension and posterior location of the placenta within the pregnant population is largely unknown.

Observational and experimental epidemiology

There are two broad approaches within an epidemiological study. These are either an observational study, where the investigator does not deliberately intervene to determine the nature or extent of exposure, or an experimental study where the purpose of the study is to intervene in order to investigate the nature and extent of an exposure.

Experimental studies

RCT's

Randomised controlled trials (RCT's) are the main type of experimental epidemiological study. In such a trial, subjects are randomly chosen from the population under investigation, subjects are further randomised into a group which will receive some kind of intervention and those who will not. Sometimes an RCT becomes a crossover study, where subjects randomised to the control group and the intervention groups are *crossed-over* at a certain period in the trial when they swap treatments or interventions. RCT's and crossover trials are particularly suitable for drug or new-treatment trials.

Schlesselmann explains why experimental epidemiology is not usually suitable when studying disease aetiology in humans. "Although the experimental method is unquestionably the most incisive approach to a scientific problem, ethical or logistic considerations often prevent its application to the study of disease in humans"[112] (p.ix).

An experimental method was not used for this study because there was no intervention involved. Furthermore, both ethical and logistic considerations were prohibitive e.g. it is not possible to randomise women to experience a stillbirth.

Observational studies

Cohort studies

The term cohort refers to a group of people who are the subject of a research study. A cohort is usually chosen because the people in it have something in common , such as;

- were all born within the same time period
- may all either be free from, or suffer from the disease under investigation
- may, or may not, have a specific risk factor or risky behaviour
- may or may not be under treatment which is under investigation[112] (p.10).

In a cohort study, a population is studied prospectively i.e. over an interval of time. The investigators apply some kind of monitoring (i.e. interview, questionnaire, or physical examination) to the participants at certain stages during the study period. One advantage of this kind of study is that randomisation is not required. Thus this method avoids the ethical problems a RCT would have of randomising a woman to experience a stillbirth. However, a disadvantage of this type of design is that huge numbers of people need to be followed up over a period of several years before there are sufficient numbers in the study to give significant results. This disadvantage meant that a cohort study was unsuitable for this investigation as a Ph.D. has a definitive time limitation.

Case-control studies

In a case-controlled study a population is chosen and from it subjects who have a disease or an outcome of interest (cases) are selected along with a group of otherwise similar people who do not (controls). The investigator then looks retrospectively at the 'exposure' levels of the two groups with respect to the 'risk factors' for the outcome under study. This study design is depicted in figure 3.1.

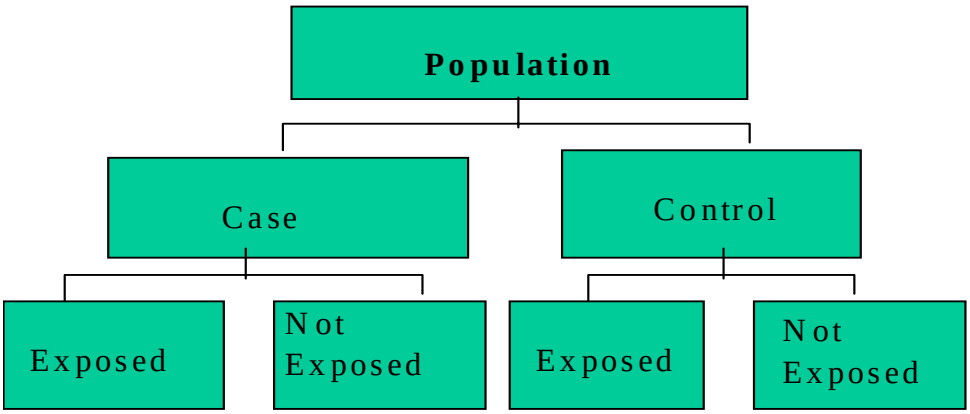


Figure 3.1 Case-Control Study Design

Why case-control?

Schlesselmann[112] indicates why case-control is an important tool for the epidemiologist.

> "Even although laboratory investigations may suggest that certain environmental, genetic, or behavioural factors alter the risk of disease, an observational study is often necessary, not only to establish the connection beyond reasonable doubt, but also to quantify the magnitude of the risk involved. In this regard, the case-control method is an important technique of epidemiologic investigation" (p. ix).

Case-control methodology was considered appropriate for this study because subjects who had a stillbirth could be readily identified within a birthing population and women who had a live birth could serve as controls. The investigator had the means to look retrospectively at pregnancies utilising case-note audit to establish exposures, which in this study were maternal hypotension and location of placenta. Also, other researchers view case-control studies as an ideal method to investigate antepartum fetal death because of its rigor and ethical safety.[113-115]

Advantages of case-control

Case-control methodology is ideally suited to studying the relationship of possible risk factors with rare outcomes. The incidence of stillbirth in South Australia is approximately 8:1000,[43] meaning that to gather information from just 250 stillbirths one would have to prospectively follow at least 25,000 pregnant women. The expense, time and money involved would render such a study prohibitive by any other method. Schlesselmann[112] summarises other advantages of Case-control studies as:

- usually relatively quick to mount and conduct and are therefore relatively inexpensive
- existing records can be used
- there are no physical risks to subjects associated with some experimental studies
- allowing the study of multiple potential causes of disease (p.18).

Each of these advantages made case-control a most suitable method for the purposes of this study.

Disadvantages of case-control

Schlesselmann[112] summarises the disadvantages of Case-control studies as:

- Relies on records for information on past exposures
- Validation of information is difficult or sometimes impossible
- Control of extraneous variables may be incomplete
- Selection of an appropriate comparison group may be difficult.
- Rates of disease in both exposed and unexposed individuals can not be determined.
- Method relatively unfamiliar to medical community and difficult to explain.
- Detailed study of mechanism is rarely possible (p.18).

Each of these disadvantages was taken into account, but none were thought to be a reason for not choosing case-control as the study method in this case. However, the way in which each disadvantage was addressed is discussed within the study design below.

The Study Design

According to Schlesselmann[112] planning for a case-control study involves defining the disease or outcome of interest, identifying a source from which the cases will be obtained, and establishing rigorous selection and exclusion criteria for both cases and controls. Each of these steps is described in detail below.

Definition of cases

Sometimes the definition of cases in a case-control study may be problematic, this is because certain diseases can either be difficult to define, hard to diagnose, range in severity or the diagnosis itself may be subjective. However, in this case the definition of a stillbirth was both objective and clear and is the one used by the South Australian Perinatal Outcome Unit,[2] namely:

> "birth of a fetus at or after 20 weeks gestation and/or with a birthweight of 400g or more, with no signs of life at birth." p.48

Source of cases

When considering the source of the cases South Australian perinatal outcome information was consulted.[116] Over the five-year study period in South Australia the number of births each year totalled approximately 18,000 with the metropolitan maternity teaching hospitals responsible for about 50% of these births. The State's largest maternity hospital is a tertiary referral centre and in 2001 (when the study was being planned) 22.6% of all births occurred at the hospital. The next largest maternity hospital in 2001 cared for 12.3% of the women who gave birth in this State.

The number of births was the deciding factor in choice of source of cases because stillbirth is a relatively rare event e.g. there were only 120 stillbirths in the State in 2001. Therefore, the largest maternity hospital was the logical choice for a source of cases.

The cases for the study were drawn from the Clinical Information Service (CIS) perinatal database maintained at the participating hospital. Permission to use these data was applied for and granted by the hospital research ethics committee (HREC) (see Appendix 1).

All cases with a discharge diagnosis of stillbirth over a five-year period ranging from April 1, 1997 to March 31st 2002 at this hospital were identified and considered as cases for inclusion in the study. This time period yielded 247 potential cases.

The following inclusion and exclusion criteria were then applied:

Inclusion criteria

All of the identified cases were considered as potential cases. Some studies at this point may narrow their study population further by focussing on one group within that population e.g. unexplained stillbirth. However, it was not this study's hypothesis that the two factors under study are causative factors for any particular cause of death but rather contributory factors to overall stillbirth risk. Therefore, all eligible stillbirths, from whatever attributed cause, were included in this study.

Exclusion criteria

The following five exclusion criteria were applied to cases where the mother:

- Had a multiple pregnancy. As well as being a well-known risk factor for poor pregnancy outcome[117] a live born/stillborn combination would be too difficult to treat during analysis. There were four twin pregnancies excluded.

- Had not attended at least three antenatal visits before the stillbirth in order to establish enough blood pressure readings. Three potential cases were excluded for this reason.

- Had no ultrasound examination that recorded the position of the placenta. Although this was a theoretical exclusion criterion, cases that did not have a record of this examination filed in their notes also had other information missing as well (see below) hence no exclusions where made on this criterion alone.

- Had a fetus weighing less than or equal to 1000gms. However, if the fetus weighed less than 1000gms and had a gestational age greater than or equal to 27 weeks it was included in the study. Births below this weight and gestation represent less than one percent of all births,[43] and matching such a baby to a live born infant may have been very difficult. 143 such cases where excluded, the vast majority of these were around 20 weeks gestation making matching to a live born infant virtually impossible.

- Had scant, absent or large amounts of indecipherable data. 22 cases were excluded for this reason. Most of these women had received their antenatal care from either an Obstetrician in private practice or a General Practitioner (GP) sharing care with the participating hospital and there was consequently either no or minimal antenatal history included in the case notes. On two occasions, the medical record was missing.

Sample size

The sample size from the participating hospital after all exclusions numbered 75 cases. As this sample size was smaller than anticipated, a decision was made to increase the statistical power of the study by employing a 1:2 case to control ratio and another hospital was recruited. The first hospital was designated 'Hospital A' the second 'Hospital B.'

Rationale for choice of Hospital B

In 2003 the next largest maternity hospital in South Australia cared for only 2,180 or 12.3% of the State's births. It was anticipated that numbers of stillbirths from this hospital would be likely to be small. Therefore, a decision was made to locate a large tertiary referral maternity hospital interstate. Victoria has chosen because it is geographically the closest State to South Australia. In the State of Victoria in 2003, there were 63,549 births, 521 of these were stillborn.[118] The largest tertiary referral maternity hospital in Victoria was approached to participate in the study. This hospital became Hospital B.

An ethics proposal was submitted to the HREC at this hospital. However, members of the HREC were concerned about allowing a non-employee access to case-notes and approval was granted after it was agreed that a research midwife employed by the hospital would collect the data (see Appendix 2). The process of ethics approval is discussed later.

The same five year time period was used in Hospital B as Hospital A i.e. all cases with a discharge diagnosis of stillbirth ranging from April 1, 1997 to March 31st 2002 at this hospital were identified from that hospital's database and considered as cases for inclusion in the study. This time period yielded 399 potential cases.

Case selection Hospital B

The same inclusion and exclusion criteria were applied as already described above and the following exclusions were made

- 16 twin pregnancies.

- Fifty potential cases had less than three antenatal visits (many of these women had actually attended regular antenatal care but their hand held obstetric record had not been included in their hospital case notes).

- Three were excluded because they did not have an ultrasound examination

- Two hundred and seventy had a fetus too small or too immature to include in the study.

- Two of the medical records were missing for the study period.

After these exclusions there were 58 cases from participating Hospital B. The combined total of participants, before selection of controls, was therefore 133.

Control group

The selection of controls is the most controversial aspect of case-control methodology. Here the purpose of control in a case-control study is given followed by a description of how the control group was identified for this study.

Purpose of control in a case-control study

In case-control studies, the purpose of the control group is to "provide an estimate of the exposure rate that would be expected to occur in the absence of a study disease-exposure association"[112] (p.76). Therefore, controls should be a selection from all the non-cases who were potentially at risk of the outcome (stillbirth) during the study period.

Definition of controls

The control group for this study gave birth to a live born infant at the same hospital as the cases. Early neonatal deaths (i.e. one occurring in the first few hours of life) were excluded from this group because it was considered possible that the variables under study could still have exerted an effect on this outcome.

Source of controls

Ideally, the control group should originate from the same population as the case population. Often case-control studies using hospital patients as a source of cases and controls can be problematic as the controls necessarily don't suffer from the disease under study but may suffer from others which can bias the study. However, in this study subjects attending the participating hospitals were all pregnant and hence the control population could be drawn from the same population as the case population with many of the same advantages of bias minimisation as a cohort study [119] (p.34).

The control group from Hospital A was drawn from that hospital's perinatal information database. A data file consisting of all live births from the same time period as the cases, apart from twin or higher multiples, were isolated and sorted into year of birth. Data were then further sorted into age of mother, gestation of pregnancy and gender of infant. Unit record (UR) numbers of the cases were then excluded from these data, as it was possible that the cases had experienced both a live birth and a stillbirth over the five-year period of the study. Whilst it is theoretically possible to include the same person as both a case and a control in a case-control study [120] this was avoided because it could have been a contentious point later. For the same reasons, once the control was selected her linking UR was removed from the database making it impossible to select her twice to control for

two different cases. When all the sorting and exclusions were completed, the controls were hand selected from the database following the matching criteria outlined below.

Controls from Hospital B were also selected from that State's perinatal database (PDCU). Matching criteria from each case were sent to the data base manager who generated a list of Hospital B unit record (UR) numbers for three potential controls. Whilst only two matched controls were needed for this study, it was considered likely that a selected control's case notes may not contain all the inclusion criteria study variables, especially if the woman had been referred to the tertiary referral centre after receiving the bulk of her care elsewhere. Therefore, one extra potential control was identified for each case so that in the event that this occurred another control would be readily available. However, on three occasions all three of the controls were not suitable and on five occasions only one matched control was identified. No further controls could be identified and the number of cases with two matched controls from Hospital B was therefore further reduced to 49. A decision was made to identify the five cases with one control within the data set, to enable them to be excluded if necessary, and use these data. This made the total number of cases 124, controls 243 and the entire study population 367.

Matching

In a case-control study, the controls should be as close a match as possible to the cases with respect to known risk factors for the outcome under study so that differences between the two groups may be considered to be due to the variables under study[112] (p.105). Matching is undertaken in case-control studies in order to address confounding. Confounding occurs when the differences between the case and control groups might arise because of other factors known to be strongly associated with the outcome of interest, in this case stillbirth. Such confounding factors may be age, race, gender, and

socioeconomic group. Researchers usually match on variables that are known to be strongly associated with the outcome being investigated in the study i.e. known confounding factors. There are many such confounders for stillbirth however, caution needed to be taken when selecting matching variables because so-called 'over-matching' may have the affect of nullifying the effect of the risk factor under study. Once matching has occurred it is impossible to assess the matching variable's impact on risk of stillbirth. Furthermore, if too many variables are chosen for matching, it may be impossible to find a match especially if the source population is small. If this situation occurs then statistical power can actually be lost especially if the matching variables are not strongly associated with stillbirth[119] (p.44-47). Bearing each of the advantages and disadvantages of matching in mind four matching criteria were chosen; infant gender, maternal age, gestation of pregnancy and year of birth.

Infant gender: exactly matched.

The gender of the baby was exactly matched as perinatal outcome does differ according to the gender of the baby. It is well known, for instance, that female babies survive better than male babies.[121] Another good reason for matching on gender is that male and female babies have different birthweight patterns and each has their own centile charts.[36]

Maternal age: matched +or- 5 years

It is accepted that maternal age, influences perinatal outcome.[122] Furthermore, it did not make good sense to compare, for example, the pregnancy of an 18 year old with a 42 year old as there are likely to be many more potential confounders which might come into play if such a comparison were attempted. This was an important consideration for this study because it is well known that blood pressure increases with age.

Gestation: matched + or - 2 weeks

Estimated date of confinement (EDC) is almost always considered to be inaccurate, apart from a pregnancy where the date of conception is known, such as pregnancy which has resulted from assisted reproduction. Ultrasound is only usually considered to be accurate to plus (+) or minus (-) one week. Furthermore, it was recognised that matching for gestational age in a study where the cases were stillborn was problematic because some babies may have died several days or even weeks before their birth. For example, a baby who died *in utero* at 34 weeks and was stillborn at 36 weeks would be considered to have a gestational age of 36 weeks. Since comparing a baby stillborn at 40 weeks with a 30 week live born infant or vice versa does not make good sense an attempt to match on gestational age, albeit coarsely, was still made.

It was determined by the researcher and her supervisors that the documented gestation at delivery was likely to be inaccurate. Hence, matching was attempted plus or minus two weeks from the gestation at delivery meaning that the cases and controls were most likely all born within three or four weeks gestation of each other. This takes into consideration babies who had died days or weeks before their stillbirth.

Year of birth: matched + or - 2 years

Standards of diagnosis and data recording may have changed over the five-year period of the study. This is particularly true of ultrasound technology, which continues to develop at a very rapid pace. It is also important that the time frame during which a subject may become eligible to be a control should be the same time period as a person could have become a case.[123] Therefore, matching was attempted plus or minus two years from the case baby's date of birth.

Bias

A well-known disadvantage of case-control studies relates to their susceptibility to bias. Bias can occur when there is a flaw in research design or execution which then leads to the researcher making an incorrect assumption about the degree of association between the risk factor and an outcome[119] (p.125). Bias is most likely to be introduced to the study at the point that controls are selected. McMahon and Trichopoulos[124] outline four considerations for selection of controls which may help minimise bias:

- elimination of selection bias
- minimization of information bias
- minimization of residual confounding by unidentified or poorly measured variables (confounding by accurately measured factors can be controlled in the analysis.)
- maximization of statistical power under the limits imposed by validity requirements and logistical constraints (p. 236).

Each of these points are briefly discussed together with ways that they were addressed within the context of this study.

Selection bias

Selection bias occurs when there are differences between cases and controls occurring as a result of the method of participant selection. This may occur when subjects at greater risk of the outcome are allocated, for any reason other than chance, to either the control or case group.

One common selection bias is socioeconomic differences between groups. If such a group were over-represented e.g. a disadvantaged socio-economic group then the study may suffer from selection bias as indicated in figure 3.2.

The way that selection bias was avoided in this study was to select all possible cases and employ matching for the controls.

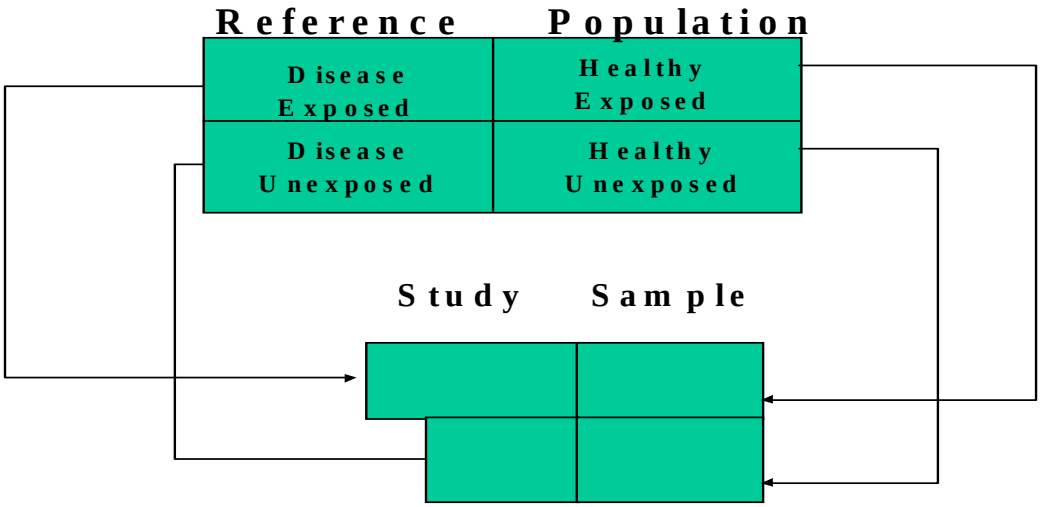


Figure 3.2 Selection Bias: one group (disease exposed) over represented in sample Adapted from Szklo & Nieto[119] (p.127)

Information bias

If the researcher tries harder to gather evidence of exposure in the case group than the control group this may lead to a distorted estimate of any relationship which is then detected between the exposure of interest and the outcome, and is known as information bias[123] (p.125).

As this study was retrospective the study variables were already recorded as an objective fact in the case-notes making it difficult for the researcher to intentionally collect data suggesting exposure in the case group as this would then have to be purposefully fabricated. Furthermore, the employment of an independent research midwife at participating Hospital B further reduced the likelihood of information bias.

Whilst it is true that the exposures of interest in this study are subject to human error and are therefore susceptible to inaccuracy it is also likely that the cases and controls should not substantially differ in accuracy of recorded blood pressure readings or placental position especially as the ultimate outcome of stillbirth was not known at the time of

these recordings. Thus, the recorded readings for the cases and controls should be equally biased. Therefore, any information bias should be randomly distributed between cases and controls in this study and is consequently termed non-differential misclassification bias. If non-differential misclassification bias is present in a study it is considered less of a problem because the researcher will tend to underestimate the 'relative risk' meaning that studies affected by this particular bias will tend to find no effect when perhaps there is one[119] (p.142).

Confounding

Confounding occurs when an extraneous or third variable, other than the exposure and outcome variable, is not randomly distributed between the case and control groups thus misrepresenting any relationship which may have been found between the exposure and outcome of interest[119] (p. 177). This relationship is graphically depicted in figure 3.3.

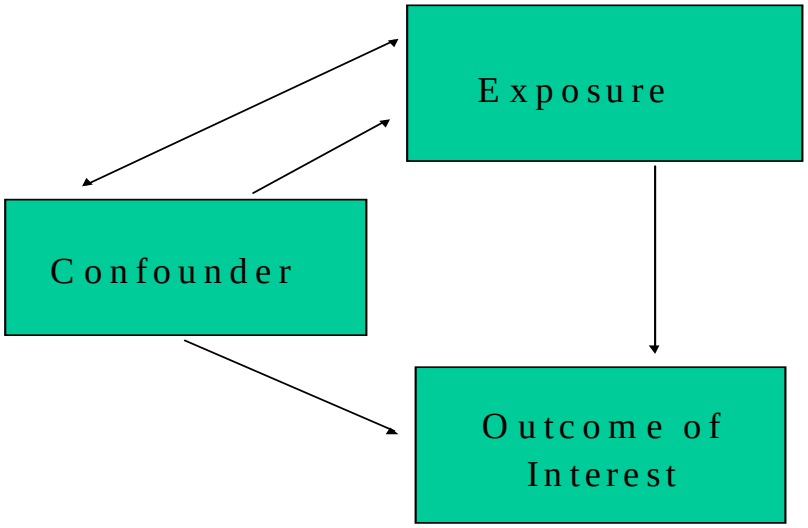


Figure 3.3 Confounding: Unidirectional lines indicate a causal relationship. Bi-directional arrow indicates a non-causal relationship and the dotted arrow indicates the study question. Adapted from Szklo M, Nieto J [119] (p.180)

Confounding can only occur when the third variable is related to both the exposure and outcome variables e.g. maternal age. The confounding may mask or hide a true

relationship (negative confounding) or exaggerate or create a relationship (positive confounding) which is not actually present. Confounding may occur during the design, data collection or analysis of a study. Therefore, researchers should be aware of potential confounding factors and if possible take steps to counteract the influence of these at each stage of a study. Whilst it is impossible to eliminate confounding factors from epidemiological studies due to the fact that people differ from each other in all kinds of ways both known and unknown, steps taken to avoid or limit confounding for the purposes of this study included:

- matching for known common confounding factors i.e. gender of baby, age of mother, gestation of baby, to ensure that the potential confounding variable is present to the same extent in the case and the control group.

- identifying potential confounders during literature review which need to be subject to modelling during analysis by logistic regression e.g. race, body mass index of mother (BMI), gravidy and parity of the mother.

- maintenance of the matched pairing during certain stages of the analysis phase of the study ensuring that each woman is compared to her specific matched controls.

Statistical power

Chance plays a part in the interpretation of all research i.e. all measurements are subject to variation due to chance alone. The power of a study is concerned with whether there were sufficient subjects to ensure that the findings were not attributable to random variation i.e. that the researcher did not make a type I or II error.

Type I and Type II errors

Ascribing meaning to an apparent difference between the case and control groups when that difference arose due to chance alone is known as making a type I error. If a difference does exist between the two groups but is not detected, then this error is known as making a type II error[125] (p.278). The main reason why a researcher makes either of these errors is due to sample size e.g. suppose a researcher planned to examine a group of 100 pregnant women in a room, 50 of these women were hypotensive and 50 normotensive. If the first eight women the researcher examined were all normotensive and the researcher stopped the research at that point assuming that all the women in the group were normotensive, the researcher would make a type I error. If on the other hand there were 75 normotensive women and 25 hypotensive women in a room and the researcher examined only eight women from that group finding that four were normotensive and four hypotensive then the researcher may assume that the mixture in the room is an equal number of normotensive and hypotensive women when in fact it is not; a type II error is made. In each of these examples, as more and more women are studied it would become increasingly likely that the researcher would see the actual relationship emerging. Thus, the larger the sample size (i.e. the more women in the room) the larger the anticipated size of the effect, (the mixture 50:50 or 75:25 is the effect size) the greater the power (the power calculations related to this study are given when discussing statistical analysis later).

Choice of retrospective case-note audit

A case-control study commonly involves some type of interview process. For example, in Herbst, Ulfelder and Poskanzer's[126] seminal study on diethylstilbestrol (DES) and early onset vaginal cancer, the investigators interviewed both the case and the control mothers

thereby establishing that seven of the eight case mothers had taken DES whereas none of the 32 control mothers had taken this drug.

Interview as a data collecting process was ruled out for this study and a case-note audit method used instead for a number of reasons. The sensitive nature of stillbirth and the enduring nature of grief made it problematic to contact the women directly. In addition the women may not have, or may not still have the antenatal records that were needed. Furthermore, the researcher could avoid some problems typically associated with interviews e.g. the problem of recall bias which can occur when the investigator relies on the subject's memory of the events under study. This may occur when a case subject is more likely to recall exposure to a particular substance or event than an unaffected control, because he or she may be aware of antecedents to the disease under study whereas the control is either not interested in or is unaware of such factors and so may not recall exposure so readily. Finally, the objective nature of the data being collected suited collection via a case note audit. However, there are inherent advantages and disadvantages to use of existing information in case-notes:

Advantages of case-note audit

When the data already exist the researcher does not need to wait for the data to be generated which means that data collection is relatively fast and easy. In addition, data from what is a relatively rare occurrence can usually be collected in more detail. Finally, the subjects need not be directly involved, which is a distinct advantage in this study because recalling details of a pregnancy which resulted in a stillbirth could have been quite traumatic for the bereaved mother.

Disadvantages of case-note audit

Limitations of a case note audit include the fact that the data were originally collected for purposes other than for research means that the researcher has no control over the creation, saving or storage of the data nor the environment in which it was created. In addition, the investigation relies on raw data collected by someone other than the researcher. Data may have been recorded by different personnel using different instruments all with different habits and styles of reporting. Therefore, the data will be inflexible, as they may not be entirely in the form that the researcher wants. Furthermore, the conditions under which data were collected are unknown. Moreover, the records may be incomplete, difficult to understand, or some handwriting may be indecipherable and/or some relevant variables may not be included in the documentation at all or may not appear to be correctly recorded. These omissions and apparent mistakes can not be checked or corrected. Lastly, some variables may be under-reported e.g. cigarette smoking, drug abuse or history of termination of pregnancy.

When planning the study, these limitations were acknowledged and account was taken that the particular variables of interest as recorded in the notes were approximate rather than precise. This is chiefly because of 'observer variation'. e.g. placental position as determined by a number of different individual ultrasonographers may be considered to be somewhat subjective however, it was thought to be unlikely that any sonographer would have mistakenly recorded the position of a placenta as posterior when in fact it was anterior or vice versa. Therefore, the documented position was considered to be adequate for the purposes of this study.

Similarly, observer variation may be a problem for blood pressure recordings because individuals have their own idiosyncratic method of taking and recording blood pressure

including adherence to differing Korotkoff 'K' sounds (disappearance or muffling) and 'digit preference' or a propensity for rounding off to the nearest whole number or multiple of five or ten. However, determination of a trend was what was required for the purposes of this study and the recorded blood pressures were considered adequate to determine the existence of any such tendency. Nevertheless, it was considered important for the purposes of this study to define hypotension.

Definition of hypotension

In order to be objective and maintain rigour it was considered important for the boundaries for classification of hypotension to be chosen from previously published studies. However, all reported studies (as outlined in the literature review) had differing methods for determining hypotension. Three of the studies used three hypotensive readings to determine their hypotensive group[72,75,76] and so this study emulated these studies by also requiring three low blood pressure readings in order to classify a woman as hypotensive.

All studies that reported an association between hypotension and poor pregnancy outcome used differing classifications for hypotension. A systolic blood pressure of 110mmHg and/or DBP of 70mmHg was used in six published studies[50,72,73,75,76,79] with two studies further defining a "severe" hypotensive group as less than 100/60[72,73]. A choice needed to be made between following one particular study's method or using a combination of approaches. Rather than choosing between using systolic and/or diastolic readings as other studies have done, the mean arterial pressure (MAP) was used for this research. The rationale for this decision is outlined here.

Use of Mean Arterial Pressure (MAP)

Mean arterial blood pressure (MAP) has been used for many years in studies examining the affect of blood pressure on pregnancy, especially high blood pressure.[127,128] One such example is a study investigating the impact of high blood pressure in the middle trimesters of pregnancy on ultimate pregnancy outcome. An average MAP of 90mmHg or more was considered to place the women in a high-risk category for stillbirth and IUGR.[67] Mean arterial blood pressure has also been used in a study examining low blood pressure. For example Goeshen, Saling and Wiktor used MAP when examining the difference between normotensive and hypotensive women undergoing a "load stress test".[51]

Henry, Miller, Kelly and Champney, claim that the physiologic and pathophysiological implications of MAP are "well understood"[129] (p.55). They go on to describe MAP as being of critical importance because it is the cardiovascular variable which measures the effective pressure that drives blood through the systemic circulation. They also graphically describe what happens when MAP falls …"as the average pressure (MAP) drops, the driving force behind tissue and organ perfusion is diminished, which leads to decreased tissue perfusion with ischaemia and potential infarction or organ failure" (p.55). Whilst these authors are referring to more general organ failure one could easily imagine that this cascade of events following a drop in MAP could also effect placental perfusion and thus the fetus's blood supply.

Meaney E, Alva F, Moguel, Meaney A, Alva J, and Webel describe the MAP as of "physiologic and clinical importance" because it is a measure of perfusion pressure.[130] Henry et.al. have also argued that neither SBP or DBP alone are sufficient to indicate levels of tissue perfusion and that "protective autoregulatory mechanisms possessed by

organs such as the brain and kidney are sensitive to changes in mean and not systolic or diastolic pressures"[129] (p.55). As this study's premise was that maternal hypotension leads to poor placental perfusion and hence fetal hypoxia and demise, the MAP was considered to be a useful measure for the purposes of this study.

MAP calculation

In an informative scientific letter to 'Heart' Journal[130] Meaney et.al., define MAP as the term used to describe a "notional average" of blood pressure throughout the cardiac cycle (p.64). They give its traditional calculation as systolic blood pressure plus twice diastolic blood pressure, all divided by three (SBP+2*DBP/3). Whilst other alternatives to this traditional calculation have been suggested,[130,131] these have not yet won general acceptance and so were not used for this study.

Determining MAP for the study participants

Mean arterial blood pressure was used to determine the blood pressure category of all the study women. Due to the method of calculation MAP equates to a range of blood pressure readings. In order to clarify and depict this range visually a ready reckoner was constructed. If the woman had three or more MAP readings over the course of the pregnancy of less than or equal to 73.3mmHg then she was categorised as 'severely' hypotensive. This is indicated in the light blue area of figure 3.4 e.g. blood pressures of 90/50 and 110/55 both fall into this severely hypotensive range. Similarly three MAPs higher than 73.3 but less than or equal to 83.3mmHg were chosen to categorise the 'mildly' hypotensive group and blood pressure readings this range is indicated by the dark blue area in figure 3.4. Finally, women with three MAP readings of greater than or equal to 103.3mmHg indicated by the pink in figure 3.4 were categorised as hypertensive. Those women whose blood pressures fell between the mildly hypotensive group and the

hypertensive group, and who recorded less than three MAP readings in the ranges described above were categorised as normotensive and blood pressures in this range are indicated by the white areas in figure 3.4.

Mean Arterial Blood Pressure Ready Reckoner

Diastolic Blood Pressure \ Systolic Blood Pressure	90	95	100	105	110	115	120	125	130
40	57	58	60	62	63	65	67	68	70
45	60	62	63	65	67	68	70	72	73
50	63	65	67	68	70	72	73	75	77
55	67	68	70	72	73	75	77	78	80
60	70	72	73	75	77	78	80	82	83
65	73	75	77	78	80	82	83	85	87
70	77	78	80	82	83	85	87	88	90
75	80	82	83	85	87	88	90	92	93
80	83	85	87	88	90	92	93	95	97
85	87	88	90	92	93	95	97	98	100
90	90	92	93	95	97	98	100	102	103
95	93	95	97	98	100	102	103	105	107

Figure 3.4 Mean Arterial Blood Pressure ready reckoner. (all numbers have been rounded to the nearest whole number)

Developing and testing the data collection tool

A data collection proforma was developed in the following manner:

Accepted risk factors for poor perinatal outcome were identified. As well as searching published literature, two other sources were utilized. These were the South Australian State Supplementary Birth Record (SBR) (see Appendix 3) and Reports from the South Australian State Maternal, Perinatal and Infant Mortality Committee (MPI).

The SBR is a data-gathering tool which is used by the South Australian Perinatal Outcome Unit. This record is completed by midwives and/or neonatal nurses following each birth in South Australia. This data collection tool has been used over many years with some minor additions, alterations and updates.

Table 3.1 Data collection proforma risk factors and reason for inclusion

Risk Factor	Reason for inclusion	Reference
Placental Site	Study Variable	Lit Review
Cause of death	The cause of death may be influenced by the study variables	MPI
Autopsy	Information from autopsy including contributing factors found at autopsy will assist in confirmation of cause of the death.	MPI
Gender	There is a preponderance of males in perinatal deaths.	[121]
Infant Weight	Very low birth weight is associated with increased perinatal morbidity and mortality .	[132]
Condition of baby	Whether the baby is macerated or fresh may indicate the relative timing of fetal demise.	[133]
Liquor colour	The presence of Meconium Stained Liquor (MSL) is a predictor of poor perinatal outcome in both pre-term and term pregnancies.	[134] [135]
Nuchal Cord	The presence of a nuchal cord is risk factor for adverse perinatal outcome.	[136]
Estimated time of Death	Prevailing factors at the time of an antepartum death may be different from those of an intrapartum death.	[137]
Gestation at birth	Preterm birth is a known risk factor for both perinatal morbidity and mortality	SBR MPI
Estimated Blood Loss (EBL)	Studies suggest that hypotension may influence amount of blood lost at birth	[72,73]
Blood pressure	Study Variable	Lit. review
Race	Australian Aboriginal and Torres Strait islanders have an increased risk of poor perinatal outcome	SBR
Gravidy and Parity	Parity influences obstetric outcome	[138]
Outcome of last pregnancy	An history of previous spontaneous loss especially unexplained stillbirth may negatively affect the outcome of this pregnancy.	[139]
Number of antenatal visits	Poor antenatal attendance is associated with poor perinatal outcome.	SBR
Tobacco smoking	A known risk factor for perinatal morbidity and mortality. The Perinatal Outcome Unit have been collecting data on tobacco smoking since 1998.	SBR (since 1998)
Medical condition present	Establishes pre-existing medical conditions such as Diabetes and Asthma	SBR
Obstetric Complications	The existence of bleeding in pregnancy through TMC, APH, PIH, suspected IUGR, Gestational Diabetes etc. all are known to increase the risk of poor perinatal outcome	SBR
Hospital admissions	Establishes how well or otherwise the woman was during her pregnancy. Some studies suggest that hypotensive women have more hospital admissions	[72 73]
Maternal Weight and Height to calculate Body Mass Index (BMI)	Maternal underweight and obesity are obstetric risk factors. Also hypotensive women may be lighter and leaner then their normotensive counterparts making BMI a possible confounding factor.	[140]
Blood group	Included as it may be a possible confounder. A study has suggested that AB Blood group may be associated with pre-eclampsia.	[141]
Lowest (Hb) Haemoglobin	Haemoglobin concentration has been associated with increased stillbirth risk The lowest haemoglobin reading in the pregnancy is associated with an increased risk of perinatal death	[8,142]
Maternal Age	Teenagers and mothers older than 35 years are at increased obstetric risk.	[3,122,143]

The MPI report was established in 1985 and specifically examines data collected from the Births, Deaths and Marriages Registration division, the Coroner's Office as well as Hospital case incident reports and the Medical certificate of cause of perinatal death.

In order to avoid 're-inventing the wheel' the data collection proforma (see appendices four and five.) was largely based on the SBR. Factors chosen for investigation and reasons for their inclusion along with the relevant citation/s are included in table 3.1.

There were 26 factors identified. A double-sided data collection proforma was then created. One side consisted of maternal factors such as medical and obstetric conditions and the other side included infant factors such as gender and weight. Whilst individual blood pressure readings and placental position are not collected by the perinatal outcome unit, the proforma was quite deliberately made similar to the SBR with the view to making data collection easier.

When constructing the tool it was noticed that the SBR has changed somewhat over the five-year study period with, for example, 25 maternal factors collected in 1997 and 35 in 2001. Tobacco smoking status was not assessed until 1998 however, this was not thought to be a problem, as this information generally would still form part of the antenatal record.

Piloting the tool

The draft data collection proforma was then pilot tested to determine if the data required were easily accessible and transferable. Early in the data collection phase the data collection tool was used by one of the supervisors and the data collected were compared with those of the researcher to determine the reliability of the proforma. Data were collected from the same three sets of case notes and it was found on comparing data

collected that researcher and supervisor were 100% in agreement with data extrapolated from case notes. This test confirmed the reliability of the tool.

Classification of cause of death

All except one of the variables collected were objective and therefore incontestable e.g. gender of the baby. However, the classification of the stillborn infants cause of death, involved some subjective decision-making. Therefore, the method used to determine the cause of death will be outlined here.

There is currently no international consensus on the classification of causes of perinatal death.[16] In the researcher's experience, making a decision regarding the probable cause of death can be somewhat problematic. This is because there is often scope to consider more than one factor as the antecedent cause of death and expert perinatal mortality committees often later change the cause of death attributed at the time of the stillbirth. When such committees are making a decision regarding cause of death, they consider the birth attendant's opinion, the perinatal necropsy pathologist's opinion, any relevant obstetric history and blood test pathology results, as well as drawing from their own expertise. Without the ability to confer with a panel of experts regarding each individual stillbirth's cause of death, the documented opinion of the pathologist who performed the autopsy was accepted as the probable cause of death. If no autopsy was performed the opinion of the attending midwife or obstetrician was considered, as well as results of any medical/pathological investigations that ensued. This was considered a satisfactory method of determining the cause of death, especially as this study aimed to examine all stillbirths from whatever cause and this variable was collected mainly for background demography of the case group.

When the data collection proforma was developed the categories for cause of death on the data collection proforma reflected those on the amended Whitfield classification (an obstetric cause specific classification). However, this scale has since been superceded by the PSANZ-PDC (Perinatal Society of Australia and New Zealand perinatal death classification). The PSANZ-PDC is somewhat more specific (with more subcategories) than the amended Whitfield and it focuses on the main obstetric antecedent i.e. the factor that precipitated the chain of events that ended in the baby's death. The main categories between the two remain very similar (see Appendix 6). It was therefore not considered necessary to change the categories for cause of death on the data collection proforma.

Ethical considerations

The National Health and Medical Research Council (NHMRC) provide extensive guidelines for conduct of Human Research Ethics Committees (HRECs). One of these guidelines states “An HREC must ensure that it is sufficiently informed on all aspects of a research protocol, including its scientific and statistical validity, that are relevant to deciding whether the protocol is both acceptable on ethical grounds and conforms to the statement”[144] (Section 2.8). In keeping with this standard, the HRECs from both Hospital A and B evaluated this research proposal's scientific and ethical rigor.

The method used to determine the scientific rigor of this study differed between the two participating hospitals. Hospital A sent the proposal to an expert for assessment and comment. This person suggested many changes and made several recommendations for improvement of the research's scientific validity such as changing the method from case study to case-control. Hospital B employed a separate scientific committee to evaluate the research. This committee extensively scrutinised and modified the proposal with particular attention to minor detail over a period of many months. After this scientific

review, the ethical attributes of the proposal were then considered by each hospital's HREC.

The main ethical issue these committees considered was protecting the participant's rights to privacy. As this study involved retrospective audit of medical records, the researcher would ordinarily be required to obtain individual patient consent before accessing each of these records. However, NHMRC Guidelines provide a framework to allow HREC's to grant a researcher access to personal information without consent under section 95 and 95a of the Commonwealth Privacy Act 2001when it is:

- Not practical to seek consent
- De-identified information (such as is available in existing data bases) will not achieve the purpose of the research
- Expected benefits of the research outweigh possible risks of a breach of privacy[144]

There was therefore an obligation to prove to the HREC's involved in granting approval under these guidelines that each of these criteria was met. The supporting argument for employing this guideline is outlined here.

The researcher considered it was not practical to seek consent from the individual women for two reasons:

The sensitive nature of stillbirth and the ongoing nature of grief would probably mean the mother who has experienced the stillbirth might suffer further trauma as a result of contact to request consent to access her case-notes. This would be particularly true if contact was made around the time of an 'anniversary' such as the stillborn baby's birth, date of burial, family birthday's, mother's day, father's day etc.

Secondly, as the cases were chosen from a five year period around 40-50% of the families may have moved accommodation in that time[145] making it difficult if not

impossible to contact them all. If not all of the eligible women could be contacted then this could introduce a substantial 'selection' bias to the study. As the numbers in the study were already small, any further reduction would considerably reduce the rigour of the study.

The HREC's were informed that it was not considered possible to use de-identified information. This was because the data required, (blood pressure readings over the course of the pregnancy and placental position during the pregnancy) were only available in the women's case notes and did not exist in current perinatal databases elsewhere. Therefore, the study could not be done unless access to the case-notes was granted.

When approaching the participating hospital's HRECs it was argued that the expected benefit of this research outweighed any potential risks as this study could provide rigorously obtained evidence relating to an area in which little research has been undertaken to date. It was further argued that the study had the potential to both enhance scientific understanding of risk factors for stillbirth as well as to provide information for maternity care providers about the possible implications on pregnancy and birth of the presence of maternal hypotension and placental location. One possible outcome of such improved understanding may be better delivery of maternity health care services. Therefore, application for ethics approval was sought under section 95 of the Commonwealth of Australia Privacy Act on the grounds that, in the case of this research, the public interest in privacy is outweighed by the public interest in research.

Both committees also ensured that the principal investigator demonstrated in the study proposal that she had thoroughly perused and understood the appropriate privacy and medical record acts.

This entire ethical approval process took seven months in the case of Hospital A and 12 months for Hospital B.

After ethics approval was finally given, data collection proceeded using the data collection proforma.

Summary

In this chapter, the rationale for the selection of an epidemiological viewpoint and choice of a case-control study design, and case-note audit method was presented. A detailed description of the methods used to identify the cases and controls was given, including inclusion, exclusion and matching criteria as well as how consideration was given to bias minimisation. The development and piloting of the data collection tool was outlined. Finally, some of the ethical considerations for this study were identified. Preparing the data for analysis and results are presented in the next chapter.

Chapter 4 – Analysis and results

Introduction

This chapter first provides a summary of how data were prepared for analysis and the process of data analysis including the software used. Key statistical terms are defined and explained and the results of the data analyses are presented. Data analysis was structured around and focussed on each of the study questions and included the demographics of the study group as well as identifying differences and similarities between case and control women on each of the study variables.

Statistical analysis software

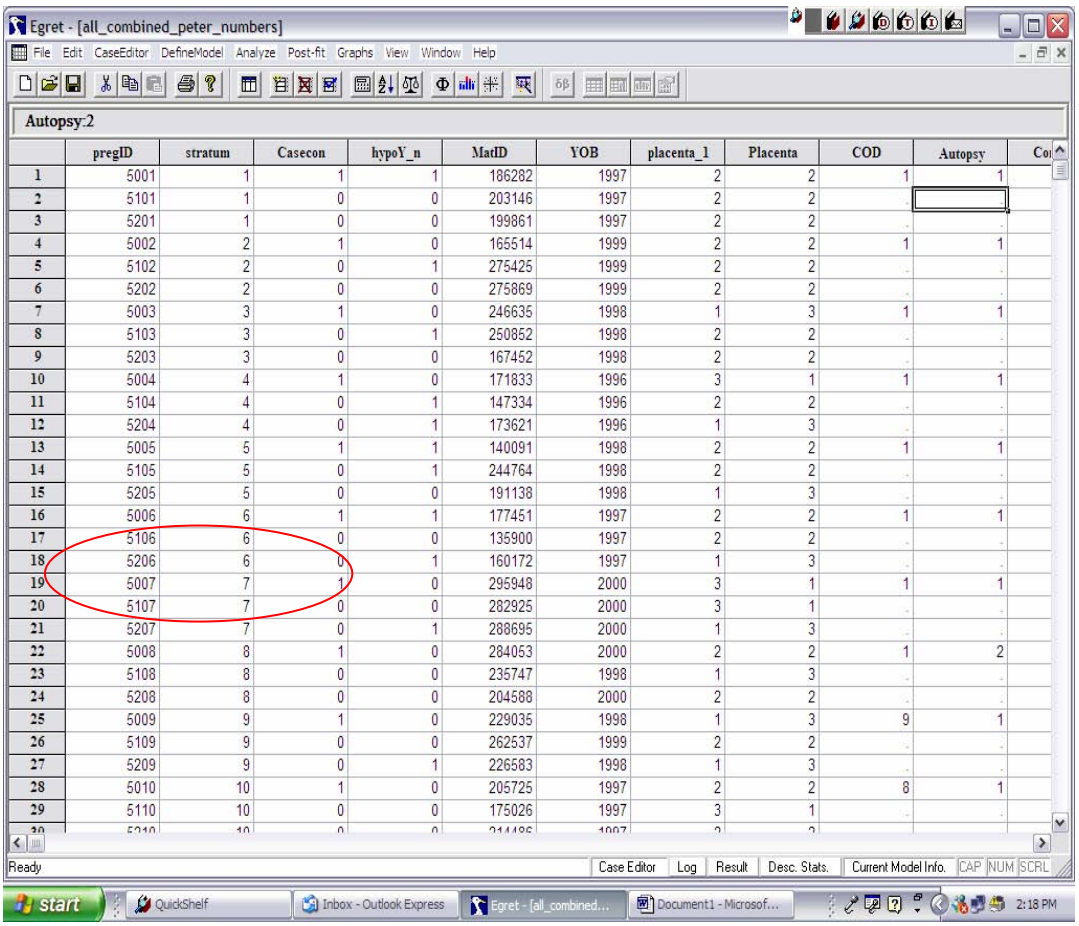
Egret for windows (Egret) is a statistical package produced by Cytel software (©1999) especially for epidemiologists and those conducting biomedical studies. Egret supplies a user-friendly spreadsheet environment with which to create, view, modify and analyse data. It was chosen specifically for this study because of its ability to handle the variable stratum size (largely two controls per case, but only one control per case in five cases) as well as conditional regression analysis. This type of conditional regression analysis is described later in this chapter.

Data entry

Initially data were entered directly from the data collection proformas into Egret. A 'case-editor' (spreadsheet) containing all variables from the data collection proforma was created. The variable headings were created to correspond directly with the study variables on the data collection proforma and the data codes were also directly entered into the case-editor. Additional variables were constructed at this stage specifically for the purposes of data analysis and are described here.

Variable Headings

A pregnancy identification number (PregID), stratum number (Stratum) and case control number (CaseCon) were all created and used in order to easily identify the source of the data (Figure 4.1). Details about how and why each of these variables was created follows:



	pregID	stratum	Casecon	hypoY_n	MatID	YOB	placenta_1	Placenta	COD	Autopsy	Co
1	5001	1	1	1	186282	1997	2	2	1	1	
2	5101	1	0	0	203146	1997	2	2	.	.	
3	5201	1	0	0	199861	1997	2	2	.	.	
4	5002	2	1	0	165514	1999	2	2	1	1	
5	5102	2	0	1	275425	1999	2	2	.	.	
6	5202	2	0	0	275869	1999	2	2	.	.	
7	5003	3	1	0	246635	1998	1	3	1	1	
8	5103	3	0	1	250852	1998	2	2	.	.	
9	5203	3	0	0	167452	1998	2	2	.	.	
10	5004	4	1	0	171833	1996	3	1	1	1	
11	5104	4	0	1	147334	1996	2	2	.	.	
12	5204	4	0	1	173621	1996	1	3	.	.	
13	5005	5	1	1	140091	1998	2	2	1	1	
14	5105	5	0	1	244764	1998	2	2	.	.	
15	5205	5	0	0	191138	1998	1	3	.	.	
16	5006	6	1	1	177451	1997	2	2	1	1	
17	5106	6	0	0	135900	1997	2	2	.	.	
18	5206	6	0	1	160172	1997	1	3	.	.	
19	5007	7	1	0	295948	2000	3	1	1	1	
20	5107	7	0	0	282925	2000	3	1	.	.	
21	5207	7	0	1	288695	2000	1	3	.	.	
22	5008	8	1	0	284053	2000	2	2	1	2	
23	5108	8	0	0	235747	1998	1	3	.	.	
24	5208	8	0	0	204588	2000	2	2	.	.	
25	5009	9	1	0	229035	1998	1	3	9	1	
26	5109	9	0	0	262537	1999	2	2	.	.	
27	5209	9	0	1	226583	1998	1	3	.	.	
28	5010	10	1	0	205725	1997	2	2	8	1	
29	5110	10	0	0	175026	1997	3	1	.	.	

Figure 4.1 Egret spreadsheet showing Pregnancy ID, Stratum, and Case Control number Identification of cases. Study number eight from Hospital A circled.

Pregnancy identification number (pregID)

A study pregnancy identification number was used to assist in easy identification of the source of all the pregnancies during analyses. All participants were allocated a four digit number. The first digit indicated the participant's participating Hospital. A five, (the Postcode for South Australia) indicated participants from hospital A and a three (the Postcode for Victoria) indicated the participants were from hospital B. Participants were further identified as cases or controls with the second digit 0 indicating a case, 1 the first

control and 2 the second. The last two digits were simply an indication of the sequence of recruitment within each hospital. For example, figure 4.1 shows how case number 8 from hospital A was allocated identification number 5008 with the first matched control for that case given number 5108, and the second for that case 5208. Thus, the pregnancy identification number was used to maintain the link between cases and their matched controls as well as to easily identify which data arose from each hospital.

Stratum

Before conditional logistic regression analysis could be performed, each case together with its matched control/s was allocated a unique stratum number. For example case number 8 from Hospital A as well as the first and second control matched to that case were all assigned stratum number 8 (figure 4.1). Similarly, participants from Hospital B were allocated a stratum number commencing at 100 (to distinguish between the two hospitals). Hence cases and controls from study number eight from that hospital were all allocated stratum number 108.

Case-Control number (CaseCon)

A case-control number (seen in the third column in figure 4.1) was also required in order for Egret to distinguish all cases from all controls. Each case (regardless of participating hospital) was assigned a one (event = stillbirth) and each control a zero (no event = live birth).

Maternal identification number (MatID)

A maternal identification number which coincided with each hospital's medical record number was used to link all data back to the original data source i.e. the case-notes. This was done in the event of any raw data needing to the checked against the original source.

Treatment of Study Variables

All of the variables listed on the data collection proformas were then entered in the same order as they appear on the proforma using the same codes as used on the proforma.

Treatment of Blood pressures

All recorded blood pressures from each pregnancy studied were used to establish the initial, minimum, average and last readings for both systolic (SBP), and diastolic (DBP) blood pressures as well as mean arterial blood pressure (MAP: rationale for this variable's inclusion is described later) and pulse pressure (PP) for each woman. The sum of hypotensive episodes recorded for each woman during the pregnancy was also calculated. Each of these readings became a separate variable in the Egret case-editor.

Data analysis process

Once all data were entered into Egret, analyses proceeded through five steps. These steps were derived from a chapter in Rothman and Greenland's text on how to analyse epidemiological data, namely:

1. Data editing
2. Data summary
3. Data tabulation
4. Data estimation
5. Data interpretation[123]

Each of these steps was applied to data analysis in this study and described here in further detail.

Data editing

Rothman and Greenland indicate the aim of data editing is to:

- Review raw data for accuracy, consistency, completeness
- Check the distribution of data

- Check for the impossible or unusual
- Check coding errors[123] (p.202).

Each of these aims was considered in the following manner. After entry into Egret, an initial univariate analysis on continuous variables was undertaken. This analysis included calculating each variable's minimum, maximum, range, median, mode, mean and standard deviation e.g. table 4.1. This simple data analysis enabled the data set to be checked. It was particularly easy to detect errors where the variables were outside the expected range e.g. if one antenatal visit was seen in the results depicted in table 4.1 it would be clearly an error as all participants were required to have three or more antenatal visits as one of the inclusion criteria.

Table 4.1: Example of initial univariate analysis (Hospital A data only)

Variable	Min	Max	Range	Median	Mode	Mean	SD
Wt/baby	400	4260	3860	2100	880	2202	1020
Gestation	25	42	17	35	38	34.4	4.6
AN visit	3	20	17	7	3	7	3.4
Wt/Mo (Kg)	46.5	144.5	98	64.35	66	71.9	23
Ht/Mo (cms.)	151	176	25	164	157	163.3	6.5
Age/Mo	17	42	25	28	28	28.5	5.36

Data which had been entered into the case-editor were then checked against the original raw data for accuracy of data entry. Coding and data entry errors, (such as those indicated above) were detected and corrected at this point. Some errors were also detected later as data analyses began e.g. equal numbers of male and female babies were expected in the data set as this was a matching variable but this was found not to be the case due to a data base coding error. The decision made regarding this situation is given later in this chapter.

Data summary

According to Rothman and Greenland[123] the aim of summarising the data is to examine the data distribution before more complex data analyses. (p210)

Many of the variables within the data set were most easily summarised in graph form. Therefore, bar graphs and frequency histograms were generated and examined.

The purpose of this was threefold

1. to guide the decisions about where to make more detailed data analysis

2. to establish what statistical tests were appropriate to use

3. to determine if the data required further summary e.g. if there were too many subcategories within a variable.

Some decisions regarding data analysis of particular variables were made as a result of this process. For example, when the graph for placental site was examined it was seen that placental site was mainly distributed between anterior and posterior therefore positions such as lateral and fundal were combined into an 'other' group.

Data tabulation

The next step in processing the data ready for analysis was data tabulation. Arranging the data into tables or lists also enabled a sense of what a particular data set was "saying" before launching a full scale conditional regression analysis[146] (p.180). Data tabulation for this study involved creation of contingency tables. Such a table usually consisting of rows and columns is often used in epidemiological studies to show the relationship between disease and exposure[147] (p.287). Creating a contingency table with other than nominal data necessitates some decision making about variable categorisation. Choices needed be made about how many categories to make and where the boundaries should be. These decisions should be made based on objective criteria prior to data analysis in order to avoid a 'gerrymander,' that is selecting the category range so the desired outcome is

seen[123] (p.206). One of these decisions involved deciding on the definition of hypotension as described in the previous chapter.

Data estimation

The final step in the data analysis process is data estimation. This was achieved in this study by a 'factor level summary'. This summary consisted of a simple sum of the categories analysed, as well as a percentage calculation and a simple odds ratio that did not take matching into account (see below). Producing this summary enabled the data to be examined to detect any deviations of interest. For example, the majority of the data set contained two controls for every case, therefore a 66/33 control to case ratio would be expected if there was no variation between the two groups on the variable under analysis. Whereas, if a different ratio was seen such as 50/50 or 90/10, then this was suggestive of a deviation within the data which may be of statistical or clinical interest. The factor level summary also guided which category to choose as the reference group to compare the data against within the conditional regression analysis.

Conditional regression analysis

Logistic regression analysis enables the researcher to assess the association of the prognostic factors modelled in the analysis e.g. between blood pressure and stillbirth. A special logistic regression analysis is used for matched case-control studies namely conditional logistic regression. Conditional regression analysis keeps track of which case is matched with which control[146] (p.179).

Epidemiologists would argue that conditional logistic regression must be estimated whenever matching has been used. The implementation of conditional logistic regression in Egret was particularly useful for the purposes of this study because there were five

case women who only had one matched control available and Egret can handle such mixed matching.

After conditional regression the results were expressed in statistical terms e.g. Odds Ratios (OR), confidence intervals and p-values. In order to assist interpretation of the results these terms need to be understood and so are defined and explained further here.

Odds and Odds Ratios (OR)

The odds of an event is the probability of that event happening, p, divided by the probability of that event NOT happening, i.e. 1-p.

$$\text{Odds} = p/(1-p)$$

In an epidemiological context, the nature of the 'event' depends on the design of the study. For example, in a prospective study of stillbirth, pregnancies would be identified and followed to the event of stillbirth itself, and interest is focused on the odds of a stillbirth, given exposure to, say maternal hypotension. This thesis, however, uses a retrospective (case-control) design – in which cases of stillbirth were identified first, and the medical records of the cases and their matching controls were examined retrospectively, to determine whether the 'event' of being exposed to maternal hypotension had occurred.

In this case if there was no relationship between stillbirth and hypotension then one would expect the odds of exposure to maternal hypotension among stillborn babies to be the same as the odds of exposure to maternal hypotension in live babies. In other words the odds ratio (OR) is defined as; Odds ratio (OR) = (*odds* of a stillborn baby being 'exposed' to maternal hypotension) / (*odds* of a live born baby being exposed to maternal

hypotension) would have a value of 1. If on the other hand there was twice the odds of exposure to maternal hypotension in the stillborn group then the OR would have a value of 2. Conversely if there was one half the odds of exposure then the OR would be 0.5.

Confidence interval (CI)

The confidence interval (CI), usually written as 95 percent CI, gives the range in which the researcher is 95% confident the 'true value of association' lies [123] (p.183). In the case of this study for example if the odds ratio was three and the 95% CI ranged between two and four. The researcher could say, with 95% confidence that the 'true' odds ratio was bracketed between two and four.

A confidence interval for an estimate of an odds ratio that contains the number one implies that the odds ratio is not significantly different from one. This means, for example, that if the odds of a stillbirth occurring in the unexposed control group and the unexposed case group were not statistically significant from one another then the CI would include the number one, whereas a CI which does not encompass the number one implies the odds are significantly different.

p-value

A probability (p) value can be defined as "a continuous measure of compatibility between an hypothesis and data"[123] (p.186). In other words, the p-value is a measure of the probability that an observed difference between two groups involved in a study might have occurred by chance. The lower the p-value, the less likely it is that the observed affect occurred by chance. Many researchers choose an arbitrary cut off value of $p < 0.05$ to indicate such a low level of compatibility. This p-value indicates that the likelihood that chance alone was responsible for a result is less than five percent. If results show a p

value of $p < 0.001$ there is less than one in a thousand chance of this result being due to chance and the result is therefore considered to be highly statistically significant.

P-values can be considered somewhat misleading if too much emphasis is placed on them because there is always the chance that the improbable has in fact occurred and also p-values close to statistical significance should not be discounted out of hand especially if the findings are of clinical interest.

Correlation Co-efficient

In their text "Making sense of data"[148] Abramson and Abramson define a coefficient as a measurement of the linear relationship between two variables. They go on to explain that " A coefficient of 1 means that a higher value of one variable is always associated with a higher value of the other, and a coefficient of -1 means that a higher value of one is always associated with a lower value of the other" (p.236). In the case of this study, when a strong positive coefficient was seen then the risk of stillbirth was great whereas when a negative coefficient was seen there was a greater incidence of this variable in the live born controls than the stillborn cases.

Abramson and Abramson also give a "rule of thumb" for strength of correlation, namely:

Strong Correlation	>0.8 (or < -0.8)
Moderate Correlation	0.5-0.8
Weak Correlation	0.2-0.5[148] (p.236).

Standard Error (Std. Error)

Standard Error is a measure of the variation around any statistical estimate. It is similar to the standard deviation from the mean but in this thesis it is used to estimate the standard error of the odds ratio.

Each of these data estimation tools were used, sometimes singly sometimes together, to analyse the data. However, the data analyses were guided by the original study questions.

Answering the study questions

In order to answer the study questions data analyses began with identifying the demographics of the study group, then moved to identifying any differences between the stillborn and live born cohorts on all study variables, before addressing each of the study questions themselves.

Demographics of the entire study group.

In this part of analysis, data were compared between the two participating hospitals as well as between case and control groups and finally just the case group were examined.

Some of these variables were used for matching controls with cases therefore no comparative analysis is appropriate (as previously explained) other than the simple check to ensure that the matching had been performed correctly. Nevertheless they do provide important descriptive information about the stillborn population. These variables were summarised using basic descriptive terms i.e. mean, median, mode and range.

Gender of baby

Although an attempt was made to exactly match gender this did not always occur. The cases and controls were selected via existing databases maintained by the two participating hospitals and on three occasions the incorrect gender had been entered into that hospital's database and hence the 'matched' control was not of the same gender as the case baby. These errors were only discovered once data collection was complete and preliminary data analysis commenced. At that stage the enormous effort involved in

revisiting Hospital A and re-employing the data collector in Hospital B was impractical especially as the numbers not exactly matched were very small. Therefore, there were 123 control and 63 case male babies and 120 control and 61 case female babies in this study and analyses proceeded including these three incompletely matched sets.

Year of birth

The range of the 'Year of birth' was six years (1996-2002) with the median year of birth 1999 and a mode of 2000. These statistics were also checked for consistency between the two hospitals and the same year of birth range was found. The range of six years varies from the study period of five years because the matching procedure allowed a variation of two years from the case baby's date of birth. This means that although all cases were born between April 1, 1997 and March 31st 2002 some of the controls were born outside this period.

Maternal age

The age range for the pregnant women in this study was 17 to 42 years. Table 4.2 shows that women from Hospital A were of very similar age to those from Hospital B. The overall study age was 28.15 years with a standard deviation of 5.47 years.

Table 4.2 Maternal age in years (descriptive statistics by hospital)

Age	Min	Max	Median	Mode	Mean	Std.Dev.
Hospital A	17	42	28	28	28.45	5.36
Hospital B	18	41	28	26	27.85	5.58

Gestational age

The gestational age range for the study ranged between 25 and 42 weeks. The overall mean gestational age for the study was 35.4 weeks (SD. 4.31). Hospital A contributed slightly younger babies (mean 34.4 weeks) to the study than Hospital B (mean 36.4

weeks). The reason for this difference is not readily apparent but may lie in the fact that Hospital A is only one of two tertiary referral maternity hospitals in South Australia whereas Hospital B is one of a number of tertiary referral maternity hospitals in Victoria. Hence, the distribution of the more premature babies may be more widely spread in Victoria than South Australia.

Table 4.3 Gestational age in weeks (descriptive statistics by hospital)

Gestation	Min	Max	Median	Mode	Mean	Std.Dev.
Hospital A	25	42	35	38	34.37	4.57
Hospital B	28	42	37	37	36.43	4.05

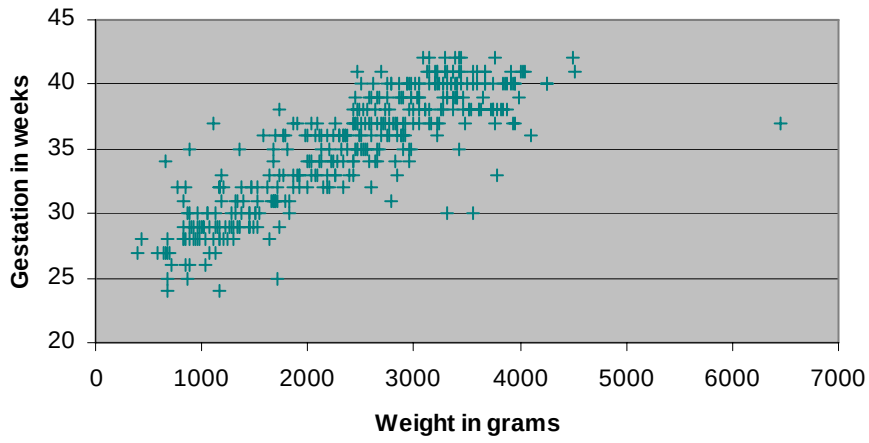
Infant weight

Overall, the study mean infant weight was 2301gms (SD. 1038gms).

Table 4.4 Infant weight descriptive statistics by hospital of birth

Weight	Min	Max	Median	Mode	Mean	Std.Dev.
Hospital A	400	4260	2100	880	2202	1019
Hospital B	430	6450	2450	430	2400	1057

Table 4.4 shows that both the median and mean weight were lower for Hospital A than B. This is probably because these babies were also about two weeks younger and infant weight and gestation are closely linked. This relationship is demonstrated for the babies in the study in Figure 4.2.



.

Figure 4.2 Infant weight for gestational age at birth (all babies, live and still)

Fetal growth as it relates to intrauterine growth restriction was examined in more depth later in the analysis

Demographics of the stillborn cohort.

Demographic data collected on the stillborn group are described below, beginning with the cause of death.

Cause of death

As previously explained the cause of death was determined either by the pathologist's report at the time of autopsy or the attending clinician's opinion at the time of the stillbirth. These causes are summarised in figure 4.3.

In this study forty-nine percent of the stillbirths were determined to have no apparent cause and were therefore classified as 'unexplained'. This percentage is somewhat higher than studies or perinatal statistics that include all infants stillborn after 20 weeks. This is probably because causes of death are known to vary according to gestational age[16] with babies born later in pregnancy being at increased risk of unexplained stillbirth.[43] Stillborn babies less than 27 weeks were excluded from this study unless they weighed more than 1000 gm and there were only two stillborn infants in this category. Therefore most infants in this study were born beyond 27 weeks and hence were at increased risk of unexplained stillbirth.

No causes of death were attributed to preterm birth however, this category is often utilised for either extremely premature infants (20-28 weeks)[116] or neonatal deaths of babies born extremely premature (but neonatal deaths were not included in this study). The selection criteria for this study dictated that all births occur beyond 27 weeks, (unless the baby weighed more than 1800 gms) therefore all but two of the stillbirths in this study

occurred later than 27 weeks and neither of these two infant's cause of death was attributed to prematurity.

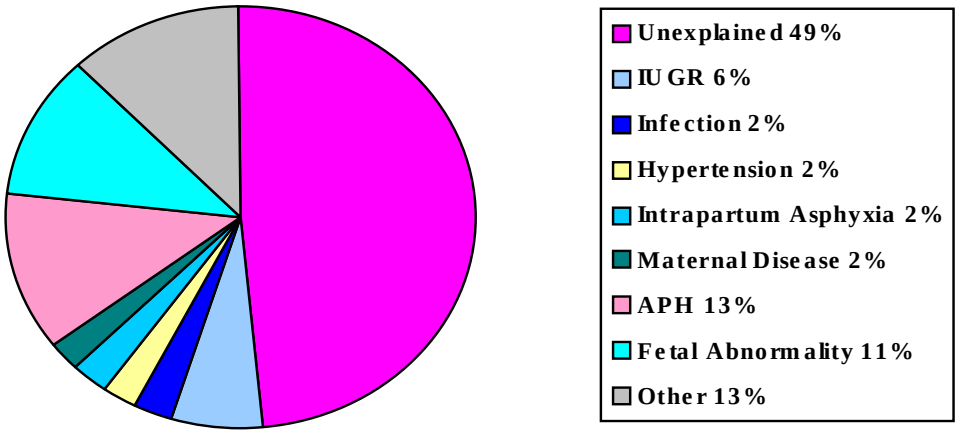


Figure 4.3 Antecedent Cause of Death

Fetal deaths in the "other" category represented 13% of the study case population. These deaths included specific perinatal conditions such as feto-maternal haemorrhage, antepartum cord complications, and uterine abnormalities (including cervical incompetence).

Thirteen of the stillbirth cases were related to antepartum haemorrhage (APH). These were from either placental abruption, or APH of unknown origin. There were no deaths in this study resulting from placenta praevia

Fetal death was only attributed to fetal abnormality if the abnormality was lethal or potentially lethal. Eleven percent of the babies in the study had a lethal abnormality.

These lethal abnormalities included abnormalities of the central nervous system, cardiovascular system and chromosomal abnormalities such as Trisomy 13.

Six percent of the stillbirths were directly attributed to the baby being growth restricted (IUGR).

When placentae showed acute chorioamnionitis and funisitis, the baby's death was attributed to infection and this accounted for two percent of the stillborn group. The causative organisms were either Group B Streptococcus or E Coli sepsis.

The deaths attributed to maternal hypertension were only two percent of the case group. These deaths were also associated with other potential causes of death such as placental abruption. However, in the case of placental abruption the hypertension was determined to be the antecedent cause of the death i.e. without the maternal hypertension the placental abruption would have been less likely to occur. This method of classifying cause of perinatal death is commonly used worldwide.[43,149]

Two percent of the deaths were considered to be due to a hypoxic peripartum event. An example of such an event occurring in labour would be cord prolapse.

Maternal diseases identified as the antecedent cause of death were essential hypertension or diabetes mellitus and in this study only two percent of the stillborn cases had these maternal diseases as the identified cause of death.

Autopsy

A large majority, 111 (89.5%) of the stillborn infants had an autopsy performed. Sixty Eight (90%) from hospital A and 43 (76%) from Hospital B. This number far exceeds the autopsy rates for metropolitan teaching (Level three) hospitals for the five years of the

study which remained close to 70%.[116] The reasons why a considerable number of this study's participants elected to have an autopsy are unclear but may lie in the fact that there is a substantial proportion of unexplained stillbirths in the cohort and an autopsy may have been offered to, and accepted by the bereaved parents in order to try to determine a cause of death.

Contributing factors found at autopsy

Data were collected indicating other factors noted by the pathologists at the time of the autopsy which were not thought to be the antecedent cause of death i.e. signs of infection, asphyxia or growth restriction which may have been either contributory factors or factors associated with fetal demise . Figure 4.4 shows the distribution of these factors in graphic form.

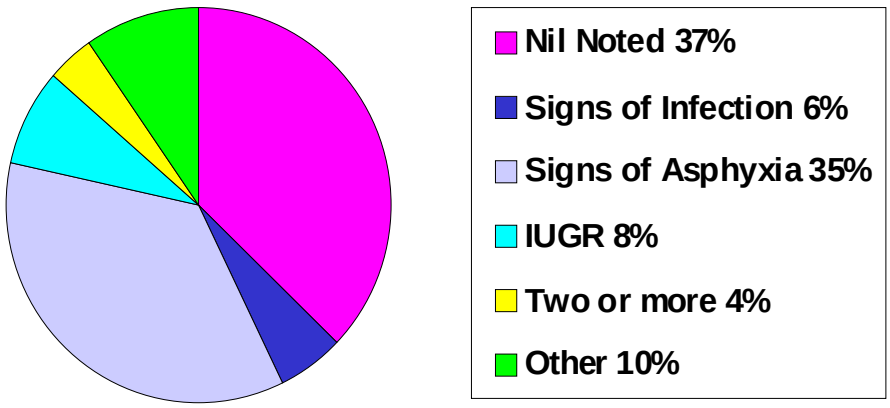


Figure 4.4 Contributing factors noted at autopsy

Thirty-seven percent of those babies who had an autopsy did not show any of these associated factors. Many (35%) of the babies showed signs of asphyxia determined by

the presence of petechial haemorrhages on heart and lungs, indicating that an asphyxial incident contributed to their death. The pathologist described eight percent of the stillborn infants as growth restricted i.e. falling below the tenth birthweight centile but did not attribute this growth restriction to cause of death. The infants who showed 'signs of infection' as a contributory factor at autopsy did not have a pathogen identified. Ten Percent of the infants had 'other' factors noted at the time of the autopsy and these included factors like two vessel cord, non-lethal fetal anomaly, excessive or absent twists in the umbilical cord.

Estimated time of death

Data were collected on the condition of the baby in order to confirm the estimated time of death. Sixty-four percent of the babies had some degree of skin or tissue maceration present, suggesting that they died greater than 24 hours before birth. This percentage agrees with figure 4.5, which confirms that the majority (80%) of the cases from both hospitals, the death was thought to have occurred in the antenatal period.

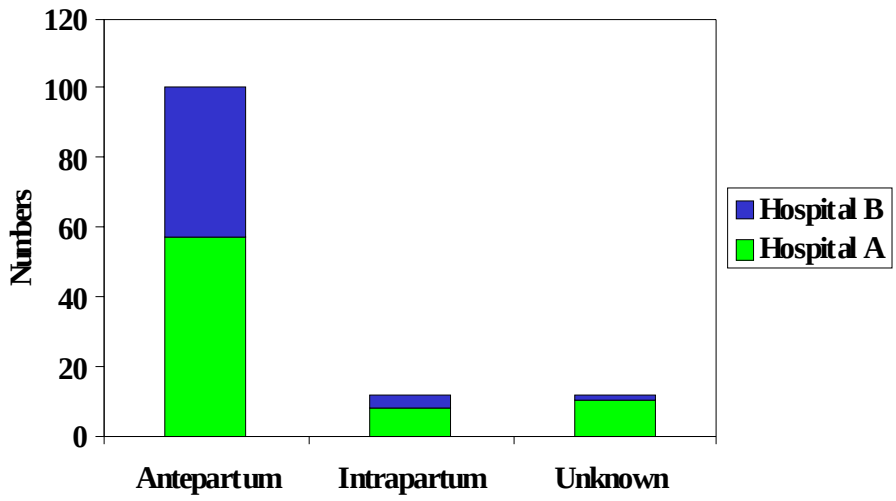


Figure 4.5 Time of death by hospital

These results are in keeping with South Australian perinatal death information which suggests that infants born weighing greater than 1000 gms rarely die in the intrapartum period[43] (p. 11).

Differences between cases and controls

In order to establish if there were any differences between the cases and controls each variable, (other than the two main study variables which were examined later) was examined using a factor level summary and then conditional logistic regression analysis in 'Egret'. These variables are presented here in the same order that they appear on the data collection proforma. The results are presented in the text then the same information is tabulated and/or presented graphically for clarity.

Colour of liquor

When comparing staining of liquor to the clear liquor group, an across the board strong association is seen between the presence of meconium and/or blood in the liquor and the stillborn group, this association is shown in table 4.5.

Table 4.5: Colour Of Liquor: Conditional Logistic Regression

Liquor	Control (n=243)	Case (n=124)	Coefficient± Std. error	P-value	Odds Ratio (95% CI)
Clear	137	16	ref	ref	1
MSL	24	52	2.95±0.44	<0.001	19.1(8.1-44.8)
MSL /BSL	4	8	2.72±0.73	<0.001	15.2(3.6-64.0)
PSL	23	8	1.11±0.56	0.05	3.02(1.0-9.0)
BSL	14	27	2.59±0.48	<0.001	13.4(5.3-34.0)
Not Noted	41	13	0.87±0.44	0.05	2.39(1.0-5.7)

These data show that in this study, stillbirth occurred 19 times more often in the presence of meconium stained liquor (MSL) than clear liquor (OR 19.1 95% CI 8.1-44.8, p<0.001), similarly a combination of MSL and blood stained liquor (BSL) carried 15 times the incidence of stillbirth (OR 15.2 95% CI 3.6-64.0, p<0.001) and blood staining

alone was seen 13 times more often (OR 13.4 95% CI 5.3-34.0, p<0.001) than clear liquor in the stillborn group. Pink stained liquor (PSL), not generally thought to be hazardous to the fetus, carries an odds ratio of three (OR 3.0 95% CI 1.0-9.0, p=0.05) meaning it is three times more likely that a baby will die with PSL. The percentages for these data are shown in figure 4.6.

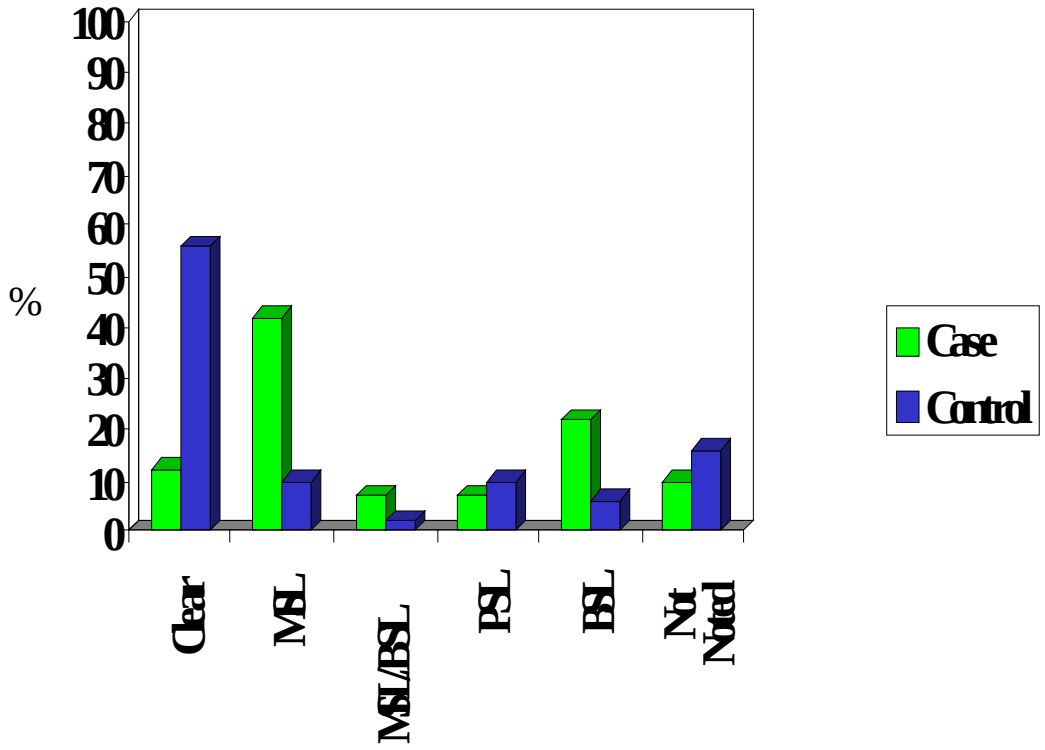


Figure 4.6 Liquor colour across the data set (MSL:Meconium Stained Liquor, BSL:Blood stained Liquor, PSL: Pink Stained Liquor)

Estimated Blood Loss (EBL)

When interpreting the data presented in table 4.6 it appears that the control group are more likely to be judged as having lost 200-499mls during the birth whereas the cases are more often recorded as having lost a minimal amount of blood. These trends were not statistically significant. Although it did appear statistically more likely that the control group did not have their blood loss at birth estimated (OR 0.1 95% CI 0.01-0.1, p=0.05).

Table 4.6: Estimated Blood Loss in mls. Conditional Logistic Regression

EBL (mls.)	Control (n=243)	Case (n=124)	Coefficient ±Std. Error	P-value	Odds Ratio (95% CI)
Min	53	52	0.54 ±0.40	0.19	1.7 (0.8-3.8)
200-499	132	50	-0.38±0.40	0.34	0.7 (0.3-1.5)
500-999	24	13	ref	ref	1
1000 +	16	8	-0.19 ± 0.55	0.73	0.8 (0.3-2.4)
No Record	18	1	-2.17 ±1.1	0.05	0.1 (0.01-0.1)

Nuchal cord

The presence of the nuchal cord was not routinely documented by the accoucher at the time of the birth. As indicated in figure 4.7, 50% of case and 90% of the controls case-notes did not have the presence or absence of a nuchal cord documented in the case notes. It is also apparent from this figure that more of the cases than controls had the presence or absence of the nuchal cord noted in their case-notes. Tests of significance were not performed on these data as numbers in the 'yes' and 'no' groups were inadequate.

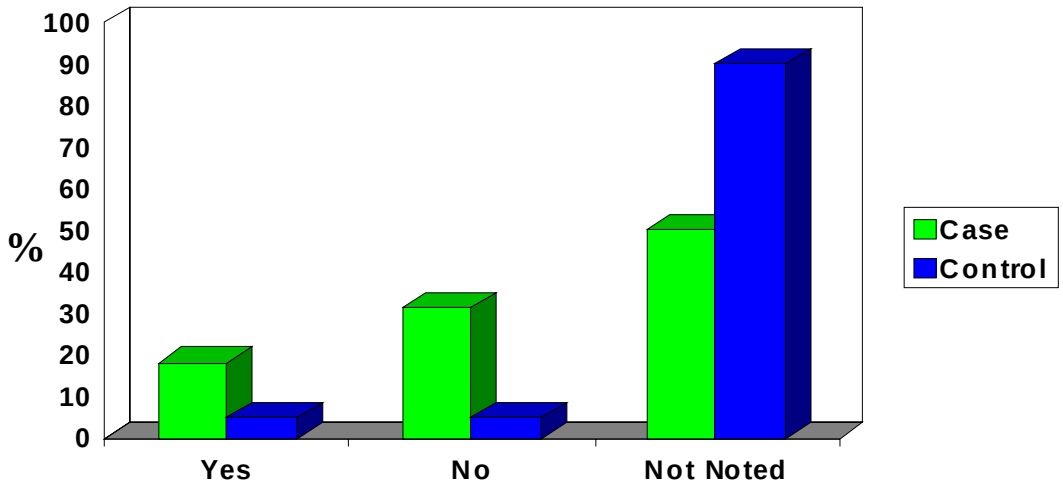


Figure 4.7 Nuchal cord documentation by case and control in percent

Race

The numbers of Caucasian cases (n=98) and controls (n=202) were almost the same in percentage terms. Aboriginal/Torres Strait islanders were underrepresented in the case group (n=2) compared with the control (n=10). There were 25 control women of Asian race and 19 case women of this background. Eleven women (6 control and 5 case) were categorised as belonging to another race e.g. African.

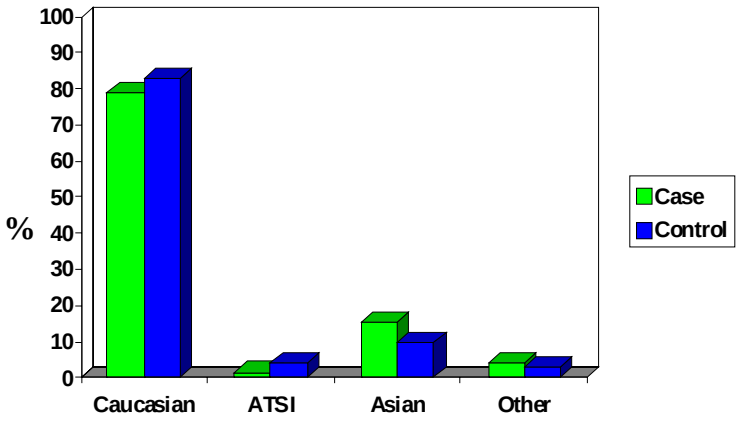


Figure 4.8 Race by case/control group in percent

Numbers of women in each racial sub-category were too small to attempt further detailed analyses. However, as non-caucasian race is a known risk factor for perinatal death[43] all non-caucasian women were combined into a category called 'non-caucasian.' This variable was used later in conditional regression analysis estimating the effect of the main study variables.

Gravidy and parity

Gravidy and parity were examined in this study because they are thought to impact on stillbirth risk. Tables 4.7 a and b indicate that in this study differences in the woman's gravidy and parity were not statistically significant when comparing live births with still.

Table 4.7a: Gravidy Conditional Logistic Regression

Gravidy	Control (n=243)	Case (n=124)	Coefficient ± Std. error	P-value	Odds Ratio (95% CI)
Primigravid	83	51	ref	ref	1
Multigravid	113	57	-0.20±0.24	0.41	0.8 (0.5-1.3)
Grand-multi	47	16	-0.64±0.36	0.07	0.5(0.3-1.1)

Table 4.7b: Parity Conditional Logistic Regression

Parity	Control (n=243)	Case (n=124)	Coefficient ± Std. error	P-value	Odds Ratio (95% CI)
Nulliparous	122	73	ref	ref	1
Primip	77	29	-0.51±0.27	0.06	0.6 (0.35-1.0)
Multip 2-3	24	16	0.04±0.36	0.91	1.0 (0.5-2.1)
Grand-multip 4+	20	6	-0.72±0.50	0.15	0.5 (0.2-1.3)

Nevertheless, there was an indication that more controls are likely to be grand-multigravid and primiparous than cases. These variables were further reduced into a binary category gravid (yes/no) as well as parous (yes /no) for the purposes of multivariable conditional regression analysis later.

Previous loss

Data were collected on women who reported a history of spontaneous pregnancy loss e.g. ectopic pregnancy, miscarriage, or stillbirth.

Table 4.8: History of Spontaneous Loss Conditional Logistic Regression

Loss	Controls (n=243)	Cases (n=124)	Coefficient ± Std. error	P-value	Odds Ratio (95% CI)
History	68	28	-0.27±0.26	0.30	0.8 (0.5-1.3)
No History	175	96	ref	ref	1

The results depicted in table 4.8 show that there was no statistically significant difference in stillbirth rates between the group who had a previous loss compared to the group who had not suffered a previous loss.

Antenatal visits

Table 4.9 shows antenatal attendance categorised into minimal (3 visits), low (4-7 visits) average (7-11 visits) and high.(more than 12 visits). Women attending antenatal care under seven times were at less risk of stillbirth than women attending more than this number of times. This trend was statistically significant when women attended antenatal care between four and seven times (OR -0.57 95% CI 0.32-1.00, p=0.05).

Table 4.9: Number of Antenatal visits

Visits	Controls (n=243)	Cases (n=243)	Coefficient ± Std. error	P-value	Odds Ratio (95% CI)
3	42	17	-0.62±0.39	0.11	0.54 (0.25-1.15)
4-7	123	50	-0.57±0.29	0.05	0.57(0.32-1.00)
7-11	59	38	ref	Ref	1
12 +	19	19	0.60±0.42	0.16	1.82(0.79-4.17)

Tobacco smoking

As table 4.10 indicates proportionally more case women were noted in the "quit smoking" group than the smoking group.

Table 4.10: Tobacco smoking status Conditional Logistic Regression

Smoking Status	Controls (n=243)	Cases (n=124)	Coefficient± Std. Error	P-value	Odds Ratio (95% CI)
Smoker	76	30	0.30±0.27	0.26	1.35 (0.8-2.3)
Quit Smoker	11	14	1.11±0.44	0.01	3.0(1.3-7.2)
Non-Smoker	130	70	ref	ref	1
Unknown	26	10	-0.14±0.44	0.74	0.9(0.4-2.0)

An analysis was made of the "quit smoking" group using the "non-smoker" group as the reference group and a statistically significant risk for stillbirth was noted (OR 3.0 95% CI 1.3 - 7.2, p=0.01) when the woman reported that she had quit smoking prior to the first visit.

Medical complications

Data were collected on a range of medical and obstetric complications in order to determine which of these variables increased the risk of stillbirth in the case group.

Table 4.11:Medical Complications: Conditional Logistic Regression

Medical Complication	Controls (n=243)	Cases (n=124)	Coefficient ± Std. error	P-value	Odds Ratio
Anaemia	33	11	-0.41±0.35	0.24	0.7 (0.3-1.3)
Urinary tract Infection	5	4	0.47±0.67	0.48	1.6 (0.4-6.0)
Hypertension (essential)	14	1	-2.13±1.06	0.04	0.1 (0.01-0.95)
Diabetes (pre-existing)	7	0	n/a	n/a	n/a
Epilepsy	4	2	n/a	n/a	n/a
Asthma	23	14	0.21±0.35	0.55	1.2 (0.6-2.5)
Other	34	36	0.94±0.28	<0.001	2.6 (1.5-4.5)
2 or more of the above	1	1	n/a	n/a	n/a

The results in Tables 4.11 indicate that the main group of women at risk of stillbirth are those with 'other' medical complications (OR 2.6 95% CI 1.5-4.5, p<0.001). This group consisted of women suffering from a wide range of other conditions including women who had tested positive for Hepatitis B or C, had a psychiatric illness or suffered from a specific medical condition such as pylonephritis.

Of note is that more of the control women were diagnosed with essential hypertension than the cases (14 controls to one case). This was a statistically significant finding (OR 0.1 95% CI 0.01-0.95, p=0.04).

Obstetric complications

None of the obstetric complications listed carried an increased risk of stillbirth in this study. The results shown in table 4.12 indicate that women diagnosed with pregnancy induced hypertension (PIH) during their pregnancy are at statistically significant less risk

of stillbirth (OR 0.3 95% CI 0.1-0.6, p<0.001) as are women with pregnancies in which intra-uterine growth restriction (IUGR) was suspected (OR 0.3 95% CI 0.1 - 0.8, p=0.02).

Table 4.12: Obstetric Complications: Conditional Logistic Regression

Obstetric Comps	Control	Cases	Coefficient ± Std. Error	P-value	Odds Ratio (95% CI)
TMC	16	9	0.18±0.44	0.77	1.1 (0.5-2.7)
APH- Any Cause	32	19	0.15±0.32	0.63	1.2 (0.6-2.2)
PIH	46	7	-1.37±0.43	< 0.001	0.3 (0.1-0.6)
Suspected IUGR	29	5	-1.15±0.50	0.02	0.3 (0.1-0.8)
Gestational Diabetes	11	3	-0.66±0.65	0.31	0.5 (0.1-1.8)
Other	66	36	0.08±0.26	0.76	1.1 (0.65-1.8)
Two or More of the above	0	2	n/a	n/a	n/a

Small for Gestational Age (SGA)

In view of the somewhat surprising finding that babies suspected of being IUGR were less likely to be stillborn, a decision was made to examine babies who were actually born small for gestational age to further investigate possible reasons for this result.

Birthweight percentile values were calculated using Roberts and Lancester Australian national birthweight percentiles by gestational age chart.[36] This tool is less than perfect for use on stillborn babies due to the fact that it was developed using data only from live born infants and it is known that babies who are stillborn have less reliable birthweight due to extensive fluid loss after death. This may mean that babies born still may falsely appear growth restricted. However, no comparable tool has yet been developed to assess birthweight percentiles for stillborn infants. Furthermore, it is a tool used by the South Australian Maternal, Perinatal and Infant mortality perinatal subcommittee when assessing if babies were affected by IUGR.

The standard definition of infants who are SGA is those whose first weight after birth was less than the 10th Centile.[150] For the purposes of comparison infants weighing

greater than the 90th centile were described as large for gestational age (LGA n=16 controls 8 cases) and those falling between these two categories were designated average for gestational age (AGA n=186 control and 72 cases).

Table 4.13: SGA conditional logistic regression

SGA	Controls (n=243)	Cases (n=124)	Coefficient ± Std. Error	P-value	Odds Ratio (95% CI)
Not SGA	202	80	Ref	ref	1
SGA	41	44	1.0014±0.26	<0.001	2.7 (1.6-4.6)

When examining the factor level summary for this variable it was noted that there were a higher percentage of SGA infants in the case group (51.8%). This category was further reduced to babies born SGA or not and analysed in the conditional regression model. A highly statistically significant higher risk of stillbirth in SGA babies was observed. (OR 2.7 95% CI 1.6-4.6, p<0.001). This strong predictor for stillbirth was also used later in a multifactor analysis.

Body Mass Index (BMI)

The women's BMI at first antenatal visit was calculated by dividing weight in kilograms by the square of height in metres. These results were then separated into thin (BMI less than 20), normal (BMI 20.0-24.9), overweight (BMI 25.0-24.9) and obese (BMI greater than 30) categories.

Table 4.14: BMI: Conditional Logistic Regression

BMI	Control (n=140)	Case (n=68)	Coefficient ± Std. Error	P-value	Odds Ratio (95% CI)
Thin	15	5	-0.12±0.72	0.87	0.9 (0.2 -3.5)
Normal	63	36	ref	ref	1
Over-weight	34	11	-0.84±0.52	0.11	0.4 (0.2-1.2)
Obese	28	16	-0.13±0.45	0.78	0.9 (0.4-2.1)

The BMI results depicted in table 4.14 give no values of statistical significance. However, a category for lean body mass was created for use in the multi-factor conditional regression model shown later because there is general anecdotal thought that lean women are also hypotensive women.

Hospital admissions

Women from the control group were more frequently admitted to hospital than the case women. This statistically significant (OR 0.3 95% CI 0.2-0.5, p<0.001) result is shown in table 4.15.

Table 4.15: Hospital admissions Conditional Logistic Regression

Hospital Admission	Controls (n=243)	Cases (n=124)	Coefficient ± Std. error	P-value	Odds Ratio (95% CI)
Admitted	121	31	-1.11±0.25	<0.001	0.3 (0.2-0.5)
Not Admitted	122	93	ref	ref	1

Lowest haemoglobin (Hb) g/dL

Table 4.16 indicates that there were no statistically significant results seen in the analysis of this variable.

Table 4.16: Lowest Haemoglobin g/dL Conditional Logistic Regression

Lowest Hb	Control n=236	Case n=119	Coefficient ± Std. error	P-value	Odds Ratio (95% CI)
Less than 89.9	6	3	0.25±0.74	0.73	1.3 (0.3-5.5)
90-100	23	5	-0.75±0.50	0.14	0.5 (0.2-1.3)
100-110	39	19	-0.001±0.30	0.10	0.1 (0.55-1.8)
110-130	144	71	ref	ref	1
Greater than 130	24	21	0.54±0.35	0.12	1.7 (0.9-3.4)

However, there was a negative coefficient noted in mild anaemia (90-100 g/dL) group and although the upper 95% CI included unity there were many more controls (n=23) in

this group than cases (n=5). This finding indicates that this may have been a significant result if there had been greater numbers in the study.

Blood group

A study by Spinillo suggested that women with an AB blood group were at increased risk of developing severe pre-eclampsia[141] therefore it was hypothesised that the same may be true for hypotensive women. The factor level summary depicted in table 4.17 indicates that there is a 50/50 ratio of Control to Case women who have the AB blood group suggesting there may be a relationship between this blood group and stillbirth. However, a detailed analysis examining both AB groups together against all other groups was not possible due to the low prevalence (total of 22) of women with this blood group.

Table 4.17 Blood group factor level summary ("odds ratio" ignores matching) Infinity indicates that there were not enough numbers in the data set to calculate an odds ratio

Group	Control (n=243)	Case (n=124)	%Controls	%Cases	Odds Ratio
A+	89	43	67.42	32.58	1
B+	27	14	65.85	34.15	1.1
O+	75	41	64.66	35.34	1.1
AB+	9	9	50	50	2.1
A-	17	6	73.91	26.09	0.7
B-	4	2	66.67	33.33	1.0
O-	20	6	76.92	23.08	0.6
AB-	2	2	50	50	2.1
Unknown	0	1	0	100	Infinity.

Did blood pressures differ between cases and controls?

This study, for reasons previously explained had less than expected numbers. Therefore, when analysing the blood pressure variables, several times there were inadequate numbers in the data set to use conditional regression analysis. When this occurred a trend analysis was performed using a factor level summary.

As this blood pressure variable was a main study variable several readings taken throughout the pregnancy were used in order to determine any statistically significant trends in the data. As mentioned in the previous chapter the systolic blood pressure (SBP), diastolic (DBP) and the mean arterial pressure (MAP) were calculated for the initial, average, minimum and last blood pressure readings and these results are presented here.

Systolic Blood Pressure (SBP)

When systolic blood pressure readings throughout the pregnancy are compared to the normotensive group (SBP 111-129mmHg), no statistically significant values were seen in the hypotensive group (SBP less than 110mmHg). However, more control than case women were noted to be hypertensive with a SBP greater than 130mmHg Statistically significant results from this hypertensive group are depicted in table 4.18 and these can be seen from the initial reading at booking (OR 0.4 95% CI 0.2-0.9, p = 0.03) through to the last reading taken before the birth (OR 0.4 95% CI 0.2-0.9, p=0.02) including the calculated average for the pregnancy (OR 0.4 95% CI 0.2 0.9, p= 0.03).

Table 4.18 Systolic Blood pressures greater than 130mmHg: Conditional Logistic Regression

Systolic > 130mmHg	**Control**	**Case**	**Coefficient ± Std. error**	**P-value**	**Odds Ratio (95% CI)**
Minimum	5	0	N/A	N/A	N/A
Initial	35	7	-0.97±0.45	0.03	0.4 (0.2-0.9)
Average	42	11	-0.86±0.39	0.03	0.4 (0.2-0.9)
Last	54	15	-0.86±0.38	0.02	0.4 (0.2-0.9)

There were five controls and no cases with a minimum SBP greater than 130mmHg These small numbers made conditional regression analysis impossible however, no woman who later experienced a stillbirth was represented in this group. i.e. all the

women who were so hypertensive during their pregnancy that their SBP did not drop below 130mmHg had liveborn babies.

Diastolic Blood Pressure (DBP)

Normotensive diastolic blood pressure is commonly considered to be between 70 and 90 mmHg and this was also adopted for this study. For the purposes of this study the hypotensive group were divided into low (60-70mmHg) and extremely low DBP readings (less than 60 mmHg). When diastolic blood pressure readings throughout the pregnancy were compared to the normotensive group, a trend towards increased risk of stillbirth was seen in the group whose blood pressure readings fell in the low DBP group. This trend was seen from the initial reading at booking (OR 1.83 95% CI 1.0-3.2, p=0.03) through to the last taken before the birth (OR 1.53 95% CI 0.9-2.5, p=0.09) including the calculated average over the course of the pregnancy (OR 1.61 95% CI 1.0-2.6, p=0.05) and minimum observed during the pregnancy (OR 2.94 95% CI 0.98-8.8, p=0.05) readings. In additional a minimum diastolic reading in the very low group was associated with a significantly elevated risk of stillbirth with a crude odds ratio of 3.5 (95% CI 1.2-10.4 p=0.02).

Table 4.19: Diastolic Blood pressure initial, minimum, average and last: Conditional Logistic Regression

Diastolic	**Control (n=)**	**Case (n=)**	**Coefficient ± Std. error**	**P-value**	**Odds Ratio (95% CI)**
Minimum Less than 60	135	78	1.25±0.55	0.02	3.5 (1.2-10.4)
Initial 60-70	93	64	0.60±0.28	0.03	1.8 (1.0-3.2)
Minimum 60-70	81	41	1.08±0.56	0.05	2.9 (1.0-8.8)
Average 60-70	102	67	0.48±0.24	0.05	1.6 (1.0-2.6)
Last 60-70	76	53	0.43±0.25	0.09	1.5 (0.9-2.5)
Last Greater than 89	40	9	-0.74±0.42	0.08	0.5 (0.2-1.1)

The hypertensive DBP group did not appear to be at significant risk of stillbirth during their pregnancy however, a last diastolic reading greater than 89mmHg was associated with an odds ratio below one indicating that diastolic hypertension at the end of the pregnancy was more prevalent in the control group i.e. that maternal diastolic hypertension at the end of the pregnancy was associated (albeit not at conventional significant levels) with a lower risk of stillbirth (OR 0.48 95% CI 0.2-1.1, p=0.08).

Pulse Pressure (PP)

Pulse pressure, namely the difference between SBP and DBP, was examined in this study because it is thought to be a measure of "arterial stiffness"[151](p.337). However, there were no statistically significant differences between the pulse pressures of cases and controls.

Mean Arterial Pressure (MAP)

As previously discussed women whose mean arterial blood pressure (MAP) was between 84-102mmHg were considered normotensive. Women whose minimum MAP fell between 73-83mmHg were at increased risk of stillbirth (OR 1.7 CI 1.0-2.8, p=0.04). However, hypertensive controls (MAP greater than 103mmHg) were at less risk throughout their pregnancy from the initial reading at booking (OR 0.2 95% CI 0.04-0.8, p=0.03) through to the last prior to the birth (OR 0.4 95% CI 0.2-0.8, p=0.0096) including an calculated average for the entire pregnancy (OR 0.3 95% CI 0.1-1.2 p=0.08) and these results are presented in table 4.20.

Table 4.20: MAP greater than 103mmHg Conditional Logistic Regression

MAP	Control (n=243)	Case (n=124)	Coefficient ± Std.Error	P-value	Odds Ratio (95% CI)
Initial MAP	20	2	-1.67±0.75	0.03	0.2 (0.04-0.8)
Average MAP	17	3	-1.15±0.66	0.08	0.3 (0.1-1.2)
Last MAP	43	9	-1.03±0.40	0.0096	0.4 (0.2-0.8)

Overall 'hypotension'

As described in the previous chapter three MAP readings over the course of the pregnancy of less than or equal to 73.3mmHg were chosen to categorise women as "severely" hypotensive. Similarly, three MAPs higher than 73.3mmHg but less than or equal to 83.3mmHg were chosen to categorise the mildly hypotensive group. Women with three MAP readings of greater than or equal to 103.3mmHg were categorised as hypertensive for the purposes of this study. Women falling between the mildly hypotensive group and the hypertensive group were categorised as normotensive. The numbers of women categorised into each of these groups are depicted in a contingency table 4.21a.

Table 4.21a: Contingency table for overall blood pressure

	Hypotensive	Mildly Hypotensive	Normotensive	Hypertensive
Case(n=124)	8	60	51	5
Control(n=243)	18	86	120	19
Total	26	146	171	24

Conditional regression analysis (which included both severe and mild overall hypotension) showed that overall hypotension was more prevalent in the case group than the control group (OR 1.9 95% CI 1.2-3.1, p=0.01). Conversely there were more control than case women in the overall hypertensive group (OR 0.45 95% CI 0.2-1.3, p= 0.14).

When the hypotensive group (including mild and severe) were fitted into a conditional regression model with other putative risk factors for stillbirth previously mentioned throughout this chapter (table 4.21b) the odds ratios remain largely unchanged (Crude OR 1.91 Adjusted OR 1.99).

Table 4.21b Hypotension as a predictor of stillbirth.

Predictor		**Unadjusted Odds Ratio**	**95% CI**	**Adjusted Odds Ratio**	**95% CI**
Hypotension	N Y	1 1.91	1.17-3.12	1.99	1.18-3.40
Non-Caucasian	N Y	1 1.28	0.73-2.26	1.37	0.75-2.51
Multigravid	N Y	1 0.73	0.47-1.16	0.82	0.42-1.63
Multipara	N Y	1 0.68	0.43-1.08	0.85	0.43-1.71
Lean BMI	N Y	1 0.63	0.22-1.84	0.42	0.14-1.26
SGA	N Y	1 2.72	1.62-4.56	2.90	1.68-5.03

If these factors were confounders then a shift of greater than 10% would occur. As this was not the case it can be assumed that hypotension is an almost entirely independent contributive risk factor for stillbirth. Once adjusted for known contributory risk factors for stillbirth there is nearly twice the risk of stillbirth in the hypotensive group.

Hypertensive disease

It was considered worthwhile to examine women who had essential hypertension or PIH more closely given the earlier results that initial, average, and last SBP greater than 130mmHg all had values of statistical significance for these blood pressures being more prevalent in the control group. Women were considered to have hypertensive disease based on the notations in the supplementary birth record (SBR). The SBR has a tick box for the attending accoucher to complete whether the women suffered from essential or pregnancy induced hypertension during her pregnancy. These data had been entered onto

the data collection proforma when data were collected. It is acknowledged that reliance on this form of detection of a condition is somewhat inaccurate due to the fact that this box might not always be ticked or may be ticked in error. Furthermore, the SBR was completed after the outcome of the pregnancy was known (potentially biasing the results towards the case group being over-represented).

Essential hypertension

Only 15 women were noted to have pre-existing hypertensive disease (14 controls and 1 case). However, when this information was fitted into conditional logistic regression statistically significant values were seen (OR 0.1 95% CI 0.01-0.95, p=0.04).

Table 4.22: Essential Hypertension

	Control (n=243)	**Case (n=124)**	**Coefficient ± Std.Error**	**P-value**	**Odds Ratio (95% CI)**
No Essential Hypertension	229	123	ref	ref	1
Essential Hypertension	14	1	-2.13±1.06	0.04	0.1 (0.01-0.95)

Pregnancy Induced Hypertension (PIH)

As indicated by the table below, women who were assessed as suffering from PIH (n=46 controls n=seven cases) were statistically significantly *less* likely to suffer a stillbirth (OR 0.3 95% CI 0.1-0.6, p=0.001).

Table 4.23a : PIH Conditional Regression

	Control (n=243)	**Case (n=124)**	**Coefficient ± Std.Error**	**P-value**	**Odds Ratio (95% CI)**
No PIH	197	117	ref	ref	1
PIH	46	7	-1.37±0.43	0.001	0.3 (0.1-0.6)

Table 4.23b PIH as a predictor for stillbirth

Predictor		Unadjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
PIH	N Y	1.0 (ref.) 0.25	0.11-0.59	0.2	0.07-0.4
Non-Caucasian	NY	1.0 (ref.) 1.28	0.73-2.26	1.4	0.8-2.6
Multigravid	NY	1.0 (ref.) 0.73	0.47-1.16	0.7	0.4-1.4
Multipara	N Y	1.0 (ref.) 0.68	0.43-1.08	0.8	0.4-1.7
Lean BMI	N Y	1.0 (ref.) 0.63	0.22-1.84	0.4	0.1-1.3
SGA	N Y	1.0 (ref.) 2.72	1.62-4.56	3.5	2.-6.3

When the PIH variable was fitted into the multiple regression model with other known predictors for stillbirth the adjusted OR shifts from crude OR 0.25 to adjusted OR of 0.17 and the OR for SGA moves from crude OR 2.72-3.52. This means that PIH and SGA are somewhat related to each other, which is of course the case. Other predictors remain substantially the same. These findings suggest that women with PIH in this study were five times less likely to suffer stillbirth.

Was placental position correlated with poor pregnancy outcome?

Initial raw data on placental position were analyzed according to the data groups anterior, posterior, fundal, lateral, praevia and other compound placental positions such as posterio-fundal results of this analysis are graphically presented in Figure 4.9. This graph indicated that posterior and anterior located placentae were the most common. Therefore, for the purposes of data analyses placental position data were summarised into three placental positions namely 'posterior', 'anterior' and 'other.' The 'other' group consisted of all placental positions mentioned above.

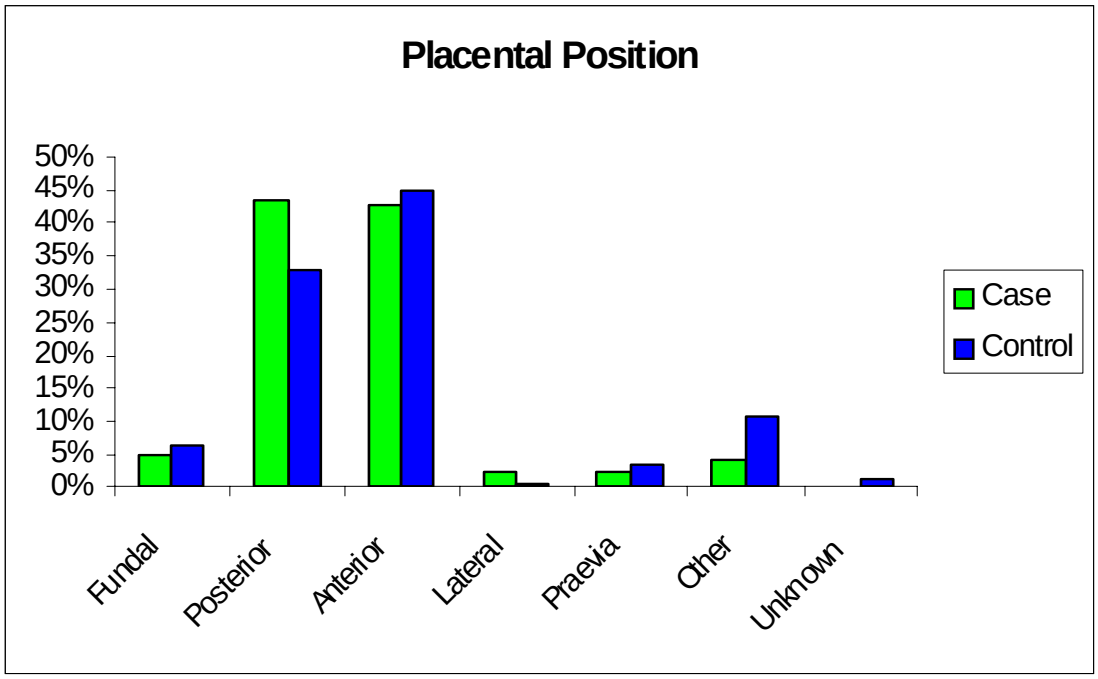


Figure 4.9 Placental Positions

When examining the placental variable results presented in table 4.24a a trend (OR 1.48 95% CI 0.9-2.4, p=0.12) towards posterior located placenta occurring more frequently in stillbirth can be seen.

Table 4.24a: Placental position (anterior as the reference group)

Placental Position	Control (n=243)	Case (n=124)	Coefficient ± Std.Error	P-value	Odds Ratio (95% CI)
Other	54	18	-0.38±0.31	0.23	0.68 (0.37-1.26)
Posterior	79	53	0.39±0.26	0.39	1.48 (0.9-2.4)
Anterior	110	53	Ref	Ref	1

Posterior placenta was then reduced to a binary outcome measure (present or absent) for which the OR was 1.64 (95% CI 1.02-2.65, p=0.04) and then fitted into a conditional regression model with the other known risk factors for stillbirth.

The odds ratios remain largely unchanged (Crude OR 1.64 - Adjusted OR 1.67) suggesting that posterior location of the placenta independently contributes to increased risk of stillbirth.

Table 4.24b Posterior Placenta as a predictor of stillbirth

Predictor		Unadjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Posterior Placenta	N Y	1 (ref) 1.64	1.02-2.65	1.67	1.01-2.77
Non-Caucasian	NY	1(ref) 1.28	0.73-2.26	1.65	0.90-3.02
Multigravid	NY	1(ref) 0.73	0.47-1.16	0.86	0.44-1.68
Multipara	N Y	1(ref) 0.68	0.43-1.08	0.82	0.41-1.63
Lean BMI	N Y	1(ref) 0.63	0.22-1.84	0.55	0.18-1.63
SGA	N Y	1(ref) 2.72	1.62-4.56	2.86	1.66-4.93

Did posterior located placenta in the presence of maternal hypotension increase the risk of stillbirth?

When the hypotension in pregnancy variable was combined with the posterior placental location variable little change was seen in the values of statistical significance (seen in table 4.25) suggesting that these two factors are independently negatively impacting on pregnancy outcome.

Table 4.25 Posterior Placenta and Hypotension as predictors of stillbirth

Predictor		Unadjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Posterior Placenta	N Y	1 (ref) 1.64	1.02-2.65	1.58	0.98-2.58
Hypotension	NY	1 (ref) 1.91	1.17-3.12	1.86	1.13-3.05

This finding is confirmed when all variables are shown in their relationship with each other in table 4.26. When all factors were combined together in a conditional logistic regression model the study risk factors mild hypotension and posterior located placenta remain statistically significant risk factors for stillbirth with the only other statistically significant risk factor being SGA.

Table 4.26 Odds ratio estimates for stillbirth, with and without adjustment for the other predictors in the table (S=Severe Hypotension, M=Mild Hypotension, Norm=Normotension, H=Hypertension N=No, Y=Yes)

Predictor	Case/Control (n=243/124)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Blood pressure	8/18 60/86 51/120 5/19	S M Norm H	1.2 (0.5 – 3.0) 1.8(1.1 – 3.1) 1 (ref) 0.55 (0.9 – 1.6)	1.2 (0.45 – 3.35) 1.8 (1.0 – 3.1) 0.5 (0.15 – 1.5)
Posterior Placenta	164/71 53/79	N Y	1 (ref) 1.6 (1.0-2.65)	 1.6 (0.9-2.6)
Non-Caucasian	98/202 41/26	N Y	1(ref) 1.3 (0.7-2.3)	 1.5 (0.8-2.85)
Multigravid	51/83 73/160	N Y	1(ref) 0.7 (0.5-1.2)	 0.85 (0.4-1.7)
Multipara	73/122 51/121	N Y	1(ref) 0.7 (0.4-1.1)	 0.8 (0.4-1.7)
Lean BMI	63/125 5/15	N Y	1(ref) 0.6 (0.2-1.8)	 0.5 (0.2-1.5)
SGA	80/202 44/41	N Y	1(ref) 2.7 (1.6-4.6)	 3.0 (1.7-5.15)

Summary

This chapter described how the data were prepared for analyses and a five-step data analysis process was described and statistical terms defined and explained. Results of the data analyses were provided through use of descriptive statistics, factor level summary, and conditional regression analysis as well as through tables and graphs. The demographics of the study group were given and each variable studied was then presented with differences between cases and controls identified. Findings from the analyses of data generated from the main study variables blood pressure and placental position were then given. These findings indicate that maternal hypotension and posterior located placenta appear to be independent risk factors for stillbirth. These results along with other findings of clinical importance such as the finding that women with hypertensive disease are subject to decreased risk of stillbirth are discussed in the next chapter.

Chapter 5 – Discussion, recommendations and conclusions

Introduction

This chapter discusses the results concerning the two main study variables given in the previous chapter and the 'secondary' findings identified in the previous chapter are examined. The concept of risk and management of pregnant women at risk of stillbirth is then discussed. Next recommendations for the management of maternal hypotension and posterior located placenta are presented along with suggestions for further research. Finally the plan for dissemination of results of this research is also outlined followed by the conclusions of this study.

Posterior located placenta

The finding that posterior located placenta may be associated with increased risk of stillbirth is new and not readily explained. Whilst there have been a small number of studies that have examined placental position as it relates to delay in third stage,[92] fetal position,[152] and nuchal cord[69] there has not been a published study which has examined placental position and stillbirth. Stillbirth is not even discussed in studies examining placenta praevia, a potential cause of fetal death due to exsanguination. Instead these studies seem to concentrate on the issue of placental migration.[86 88]

Whilst the reasons why a posterior located placenta carries an increased risk of stillbirth are unclear this researcher puts forward two potential reasons for consideration. It may be that either the structure of the posterior uterine wall is somehow at fault, or the pregnant woman adopting a supine postural position negatively impacts on a pregnancy when the

position of the placenta is posterior. These two hypotheses are further discussed and explained here.

Structural

A placenta located on the posterior uterine wall may be less efficient due to the anatomy of that wall. The posterior wall of the pregnant uterus is known to be longer[88] which may mean that as the uterus expands to accommodate the pregnancy, maternal supply is forced to be more spread out over this larger area and as a result these pregnancies may suffer due to a reduced maternal blood supply. Whilst there has not been a study which supports this theory Chapman et.al.[84] found an association between "low-lying" placenta at the less than 24 week scan and SGA. They suggested that "perhaps implantation in the lower part of the uterus provides inadequate conditions for normal placental growth and perfusion" (p. 848). This may also be true for placentae which implant on the posterior uterine wall. At odds with this explanation is one study that examined the perfusion of posterior wall placentas using an isotopic technique and found no differences between the placenta flow index between the anterior wall placentas and those located on the posterior wall.[153] The authors of this study offered no information in their paper about why they had undertaken this study. However, their findings imply that the problem with posterior located placenta may not be due to reduced or inadequate maternal blood supply.

A posterior located placenta may be associated with increased risk of stillbirth because of other causative risk factors for stillbirths which are also linked with posterior placentae e.g. nuchal cord. Cord around the neck is known to be associated with posterior placenta and increased risk of fetal distress.[69] It may be that babies with both nuchal cord and posterior located placenta are at increased risk. This link could not be supported in this current study due to the lack of documentation of nuchal cord in the study case-notes.

Positional

Another possible reason which might explain why posterior located placenta is associated with increased risk of stillbirth, is because of maternal position. If a woman with a posterior placenta sleeps in a supine position it is possible that the weight of the gravid uterus overlying the placenta compromises placental perfusion.

A study by Magann, Roberts, McCurley, Washington, Chauhan, and Klausen,[154] found that sleeping position around the time of implantation influenced placental site. If a woman adopts a supine maternal sleeping position at the time of conception then perhaps she may continue to sleep on her back throughout their pregnancy and it may be this postural position rather than the position of the placenta *per se* that puts the baby at risk. Whilst research has shown that pregnant women tend not to sleep on their backs because they naturally adopted a sleeping position which minimises the likelihood of aortocaval compression[155] this may not be the case for all women. Further research is also required in this area and some possible lines of enquiry will be suggested in the following chapter.

Limitations of the posterior located placenta finding

The retrospective nature of this study means that a number of different sonographers performed the ultrasound which reported the position of the placenta. Each of these had their own reporting style and some may have been more experienced than others. However, it was thought that sonographers were no more or less likely to report one position over another especially as the outcome of stillbirth was not known at the time of the ultrasound.

The researcher found the reported placental positions were sometimes difficult to classify e.g. "Posterio-fundal" "Posterior placenta with a fundal lobe" in this case the main

reported position was the one which was noted. This strategy is in keeping with another study which explored placental migration throughout pregnancy.[88] Therefore, if the placenta was reported as 'posterio-fundal' then it was considered to be neither posterior nor fundal and was classified as 'other' whereas the 'posterior placenta with a fundal lobe' was considered to be 'posterior' for the purposes of this study. A larger prospective study where the placental positions are determined by one experienced sonographer would therefore be useful to confirm the results of this study.

A limitation of this study is the small sample size which resulted in each placental position subgroup contained less than one hundred participants. Posterior placental position was found in a total of 132 women in the study. It was therefore not possible to investigate any potential biases such as the influence of gravidy and parity on placental position. It would be important to confirm the finding that posterior located placenta increases the risk of stillbirth through a larger study prior to making substantial changes to antenatal care.

Finally, it is noteworthy that currently a placental assessment is largely confined to reporting the attachment position. As more is known about the impact of placental insufficiency on pregnancy outcome, and as obstetric ultrasound becomes more technically sophisticated, there has been a call for placental assessment to include such detail as placental thickness, texture and cord insertion,[156] as each of these factors is known to impact on perinatal outcome. Such information may provide insights into the reason why it appears that the posterior located placenta is associated with the risk of stillbirth.

Maternal Hypotension in pregnancy

This study found that low DBP readings (between 60-70mmHg) throughout pregnancy were associated with a statistically significant increased risk of stillbirth. In addition, this study found a minimum diastolic reading of less than 60mmHg carries a significant risk of stillbirth with a crude odds ratio of 3.5 (95% CI 1.18-10.41, p=0.02).

This study did not show a statistically significant association of systolic hypotension with stillbirth. However, after combining both systolic and diastolic blood pressures to calculate the mean arterial blood pressure (MAP) the analysis did suggest that women with a minimum MAP between 73-83mmHg were at increased risk of stillbirth (OR 1.69 CI 1.02-2.81, p=0.04). Furthermore, this study found that three MAP readings of less than 83.3 during the course of the pregnancy carries almost twice the risk of stillbirth even after adjusting for race, gravidity, parity, BMI and SGA (and matching for maternal age, gestational age, gender and year of birth.)

As outlined in the literature review there has been little research examining the effect of maternal hypotension on poor pregnancy outcome. These studies have first chosen a group of women who were hypotensive and either prospectively followed them through their pregnancy taking note of outcomes[70,72,73] or examined pregnancy retrospectively via case-note audit or data bank analysis.[71,75,76,79] As stillbirth is a reasonably rare event only two[71,79] of these studies had more than a few stillbirths within their study cohort and none of these studies specifically set out to explore the relationship between stillbirth and maternal hypotension. In addition, the two blood pressure studies with the largest numbers of stillbirths did not have stillbirth as their study's focus. Friedman and Neff set out to examine the effect of hypertension on pregnancy and they made the incidental finding that maternal hypotension in pregnancy also impacts on poor pregnancy

outcome[71] whilst Steer et.al. examined a group of women with hypotension within a large birthing population.[79]

In this current study a stillborn group were first identified and matched with women whose babies were live-born. Then the impact of the presence of maternal hypotension on this group was examined to determine any affect it may have had on the outcome of the pregnancy.

Other studies have supported the need to allow for known risk factors associated with stillbirth in analysis. A previous study which found that maternal hypotension was associated with poor pregnancy outcome specifically SGA, and premature birth[75] was thought to have been confounded by that study's failure to take into account maternal age and BMI.[76] In order to avoid such criticism, in this study, controls were matched to cases on the basis of maternal and gestational age, year of birth and infant's gender. During the analysis adjustments were made for non-caucasian race, lean BMI, multigravidy, multiparity, and fetal growth and yet the results still confirmed that maternal hypotension impacts negatively on stillbirth incidence.

Zhang and Klebanoff[76] also criticised Friedman and Neff's[71] study for examining only maximal DBP as they thought that "maximum blood pressure can be influenced by the level of baseline blood pressure, the degree of rise in late gestation, and the gestation at delivery" (p.642). Therefore, in this study a range of different measures of maternal hypotension were examined throughout pregnancy rather than relying on only one method or one time of measurement as other studies have done. This study has found a consistent level of risk of stillbirth associated with low DBP and MAP but not low systolic blood pressure.

The findings presented here offer an explanation as to why the earlier study by Wolff, Bauer and Bolte[74] did not find the same degree of association between a range of poor pregnancy outcomes and maternal hypotension as the earlier hypotensive studies by Grunberger, Leodolter and Parschalk[157] and Harsanyi and Kiss[73] These studies used differing definitions of maternal hypotension. The former used only the SBP whereas the latter used a combination of SBP and DBP. Just as Wolff, Bauer and Bolte[74] did not find a statistically significant level of poor outcome risk for women with systolic hypotension neither did this study however, statistically significant differences were found for DBP and MAP.

It is certainly problematic that all previously published studies have defined maternal hypotension differently. For example, one study examined the role of automated blood pressure readings in pregnancy and identified six different common definitions of gestational hypertension and four different definitions of maternal hypotension in pregnancy.[158] With no standard definition to guide them, previous investigators who have examined the impact of maternal hypotension on pregnancy outcome have employed a variety of definitions of maternal hypotension, focussing on either the SBP,[74] the DBP,[71,76,79] maximal readings for both SBP and DBP[70] or a specific blood pressure reading e.g. 110/70mmHg[75] or combined low readings.[72,73]. Hence this study examined the affect of both low DBP, and SBP as well as MAP on stillbirth incidence in order to discover which of these readings is the most dangerous for the fetus but also to attempt to provide maternity care providers with guidelines on levels of maternal hypotension which may increase a woman's risk of stillbirth. It would appear that for the women examined by this study that low SBP is not as dangerous to the fetus as a low DBP. Diastolic readings between 60 and 70mmHg also appeared to be associated with statistically significant increased risk. However, the most telling reading, and therefore potentially the

most useful, is the finding that three low MAP readings less than 83.3mmHg appears to carry approximately double the risk of stillbirth. This finding needs to be confirmed by future research. Such research should also be designed to shed light on the possible aetiology for maternal hypotension's negative impact on stillbirth rate. A possible mechanism is suggested here.

Reduced placental perfusion

Maternal hypotension in pregnancy may have a negative affect on stillbirth in much the same way as maternal hypertension. A reduction in maternal blood flow to the placenta as a result of increased vascular resistance present in hypertension causes a resulting decrease in fetal perfusion of the placental villi.[159] The same may be true of reduced maternal blood flow in the placenta as a result of maternal hypotension. This notion is supported by a report that the placentae from pregnancies where women suffered hypotension showed a reduction in villus cross-sections leading to a shortening of the "feto-maternal" diffusion path.[160]

The 'zeroth law of thermodynamics' gives a well-known principle of physics, namely that two adjoining thermodynamic systems with differing properties (i.e. temperature, pressure, volume etc) will attempt to come into equilibrium. When applying this to the placental system it can be hypothesised that as the maternal blood pool within the intervillous space reduces in pressure, due to maternal hypotension, the fetal intervillous pressure increases to compensate. This may cause the feto-maternal membrane at the edge of the chorionic villi to expand. At the same time, the increased pressure within the fetal system compared to the low maternal system also results in reduced perfusion because the tendency for blood not to flow towards the area of increased pressure.

This hypothesis may also provide a possible reason why severe maternal hypotension was not a risk factor for stillbirth in this study. Women who have severe hypotension may have placentae which simply adapt to this state by permanent chorionic villi expansion. However, women who have some kind of hypotensive dysregulation either, orthostatic, or during sleep may require the chorionic villi within their placentae to constantly adapt to their altered state, sometimes expanding other times contracting. It may be this stress that finally results in reduced placental function, poor placental perfusion and fetal demise. An investigation of the chorionic villi in placentae from women who suffer from maternal hypotension during pregnancy would assist in confirming this hypothesis.

This hypothesis may also explain why a hypotensive pregnant woman may not necessarily be aware of any hypotensive symptoms herself. Within the bounds of the blood circulatory system the uterus is functionally regarded as a peripheral organ, that is, it has no auto-regulatory affect on the blood supply.[51] In contrast to central organs like kidneys and cerebrum, a lowering of the maternal MAP is known to lead to an "over-proportional reduction of the uterine-placental perfusion even at constant blood volumes and steady heartbeat frequency"[51] (p.420). This means that it is possible that during reduction of uterine-placental perfusion the pregnant woman herself may not experience any signs that anything is amiss but her unborn baby may suffer substantial, even, life threatening hypoxia. Further research is also required to confirm this hypothesis along the lines suggested later in this chapter.

Limitations of the maternal hypotension finding

The following possible and potential limitations should be taken into consideration when interpreting these results.

Firstly, the retrospective nature of this study prevented specific medical information being obtained such as whether the women who were hypotensive were also more likely to be affected by any other specific pathological disorders such as renal or endocrinological problems which would also independently of their hypotensive status increase their risk of stillbirth. Further study should identify whether knowledge of these factors and consequent changes in management of pregnancy makes any difference to the incidence of stillbirth for women who suffer from hypotension.

The validity of choosing three MAP to determine the presence of essential maternal hypotension in pregnancy is not known. It was also unknown whether the women came into the pregnancy with hypotension or whether the maternal hypotension developed during the pregnancy. Further investigation should identify if women who are normally physiologically hypotensive are at more or less risk than women who develop hypotension during pregnancy. Such a study should also investigate the impact of sleep on hypotensive women as outlined later in this thesis.

This study is limited by the casual nature of the blood pressure measurements. The blood pressure readings were taken at varying time points throughout the day depending on the timing of the antenatal visit. However, it is well known that blood pressure has a circadian rhythm and generally drops during sleep.[49] Whilst it is known that there is a 12-19% drop in blood pressure during sleep,[161] no study to date has specifically examined a hypotensive pregnant woman's blood pressure whilst she is asleep. The following questions could be postulated; Does her blood pressure fall further during sleep? Do some women become more hypotensive during sleep than others? Do some women have a reverse circadian affect i.e. blood pressure rising whilst sleeping?

This study's finding that women who have very low MAP readings below 73.3mmHg are not at increased risk of stillbirth suggests that perhaps when a woman's blood pressure is consistently low, that there is some compensatory mechanism at work which protects their fetus from stillbirth. Whereas the woman whose blood pressure is borderline low during the day may fall to unsustainable levels during the night and it may be this fall or perhaps the instability of the maternal state from day to night that is responsible for the baby's demise.

Finally, it has long been known that blood pressure steadily rises from the middle of gestation to the day of birth.[162] As previously mentioned this study's case population had a substantial proportion of premature babies and therefore perhaps have lower blood pressures simply because they were still in the mid-gestation 'blood pressure 'slump.' There were not enough numbers of term pregnancies in this study to isolate and analyse just their blood pressures to determine the possible impact (if any) of this potential limitation on this study's findings.

Secondary findings

In this part of the chapter some of the secondary findings made in this study are discussed. These secondary findings were not the prime focus of this study but they are reported here because they relate to the outcome of stillbirth and therefore may be of interest to clinicians and researchers alike.

Liquor colour

This study found that meconium stained liquor (MSL) is much more likely in the case group than the control (OR 19.09 95% CI 8.13-44.0, $p<0.001$). This is not an unexpected finding and is supported by other studies which have also reported varying degrees of

association between liquor staining with meconium and perinatal death. One study reported a perinatal mortality increase from 2 per 1000 births with clear amniotic fluid to 10 per 1000 with meconium ($p<0.001$)[135] and a second reported a statistically significant higher risk of intrapartum and neonatal mortality in the MSL group (1.7/1000) compared with women with clear AF (0.3/1000).[163]

This study also found that blood stained liquor (BSL) is 13 times more likely in the stillborn group (OR 13.37 95% CI 5.263-33.96, $p<0.001$). There are a paucity of studies relating to BSL and poor perinatal outcome. Placental abruption has been linked to blood in the liquor and therefore may be the cause of some of the BSL in the study group however only eighteen of the 51 placental abruptions had BSL or a BSL/MSL combination (eleven controls and seven cases) leaving the remaining 33, who had blood in the liquor either in combination with meconium or alone, without an obvious cause for the staining, reported in the case notes. Blood stained liquor is also mentioned in association with ruptured uterus[14] however, this was not associated with fetal death in this study. No published study has examined an association between stillbirth and the presence of blood or pink stained liquor therefore further investigation at a later time may be warranted to establish why it is so much more common for stillborn babies to have BSL.

Estimated Blood Loss

When examining the estimated blood loss variable it was noted that there was a tendency for the control group to be judged as having lost 200-499mls during the birth whereas the cases appeared to be more often recorded as having lost a minimal amount of blood. These trends were not statistically significant but are clinically interesting.

There are two possible explanations for this trend. It is possible that there is in fact less bleeding associated with the stillbirth than the live birth perhaps because the stillborn baby's placenta has ceased to function. It is however, also conceivable that the accoucher who is naturally distracted at the time of the stillbirth, estimates blood loss to be a minimal amount at the time of documentation of the birth.

In this study it was statistically more likely that the control mothers did not have their blood loss at birth estimated (OR 0.11 95% CI 0.01-0.98, p=0.05) at all. All but one of the stillborn cases had an estimated blood loss recorded whereas eighteen of the controls had this information missing from their case notes.

There is discussion in the literature about estimation of blood loss and birth, related to accuracy of estimation and documentation[164], as well as known risks of increased bleeding and stillbirth e.g. placenta percreatea/acreata.[87] A literature search revealed no published material on the relationship between stillbirth and minimal blood loss, making this an area of possible further study. Whilst this result has no bearing on the primary hypotheses of this thesis, it is interesting from the point of view of expectant management of the third stage and documentation of stillbirth.

Nuchal cord

Nuchal cord is known to be present in around one third of all pregnancies at term.[165] However, the results of this study suggest that the presence of the nuchal cord is not being documented. Ninety percent of the controls and 50% of cases did not have the presence or absence of a nuchal cord documented in the case notes. This lack of documentation may have arisen as a consequence of the conflicting opinion in literature reporting the impact of nuchal cord occurrence on fetal outcome. For example, some

studies have not found significantly elevated risk of adverse outcome associated with the presence of a cord around the neck.[166,167] But in a population based study Rhoades, Latza, and Mueller, demonstrate that nuchal cord is associated with increased risk of a range of poor perinatal outcomes i.e. fetal distress, MSL, and low APGAR score at five minutes of age.[136] One suggested explanation of why a fetus with a nuchal cord may be at increased risk is concerned with the tendency of the nuchal cord to be straighter[168] and therefore less resistant to a range of intrauterine events that may lead to compression of the vessels within the cord.

Of note in this study was the observation that the presence or absence of a nuchal cord was less likely to be documented after a live birth than after a stillbirth (OR 0.24 CI 0.12-0.48, $p<0.001$). The researcher's experience suggests that the accoucher may be more likely to be looking for possible reasons for the stillbirth and therefore documents it's presence or absence. Further research could clarify if this is in fact the case.

Gravidy and parity

This study found no statistically significant risk associated with a woman's gravidy or parity. This finding is not in agreement with other studies which have found that women having their first baby are at increased risk,[7] as are women who have had more than four babies.[138] The small numbers involved in this study may be the reason why such a dependence was not observed.

Previous spontaneous loss

This study's finding that a history of previous pregnancy loss did not put the women at increased risk of stillbirth is also at odds with the literature.

For example, Kashanian, Akbarian, Baradaran, and Shabandoust recently reported that women who have previously suffered a miscarriage were at increased risk of fetal death.[169] Similarly Robson, et.al.[139] also reported a correlation between previous history of pregnancy loss and poor outcome in later pregnancies.

Again it might be argued that this study did not find an associated risk with previous spontaneous loss and stillbirth because of the small numbers. Only 28 cases and 68 controls had suffered a previous spontaneous loss. However, it may also be argued that the spontaneous loss 'rate' is higher than usual in the controls because they were receiving their antenatal care at a tertiary obstetric hospital to which they had been referred because of their history of previous spontaneous loss.

Antenatal attendance

The findings of this study suggest that women who attended antenatal clinic four to seven times were less likely to suffer a stillbirth (OR 0.57 95% CI 0.32-1.00, p=0.05). None of the other antenatal visit groups (three, 7-10 or12 plus) showed any values of statistical significance. However, there was a trend towards a higher likelihood of stillbirth associated with more than 12 antenatal visits.

The aim of antenatal care is to deliver appropriate effective care to pregnant women. Such care includes screening for fetal and maternal well-being as well as implementing preventative measures and /or treatment for known pregnancy related problems. The actual number of visits a woman makes to her maternity care provider should be timed to coincide with when these screens and other interventions are delivered during the pregnancy.

In a systematic review of 10 studies examining antenatal visits from both developed and developing countries[170] no statistically significant association between few antenatal visits and poor pregnancy outcome was observed. This review makes the recommendation that women experiencing low risk pregnancies should see their maternity care provider a minimum of four times. The results of this thesis appear to support this advice as it was noted that women attending antenatal care provider four to seven times appeared to be at less risk of stillbirth.

Conversely, women seen greater than 12 times may have been at increased risk because a problem was detected in her pregnancy which was being monitored but which ultimately resulted in the baby's demise.

The number of antenatal visits attended may also provide one explanation why there were only a few (n=2 case and n=10 control) Australian Aboriginal women in this study because these women tend to be poor antenatal attendees.[43]

Tobacco smoking

This study found that the women who indicated that they had “quit” smoking were three times more likely to suffer a stillbirth than women who were non-smokers (OR 3.03 95% CI 1.27 - 7.24, p=0.01).

There are no published studies that support this finding. In fact studies examining the affect of smoking on pregnancy suggest that women who quit prior to the end of the first trimester of pregnancy reduce their risk of stillbirth to levels similar to those who have never smoked.[171] There are also many studies that support the opinion that smoking in pregnancy is detrimental to fetal and later infant health[7,10,37,38,172] however, this study did not find the smoking group of women were at increased risk of stillbirth.

The reason why the women who stated that they had "quit" smoking were actually at significant increased risk of stillbirth even than women who continued to smoke is unclear and warrants further investigation at another time.

Obstetric and medical complications

None of the obstetric complications examined carried an increased risk of stillbirth in this study. Furthermore, this study found that the women at risk of stillbirth were not at increased risk of suffering from any medical complication besides those with 'other' medical complications (OR 2.57 95% CI 1.47-4.49, p<0.001). This 'other' group consisted of women suffering from a wide range of other conditions including women who had tested positive for Hepatitis B or C, had a psychiatric illness or suffered from a specific medical condition such as pylonephritis.

When examining the range of medical complications investigated in this study it was of note that more of the control women were diagnosed with essential hypertension than the cases (14 controls to one case) and that this was a statistically significant finding (OR 0.12 95% CI 0.01-0.95, p=0.04). This finding is echoed by another Australian case controlled study by Alessandri, Stanley, Garner, Newnham, and Walters which was similar in size to this one (174 cases/344 controls).[115] They reported what they called a paradoxical finding between the stillborn cases experiencing less medical and obstetric complications than their control group. Alessandri's study did not directly examine women with essential hypertension, but found a statistically significant lower proportion of controls than cases took antihypertensive therapy (OR 0.13 95% CI 0.03-0.55, p=0.006).

This study found that women diagnosed with Pregnancy Induced Hypertension (PIH) during their pregnancy are statistically significantly less likely to suffer a stillbirth (OR 0.26 95% CI 0.11-0.59, p=0.001). Alessandri also reported that women with PE were at less risk of stillbirth (OR 0.39 95% CI 0.18-0.83, p=0.015).

It is also intriguing that this study had seven control women who had pre-existing diabetes but no case women with this disease. Alessandri had four control women and no case women who suffered from pre-existing diabetes.[115]

In this study, women with pregnancies in which intra-uterine growth restriction (IUGR) was suspected were much less likely to suffer a stillbirth (OR 0.32 95% CI 0.12 - 0.84, p=0.02).

When these findings are considered together they appear to be pointing to the fact that women who suffer from a known medical or obstetric antecedent for stillbirth risk are at less risk of stillbirth than those who don't. One possible explanation for this seemingly paradoxical finding may be that women at known risk of poor obstetric outcome are being identified, closely monitored and treated throughout their pregnancy and that this antenatal care is saving babies lives. The fact that many more of the control women than case women were hospitalised during their pregnancy (OR 0.33 95% CI 0.20-0.54, p<0.001) also lends weight to this argument. However, this is apparently at odds with this study's finding that women who have greater than 12 visits tend to be at increased risk unless this is because these women suffer from less common obstetric and medical disorders which perhaps do not yet have effective care and /or treatment and that is why they are still suffering stillbirth. This conclusion needs to be validated by further research.

Fetal growth

This study found a discrepancy between *low* risk of stillbirth for babies suspected of having IUGR and *high* risk of stillbirth for infants actually born SGA. The reason for this may lie in missed diagnosis. Twenty-nine controls and five cases were suspected of being IUGR but 41 controls and 44 cases actually were SGA. The dangers of fetal growth restriction for the baby are well known[37,150] and this may mean that when IUGR is recognised during the pregnancy, the woman is monitored more closely, thereby avoiding an adverse outcome. However, when IUGR is not detected the infant is at nearly three times the risk of stillbirth (OR 2.72 95% CI 1.62-4.56, $p<0.001$).

It is not known if growth restriction *per se* is the cause of the baby's death or if the underlying cause of death first causes growth restriction and then fetal death.[173] However, failure to diagnose and manage a pregnancy in which IUGR has occurred may result in a "potentially preventable stillbirth."[174]

Body Mass Index

There is good evidence available to antenatal care providers that both very thin women[175] and overweight/obese women are at increased risk of a range of adverse pregnancy outcomes including stillbirth.[9,176] However, this study showed that no group represented within the BMI variable was at increased risk of stillbirth. This discrepancy between this thesis' finding and other published literature may be related to the fact that BMI at booking could only be calculated for 56% of the total study group, usually because one or other of the height or weight were not recorded. Furthermore, calculating the pregnant woman's BMI during her first antenatal visit is becoming increasingly rare. For example, during the data collection period of this study the percentage of BMI's able to be

calculated for the entire study group steadily fell from 70% to 46% the reasons for this decline are unclear.

It is generally thought that people of lean body mass are to be more likely to also be hypotensive. However, a search for literature supporting this notion proved fruitless. This suggests, as it is well known that increasing blood pressure is positively related to increasing body mass index[177] that a general assumption has been made that the reverse is also true. Further research is required which examines any possible relationship between women with a low BMI and hypotension.

Hospital admission

As previously mentioned the control group were statistically more likely to have been admitted to hospital than the cases (OR 0.33 95% CI 0.20-0.54, $p<0.001$). One possible reason why this may be so is because women who have been diagnosed with a pregnancy complication which requires admission to hospital also tend to then come under close scrutiny and management for the remainder of their pregnancy and that this care results in them being more likely to achieve a live birth. This notion is supported by examining the raw data. Whilst the reasons for the hospital admissions were not collected it is noted that 46 (40 controls and six cases) of the admitted group were also diagnosed with PIH suggesting that PIH is being diagnosed and where appropriate managed by admission to hospital. Meanwhile women who are considered at low risk are not being subjected to the same degree of intervention and scrutiny and this means that for some a stillbirth may occur.

Lowest haemoglobin

This study revealed no values of statistical significance in either the lowest recorded haemoglobin nor the group whose haemoglobin was greater than 130g/dL throughout their pregnancy. However, most published literature claims that women with anaemia are at increased risk of stillbirth[178-180]. This is because haemoglobin carries oxygen and thus maternal anaemia can lead to fetal hypoxia. Conversely, one study reported an increase in stillbirth risk associated with a lowest haemoglobin concentration greater than 130g/dL[181] This finding is thought to be related to increased blood viscosity affecting placental perfusion.

That this study did not show any associated risk with either low or high Hb levels may be due to insufficient statistical power. There were also 12 missing values for this variable, which may have affected results. However, this finding may also be related to the fact that the risk of being anaemic in pregnancy is well known that these women at risk are being detected, closely monitored and treated.

Hypertension

One of the most interesting as well as surprising observations that this study made was that women with any degree of hypertension during pregnancy are statistically significantly less likely to suffer a stillbirth. This reduction was noted in women reported to be essentially hypertensive, (OR 0.12 95% CI 0.01-0.95, p=0.04) as well as those suffering PIH (OR 0.26 95% CI 0.11-0.59, p=0.001). This observation is discussed further here.

When discussing the impact of hypertension in pregnancy it is important to understand that there are a number of different hypertensive states that can affect pregnancy

outcome. Hypertension during pregnancy comes in many different guises. The woman may already suffer from hypertension and this may be secondary to other conditions, (e.g. renal, renovascular and endocrine disorders) or pre-existing / essential hypertension. It may arise *de novo* in pregnancy as gestational hypertension, often called pregnancy induced hypertension (PIH). PIH may also overlie existing hypertensive disease. PIH can be considered mild if high blood pressure occurs in isolation, but it may affect many organ systems and can progress to pre-eclampsia (PE), eclampsia (sometimes called toxaemia) and HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. The overall incidence of hypertensive diseases on pregnancy depends on the definition used and ranges from 2-10%.[182] However, whatever the source of the hypertension it is now well known that maternal hypertension in pregnancy decreases utero-placental perfusion, thus putting the developing fetus at high risk of growth restriction and death.[183]

Whilst studies reporting the impact of hypertension on pregnancy outcome quite rightly focus on prevention, treatment and management, many studies are now also reporting dramatic drops in stillbirths as a result of the active and oftentimes aggressive treatment and management of all forms of this disease.

There are many studies reporting this for example, in a large study examining 88,651 births including 709 stillbirths over a 30 year study period, stillbirths attributed to hypertensive disease as well as maternal diabetes dropped to a low rate of less than 2/10,000, this was attributed to "aggressive management of these conditions."[16] In addition, the hypotension study by Steer et.al.[79] excluded all women with hypertension from their study population but they noted that 93.4% of the perinatal deaths occurred in women without any history of hypertension in their pregnancy leaving only a small percentage of women who were hypertensive suffering stillbirth. Furthermore, in a

prospective randomised trial, Phippard, Fischer, Horvath, Child, Korda, Henderson-Smart, Duggin, and Tiller,[184] showed that early treatment of women with mild to moderate hypertension prevented progression to PE and there were no perinatal deaths in their study group.

In their case-control study, Alessandri et.al.[115] found a significant difference between cases (stillborn) and controls (live born) for 'Pre-eclampsia' with many more of the controls than cases suffering this disorder (OR 0.39 95% CI 0.18-0.83, p=0.015). This difference was even more pronounced in a group of low birth weight cases and controls (OR 0.14 CI 0.04-0.49, p=.002). Other than making a general statement "it therefore appeared that pregnancy and medical complications were protective for this type of (antepartum unexplained) stillbirth" (p.716) this interesting finding is not discussed in Alessandri's paper.

The incidence of full-blown eclampsia has also reduced substantially in recent years. One recent study[183] showed a 20 fold reduction, noting that eclampsia used to occur as often as once a week and now is a rare event. This reduction was attributed to "a tremendous improvement in antenatal and perinatal care" (p.52). Tan described such care as including regular antenatal attendance, early detection of hypertension, treatment, management and delivery with subsequent excellent neonatal nursery care. In addition they noted that many tertiary hospitals worldwide have instituted a high risk pregnancy service which consists of physicians, obstetricians, midwives and others working together to ensure the best outcome for mother and baby and that such services were having a positive affect on stillbirth outcome.

Thus this study's finding that women with hypertension during pregnancy are at decreased risk of stillbirth is a finding that other studies whose chief focus is examining

detection, treatment and management of pregnancy induced hypertension are also beginning to report.

However, this is not a finding being generally reported from population-based studies. Three such studies are used as examples here.

In a large population based study examining all births in the Nova Scotia area within the study period (135,466 births) Allen et.al.[39] reported that women in their study were 1.4 times more likely to have a stillbirth if they suffered with any hypertensive disorder than those women who did not. This risk remained constant over many years 1988-2000.

A study by Dodd et.al.[117] examining a population of 191,941 births in South Australia over a ten year study period from 1991-2000 also found an increase in stillbirth risk for women with any form of hypertension in pregnancy although they did report that as the pregnancy advanced that this risk became "less dramatic" becoming similar to the risk of normotensive women at term. Interestingly they echo this study's suggestion that reduction of stillbirth risk may be associated with treatment of hypertension including medication or induction of labor. However, they also suggest that this trend "may be a reflection of disease severity, with women with severe pre-eclampsia presenting and giving birth earlier in gestation"(p.1736).

In an earlier population based study of 11,000 pregnancies over a 15 year study period Piper, Langer, Xenakis, McFarland, Elliott, and Berkus, examined outcomes for growth restricted fetus' and found that preterm hypertensive SGA pregnancies had nearly half the risk of perinatal mortality when compared to their normotensive group but that this affect was reversed as the pregnancy advanced to be three times the risk at term. [185] These authors suggest that including all gestations within their study "masked the impact of

hypertensive disorders on neonatal mortality in preterm gestations" (p.198). This thesis' population had a mean gestational age of 35.4 weeks and in spite of the fact that gestational age was matched, did include all gestational ages within analysis therefore it is possible that there may be elements of this same "masking affect" present within this research.

Limitations of the hypertensive finding

As previously mentioned data were collected from case-notes retrospectively, recorded blood pressures were not taken in 'controlled' research conditions but as part of routine antenatal care. This means that there was an element of lack of control for the blood pressure measurements and this may be considered a limitation. However, this study was exploratory in nature and the retrospective design was not considered to bias the results especially as the antenatal care provider at the time of taking the blood pressure had no way of determining the ultimate outcome of the pregnancy and thus the blood pressure readings should not be especially biased one way or another.

There are two possible sources of bias, which may have influenced the finding that hypertensive women are at less risk of stillbirth. The first may be to do with the age of the study population. Maternal age was a factor which was matched for in the study design and as previously explained following matching the researcher can have no more to say about the possible influence such factors may have had on study outcome. However, a study by Duckitt and Harrington[182] found that women aged 34 and older were at increased risk of developing PE and it is well known that older women are also at increased risk of stillbirth.[122] Because this study matched on maternal age a preponderance of older women within the case group would have increased the numbers of older women included in the control population. These women may also have been

more likely to be hypertensive however, the mean maternal age of 28 years (± 5 years SD with a mode of 27 years) for this study suggests that maternal age was probably not implicated in the reasons why hypertension was more prevalent in the control population.

In a similar manner the gestational age of the study group may also have been another possible source of bias. Seventy-five percent of the study group were premature. This is because the case group had a high percentage of premature stillbirths and the control group who were matched within two gestational weeks were then also premature. Hypertensive pregnancies are often managed aggressively and delivered early therefore, prematurity is highly associated with maternal hypertensive disease.[174] Thus, when the control group were selected they may also have been more likely to be hypertensive.

For these two reasons it is possible that there was a problem with overestimating the affect of hypertension in this study. However, maternity care providers should maintain best practice with all women who present with hypertension in pregnancy as this study seems to show that the best practice protocols for managing hypertension are having a positive affect on lowering stillbirth incidence for this group of women.

Summary of secondary findings

During analysis this study found a number of factors associated with stillbirth which were described and explored in this chapter. Of particular interest is this study's finding that known obstetric and medical complications of pregnancy particularly hypertension appear not to be associated with increased risk of stillbirth. This finding reflects positively on current best practice and antenatal management.

General strengths and weaknesses of the study

Weaknesses

One problem with the case study population selection was that 77 of the eligible stillborn case records could not be properly reviewed. This was either because some women who birthed at the study hospitals did not have their antenatal care at the hospital (73 cases) or because the medical record was missing (four cases). The record of antenatal care that was provided by a private obstetrician or rural maternity care provider was not always included in the case-notes. Thus privately insured women as well as women who lived in rural and remote areas are under represented in this study. Whilst it is not likely that these women differ significantly in their blood pressures or placental position from the women who were included as cases in this study, it is a limitation which affects the generalisability of the results as it is likely that potential control women would have also been from this group.

The four missing case-notes, although only a tiny percentage of all eligible cases, may have been missing because they were complicated cases, although inclusion of these obstetric complications would have been unlikely to have affected some of the overall results.

Another limitation was the eventual small sample size of the study. Small numbers did prevent statistical comparison on some less frequent obstetric complications as well as detailed analysis of some of the findings. It was also not possible to examine sub-groups within the stillborn group e.g. the unexplained stillbirth group. This limitation may also have particularly affected the hypertensive result, as there were only a few hypertensive women in this study. However, it is considered that there were large enough numbers on the two main variables of this study for the findings of this thesis to be valid.

Finally, the use of two different data collectors may have influenced the reliability of the data collection. This might have arisen if one data collector tried harder to include all eligible cases into the study than the other. The data collector at hospital A had more time to peruse the case-notes in depth and many times found antenatal records of women 'retrieved' from other hospitals in unlikely areas of the case-notes e.g. 'correspondence' or loosely placed in the back pocket of the notes. This may account for the discrepancy in less raw numbers available but more cases collected from Hospital A than Hospital B which potentially had more cases to contribute due to its higher birthing population but in fact contributed less cases overall to the study.

In view of these limitations, caution should be employed when interpreting the results of this retrospective study. As explained previously, in contrast to experimental studies, causation cannot be inferred from the findings from this type of study, neither can alternate explanations be eliminated. It is therefore not this study's claim that maternal hypotension or posterior located placenta cause stillbirth, but rather that they may be part of the web of causation that has many different strands which may be interrelated in complex ways.

Strengths

In spite of the above limitations, this study also has a number of strengths. Data collection over a five-year period avoided seasonal or yearly incidences, which may have influenced the results of a study conducted over a shorter time frame. Another strength is this study's case-control design as results from case-controlled studies are generally considered to produce high-level evidence on relatively rare events.

Generalisability of results

As this study's population consisted of regular antenatal attendees who birthed at urban tertiary referral centers, generalisability to a pregnant population attending level two, one, or community maternity care provider cannot be inferred. Neither can these results be generalised to those women who intend to birth in those settings. Furthermore, the study population was chiefly Caucasian women living in a developed nation and so little can be said about whether these results are generalisable to a non-caucasian population or women from developing nations.

Whilst it is clear that more research is needed to answer questions raised by this current study it also appears that neither maternal hypotension nor posterior located placenta are as benign as previously thought. This study's findings along with the work of Steer et.al.[79] lends some credence to the earlier German studies findings that maternal hypotension in pregnancy increases the risk of stillbirth. The findings of this study also suggest that women who have a posterior located placenta are at increased risk of stillbirth. Therefore, it is suggested that maternity care providers should begin adopting a vigilant attitude towards monitoring the pregnancy of hypotensive women as well as women with a posterior located placenta. Recommendations and suggestions for incorporating these possible new risk factors into midwifery practice are made next.

Adopting a "triple risk" model

A commonly accepted model for examining SIDS risk was proposed in 1993 by Rognum and Saugstad.[186] This model suggests that SIDS happens when three factors occur in combination i.e. a vulnerable infant; a critical developmental period in homeostatic control; and exogenous stressor(s). However, their model makes it clear that even if all of these factors are present the infant may not succumb to SIDS. This approach may be

adopted to explain the risk of stillbirth in the light of the potential risk factors identified by this study (figure 5.1). This research has identified two more possible contributory factors to stillbirth which could be included in these risk circles, namely maternal hypotension, (a critical event) and posterior located placenta (an intrauterine factor).

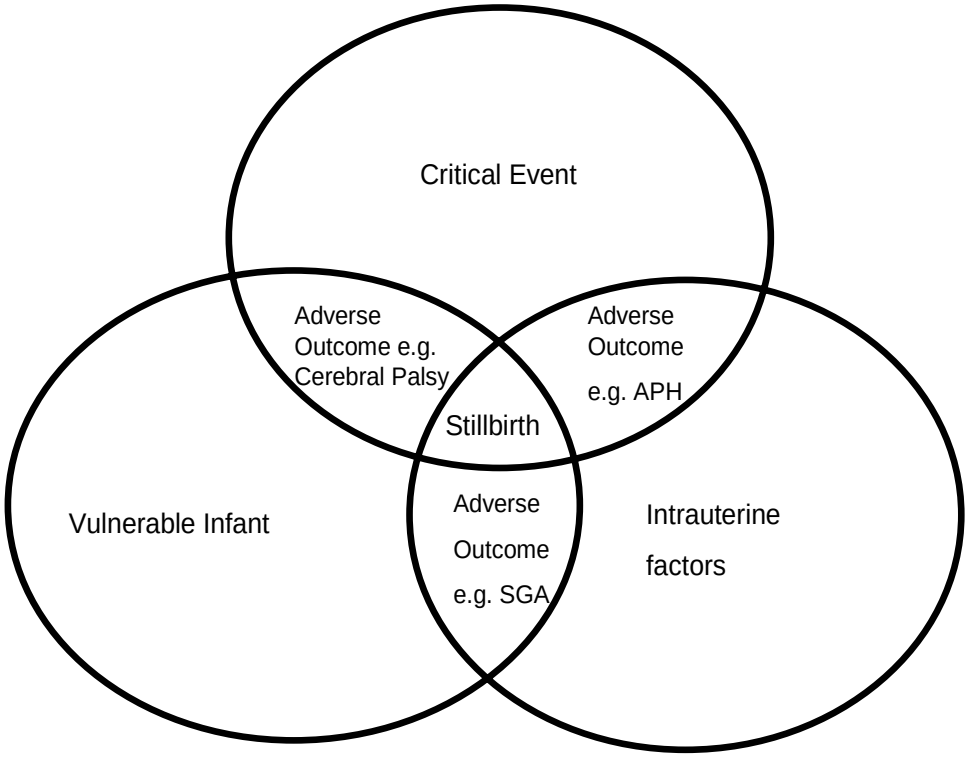


Figure 5.1 "Triple risk" SIDS model adapted from Rognum and Saugstad[186]

Suggested maternity care provider response to these new factors is now explored.

Management of pregnant women at risk

Maternity care providers' role in provision of antenatal care is multifaceted involving screening, information, support, assessment, professional advice and ongoing care for the expectant parents and their unborn baby. Each of these is considered when making the recommendations for practice in light of the findings from this study.

Maternal Hypotension: What can be done?

The results of this study suggest those women with diastolic readings less than 60mmHg during their pregnancy as well as women whose DBP ranges between 60-70mmHg are at increased risk of stillbirth. Furthermore, women who have had three MAP readings during their pregnancy between 73.3 and of 83.3mmHg are also at increased risk of stillbirth. These finding leads to the question "what can midwives and obstetricians do?" The answer lies in current best practice management of at risk pregnancy for which there is no current treatment available for the risk factor other than expectant management e.g. placenta praevia. When maternal hypotension of pregnancy occurs expectant management by close monitoring of maternal and fetal wellbeing is recommended.

Antenatal care and advice

The following 4-step plan of antenatal management of hypotensive pregnancies is suggested:

1. identifying hypotensive pregnant women at risk

2. suggesting 'protective' actions for the hypotensive pregnant woman

3. monitoring fetal well being

4. adopting appropriate intervention strategies which may include induction of labour.

Each of these steps is discussed here.

Identifying hypotensive pregnant women at risk

Assessing women at their antenatal booking visit may be a vital first step in identifying hypotensive women. Whilst booking blood pressure may assist in identifying women who are hypotensive this reading may not necessarily be low especially if the woman is anxious. Therefore, ascertaining from women at their booking visit if they have a history of hypotensive symptoms will be helpful. The antenatal care provider should determine if the woman reports symptoms of postural hypotension i.e. dizziness when rapidly changing posture from lying to standing. Another commonly reported symptom of hypotension is tiredness, in a large cross sectional population based study adults with systemic hypotension consistently reporting persistent tiredness [187] and in a study examining pregnant women Hohmann et.al.[78] also list tiredness as one of seven common symptoms of hypotension. Whilst tiredness could be said to be a common symptom in many early pregnancies, Hohmann et.al. found that all seven of these symptoms of hypotension namely tiredness, cold extremities, headache, dizzy spells, paraesthesia, sudden temporary darkening of vision, and double-sightedness/eye flutter were twice as common ($p < 0.05$) and more intense ($p < 0.01$) in hypotensive women.[78] Therefore, one method of identifying hypotensive pregnant women could be by using a Likert Scale consisting of these hypotensive symptoms along with a measure of frequency and intensity which women fill in at their first antenatal visit. A suggested proforma for this assessment is included in Appendix Seven. If women appeared to suffer from a number of hypotensive symptoms in early pregnancy and later in the pregnancy had low DBP and/or MAP readings then these may be the women for whom additional monitoring is required.

Protective actions for the hypotensive pregnant woman

It is standard practice to inform all pregnant women to avoid sleeping on their back during pregnancy in order to minimise the effects of postural hypotension and aortocaval compression. In light of the findings of this study it would seem to be particularly important that antenatal care providers are vigilant in informing hypotensive pregnant women to avoid the supine position in order that they do not compound an already potentially compromised fetal blood supply. This may be achieved by encouraging the pregnant woman to sleep with a wedge or small pillow positioned so she can not lie flat on her back. Another strategy that has been suggested is sewing a tennis ball into the back of nightwear so that it becomes impossible for the pregnant woman to sleep on her back. However, such a strategy may not find favour with many women for obvious reasons.

Hohmann and Kuenzel[50] recommended that severely hypotensive women wear compression stockings in order to prevent pooling of blood in the lower limbs and assist venous return. This simple intervention may be suitable and useful for all hypotensive women to adopt.

Herbal remedies may also be useful in slightly raising blood pressure. There is anecdotal support for the use of both Clove and Rosemary oils to improve circulation when rubbed in to 'pulse points'.[188] An older study[189] suggests taking yohimbine to improve hypotension, however its safety in pregnancy has not been established.

Investigating pregnant women at risk

Some women start their pregnancy at increased risk of pregnancy complications, for example if the woman is over 35 years of age. Other women will develop complications

as the pregnancy progresses, for example gestational maternal hypertension. Pregnant women with hypertension currently undergo a battery of tests to assess renal and liver function but there is currently no accepted comparable test for pregnant women who are hypotensive. However, one study identified low levels of human placental lactogen (HPL) in hypotensive pregnant women. Goeschen, Saling and Wiktor[51] observed that 56% of the hypotensive pregnant women they studied had a level of HPL below the 10th percentile. This is a potentially important finding because HPL is a measure of placental function, therefore measuring HPL may be useful as it could assist in the detection of those pregnant hypotensive women who are at particular risk of stillbirth. However, as this is a finding which has only been reported from one study, more research is required before this could be adopted as a diagnostic test in pregnancy. Nevertheless, this does indicate that it is possible that once more is known about which women are at increased risk of maternal hypotension in pregnancy and the types of investigations that assist in detecting if they are at increased risk of stillbirth that recommendations adopted for hypertensive women and older women will also be developed for this group.

Monitoring fetal wellbeing

There are several methods for determining fetal well-being, most are controversial in their effectiveness for preventing or minimising fetal morbidity and/or mortality but they are outlined here because they are commonly used and may be useful in aiding detection of hypotensive pregnant woman at risk.

A low cost but potentially effective strategy in monitoring the wellbeing of a fetus is by the pregnant woman undertaking a daily fetal kick count. Recommending fetal kick counts may have lost favour with some because there is no general agreement on what constitutes reduced fetal movement and individual mother's perception of fetal movement

varies from woman to woman. However, suggesting hypotensive women keep a fetal kick chart may be of benefit because it is known that the fetus responds to chronic hypoxia and reduced placental supply by reducing movements in order to conserve energy.[190] Also some studies have found that women who are monitoring the well being of their baby in this way reduce their risk of stillbirth.[191-194] When explaining how to keep a fetal kick chart to the woman the midwife would need to be careful to keep the focus of this explanation on the potential usefulness of monitoring fetal well-being rather than on the potential for avoiding a stillbirth.

When investigating fetal wellbeing, serial Umbilical Doppler velocimetry studies, Biophysical profiles, or Cardiotocography (CTG) may also be helpful.

It is well known that conducting an antenatal CTG has no apparent effect on perinatal mortality or morbidity.[195] It is also well known that the use of electronic fetal monitoring (EFM) is fraught with disagreement and confusion about terminology and the trace itself is open to subjective interpretation. One common problem with CTG interpretation is determining the difference between a fetal 'sleep' trace and a trace with reduced variability. Vibroacoustic stimulation may be one worthwhile method that midwives can use to elicit fetal reactivity[196] in order to differentiate between the abnormal and the 'sleep' trace. Even though the use of EFM to determine fetal wellbeing is fraught with controversy, it is accepted that an abnormal trace (one with reduced heart rate variability less than five beats per minute, and/or decelerations of the complicated variable or late kind) is associated with poor outcomes and therefore a CTG may be of some value especially when it is used in tandem with other methods of assessing fetal wellbeing.

Another controversial test of fetal health is Doppler velocimetry. Investigating the pattern of waveforms in the umbilical artery was first reported in 1977.[197] Whilst it is known that

abnormal waveforms may indicate fetal compromise it is also recognised that acting on this result in isolation is associated with inappropriate intervention including early delivery. Therefore, it is suggested that the use of Doppler ultrasound should only be used judiciously and in tandem with other indicators of poor fetal prognosis.[197] There is one study that supports this suggestion, it examined outcomes when conventional CTG surveillance was combined with maternal report of decreased fetal movements and doppler velocimetries and concluded that there may be reassurance value in combining all three of these techniques.[198]

A 'biophysical profile' consists of a CTG, in combination with an ultrasound which examines fetal breathing movement, fetal movements, fetal tone and amniotic fluid volume. It is particularly used in North American, because it is thought that performing each of the tests involved in the 'profile' enhances the ability to detect poor fetal health.[199] However, there is at present no definite conclusion regarding this profile's reliability. Nevertheless, amniotic fluid volume is known to be reduced in the presence of placental dysfunction because of the diminished fetal renal perfusion[190] therefore performing either a biophysical profile or assessing diminished amniotic fluid volume may be a useful measure of fetal assessment when the pregnant woman is hypotensive due to the possibility that hypotension may result in placental hypoperfusion. Maternity care providers need to always consider the cost versus benefit of these tests especially in view of the ‘cascade of intervention’[200] which can result.

Intervention strategies

The findings from this study suggest maternity care providers (midwives and obstetricians) need to adopt a high degree of vigilance towards women who are hypotensive during pregnancy whilst awaiting further research which will answer

questions including the effect of maternal hypotension on poor pregnancy outcome and effective management strategies which reduce the risk of stillbirth in these pregnancies. This strategy includes a challenge to maternity care providers as it involves detecting and managing a group of women within the pregnant population who were previously considered low risk whilst avoiding subjecting 'normal' women to a 'cascade of intervention' which may not be necessary in their case.

Posterior located placenta: What can be done?

Clearly if the placenta is in the posterior position then nothing can be done to move it. However, once it is known that the placenta is posterior then this affords the maternity care provider with the opportunity to expectantly manage the pregnancy along the lines mentioned above in order to attempt to avoid a stillbirth. There is however research which has shown that maternal sleeping position around the time of implantation can influence placental position[154] therefore, in addition to the expectant management outlined above the following recommendation is made:

Maternal sleeping position

Women actively planning a pregnancy may benefit from information that highlights that they should sleep on their abdomens during the expected time of implantation so that the conceptus is more likely to implant on the anterior uterine wall. If sleeping on the abdomen is not possible due to possible neck or spinal problems then women should be informed at the very least to try sleeping on their sides.

It is important to reinforce that pregnant women should avoid sleeping on their backs throughout pregnancy but rather adopt a side-lying position supported with pillows.

Further research is needed to quantify the risk that posterior located placenta poses to pregnancy outcome as well as to explore preventive and management options of a placenta in this position. Meanwhile the results of this research would suggest that maternity care providers need to consider adopting a cautious attitude for women who have a posterior located placenta. It is recognised that at present there is little that can actually be done because intervention such as induction of labour with its associated risk of caesarean section[201,202] is not warranted based solely on the findings of this small exploratory study.

Unanswered questions

This study's findings should highlight that both maternal hypotension and posterior located placenta are concerning and that these require increased vigilance however, further prospective studies are necessary before large scale changes in maternity care can be recommended. Therefore, epidemiological studies using rigorous design aimed at clarifying the role that maternal hypotension and placental position play in stillbirth risk should be planned including a population which is sufficiently large to allow stratification into sub-groups such as preterm and term as well as hypotensive and normotensive. Examples of such studies could include:

- A large prospective study examining outcomes for hypotensive women whose pregnancies are expectantly managed due to knowledge of their hypotensive state.

- A study examining placentae from women who had maternal hypotension during pregnancy to determine if there are differences between placentation of these placentae compared with those from normotensive pregnancies.

- A study which identifies if hypotensive women are more prone to reduced liquor volume.

- A sleep study to determine what happens to the mildly hypotensive woman's blood pressure during sleep. This may be achieved prospectively in a sleep laboratory equipped with electronic fetal monitoring.

- Determinants of posterior placental position. A survey asking newly pregnant women about their habitual sleeping position followed by ultrasound confirmation of placental position at the mid-trimester scan may be one research strategy. This knowledge will enable care providers to be confident about the advice that women planning a pregnancy should sleep on their abdomens during the time of conception.

- A large prospective study comparing outcomes for women who have a posterior located placenta with pregnancies with other placental locations. Ideally, placental location should be identified by one experienced sonographer to limit observer variation.

In addition to these studies the 'other' findings from this study warrant further investigation along the following lines:

- A prospective study examining pregnancies with blood stained liquor to determine if there is any explanation for the blood's presence in the liquor. Such a study could ask the women who were noted to have blood in the liquor at birth to complete a questionnaire which might include information regarding recent history of fall or other blunt trauma as well as the attending accoucher completing any apparent reason why they think the liquor may have been blood stained.

- A prospective study estimating blood loss at time of stillbirth to determine if blood loss can be expected to be minimal as this study suggests.

- The retrospective nature of this study precluded data collection on one of the risk factors that Jason Collins[115] proposed i.e. length and thickness of the umbilical cord. In addition, another study found a relationship between excessive twists and spirals and unexplained stillbirth. Therefore, a prospective study is recommended to determine if a fetus is at greater risk of poor pregnancy outcome including stillbirth if it has a long, thin, excessively twisted or coiled umbilical cord. This study could also include nuchal cord occurrence.

- The finding that women are at increased risk of stillbirth if they have "quit" smoking should be investigated through a large prospective trail. Such a trial may determine if women who state that they have quit actually resume smoking during the pregnancy or if these women adopt other at risk related behaviours such as drinking too much coffee[12] or taking other recreational drugs.

- Results from this study suggest that women who suffer from hypertension and other medical and obstetric disorders which place women in a high-risk category are actually at less risk of stillbirth, this finding could be examined by a large randomised control trial.

- Further research is required to establish if women who have a lean BMI are more likely to be hypotensive.

Implications for practice

The implications of this study's findings are important for the development of standards of antenatal care including monitoring of women who have maternal hypotension during pregnancy or who have a posterior located placenta. Antenatal care providers can potentially avoid some stillbirths by adopting expectant management of women with these risk factors. However, it is recognised that further research is required which should inform current clinical practice, pregnancy management and diagnostic abilities. Until this has occurred, many babies may still be at increased risk of stillbirth. Furthermore, antenatal care providers following current best practice guidelines by themselves can only address one side of the risk associated with these factors. Women should also be aware of these potential risk factors and once aware pay close attention towards monitoring the wellbeing of their own unborn baby.

Research to practice nexus

A problem, which faces all researchers, is getting their research both known and accepted into practice.[203] This has been referred to as a 'nexus' because a nexus is the means of connection; in this case the nexus is the connection between research and practice.

Barriers to the implementation of research

There are some expected specific barriers to the adoption of this research into midwifery practice. These are lack of critique skills, disbelief, resistance to change and fear of legal action.[204] Each of these barriers is discussed here:

Lack of critique skills

It is possible that maternity care providers may lack all the necessary skills to critically analyse research. Many of these health professionals may be novice researchers and/or

beginners in critically evaluating and interpreting the results of research. In the case of midwives who were hospital trained they may lack even rudimentary research skills because this was not included in the hospital based training. In addition the use of best available evidence is not necessarily accepted. Even publication in a peer-reviewed journal does not guarantee general acceptance of research. All of these factors combine together to mean that the results of current research may not be read, nor understood.

Disbelief.

It is possible that maternity care providers may disbelieve that maternal hypotension or posterior located placenta during pregnancy could be a problem for the unborn baby. This is because there is a long held belief that maternal hypotension in pregnancy is good because it is not hypertension and that placental position is irrelevant if it is not low. Therefore, there needs to be quantum shift in thinking. Impetus for change in this thinking will start to come from knowledge of and education about this research.

Resistance to change

Changing practice to take note of any research may be resisted by some because of the associated risks of a cascade of intervention when choosing, for example, to induce labour.[205] Of course, it is not always possible for an individual midwife or obstetrician to implement changes based on new evidence especially if they are not an independent practitioner.

Fear of legal action

Provision of antenatal and birthing care is becoming more of a litigious minefield. This encourages clinicians to provide the usual and accepted standard of care and not to take risks. This means that research needs to be proven by rigorously produced high level

evidence prior to it being generally accepted and adopted into practice. For this reason and given the preliminary nature of this study further research is required on both maternal hypotension and posterior located placenta prior to practice change occurring.

Spheres of influence

Taking these anticipated barriers into consideration a plan has been formulated which will facilitate the dissemination of the results to maternity care providers worldwide. Such a strategy needs to address each of the above barriers in order to maximise the chances of this research being known and thought about by all who provide care during pregnancy. This plan involves use of the researcher's spheres of influence at local, national and international level. Strategic networking will broadly address the anticipated barriers to acceptance of this research in order to better disseminate the findings of this research.

Local spheres of influence

Individuals, groups and organisations within the researcher's local spheres of influence will be contacted. This contact will include a synopsis of this study along with an offer to present the findings. The aim of this contact is to impart knowledge of this research as well as demonstrate the importance of this research to pregnancy outcome. The following contact is planned:

- One-on-one with midwife colleagues especially those involved in provision of antenatal care and /or antenatal education.

- Directors of Nursing and/or Midwifery unit heads at maternity hospitals, both public and private offering to hold informal teaching sessions at "handover" time.

- Those involved in midwifery curriculum planning in local universities to include knowledge of these two risk factors is included in undergraduate and postgraduate midwifery programs.

- Talking to obstetrician colleagues on an ad hoc basis as well as disseminating information about this research directly to the College of Obstetricians through the Director of Education.

- Maternity care providers who have a particular interest in causes of perinatal death such as those serving on the perinatal sub-committee of the South Australian Department of Health.

- Pregnant women themselves can be made aware through a carefully worded media release as well as information provided to internet web site managers whose sites give information regarding pregnancy related issues.

National and international spheres of influence

Dissemination of these findings by teaching, speaking at conferences and publication will help raise the profile of this research. Therefore, the following dissemination strategy is planned:

- Presentation of the findings of this research is planned at selected conferences, which are likely to be attended by maternity care providers both nationally and internationally.

- Publication of the findings of this research should be in high impact peer reviewed journals to maximise the dispersion of information through the high readership of these journals.

- Direct contact with some of the people who assisted with the generation of this research e.g. Dr Jason Collins, as well as staff at Hospital B who assisted in the data collection.

- The researcher has a number of private contacts with maternity care providers as well as academics who teach midwifery at a national level.

- A press release is also planned regarding the results of this research to local and national media including television, radio, and print media.

- Use of the Internet. There are a number of midwife 'chat rooms' and 'bulletin/message boards' in existence around the world. Therefore a posting of the abstract of this thesis onto such a board will reach many maternity care providers directly and enable immediate feedback and discourse.

Conclusion

This study aimed to determine if there is a relationship between maternal hypotension and stillbirth, as well as to detect if there is a relationship between the posterior location of the placenta and stillbirth and assess if any relationship is compounded when the two variables are both present.

These aims were fulfilled through a retrospective case note audit using case-control method. Data were collected on women who had suffered a stillbirth and compared to

women who had delivered a live born infant. Factors known to be associated with stillbirth were either matched or controlled for in analysis. Results showed that women who had low diastolic readings during pregnancy were at increased risk of stillbirth. In addition, those women who had three MAP readings less than 83.3mmHg were at approximately twice as likely to suffer a stillbirth as 'normotensive' women. A similar risk was found for women who had a posterior located placenta. In this study, both maternal hypotension and posterior located placenta were determined to be independent risk factors for stillbirth.

This study is the first to specifically examine a stillborn population in order to explore whether maternal hypotension and posterior located placenta negatively impacted on stillbirth incidence. The results of this study suggest that both maternal hypotension and posterior located placenta are probably independent contributory risk factors for stillbirth. Whilst the reasons for this finding need further exploration these findings require maternity care provider's immediate attention.

Effective ways of identifying and managing those pregnancies, which are at increased risk because of these factors, need to be identified through further research. Some ideas for further research using a reproducible definition of hypotension have been proposed and plans for dissemination of these results have been outlined.

Whilst one could argue that neither maternal hypotension nor posterior located placenta are amenable to change it is hoped that as a result of knowing about the findings of this research, maternity care providers adopt a vigilant attitude towards hypotensive women or those with a posterior located placenta and that this will lead to a reduction in stillbirth incidence.

Epilogue

It is one of the most beautiful compensations of this life that no man can sincerely try to help another without helping himself.

Ralph Waldo Emerson

… the woman lets out a primeval scream and grunts loudly. The midwives can immediately see some of the head and one of them dons a pair of gloves ready to assist with the birth. The other speaks softly and reassuringly to the woman. Another contraction seizes the woman, this time the scream is blood curdling and she pushes again… the head 'crowns' and then delivers. The midwife eases a nuchal cord over the baby's head and guides the woman's hands under her baby's arms as she births the rest of her baby.

The woman greets her new arrival with a delighted, "hello". He is a perfectly formed baby. His hair is dark and curly…just like his mother's. He has big hands and big feet, just like his father. He is perfect in every way and his lusty cries fill the room with joy, bringing a tear to the eye of even the experienced midwife attending the birth.

Appendix One: Hospital A HREC approval

Women's & Children's Hospital
ADELAIDE

72 KING WILLIAM ROAD
NORTH ADELAIDE
SOUTH AUSTRALIA 5006

TELEPHONE (08) 8161 7000
FACSIMILE (08) 8161 7459

www.wch.sa.gov.au

13th June 2002

Mrs J Warland
23 Woodfield Ave
FULLARTON SA 5063

Dear Mrs Warland

Re: A retrospective case-control study to determine if maternal hypotension and placental position are associated with stillbirth. REC1302/4/2005

Thank you for your letter dated 15th May 2002 in which you responded to matters raised by the WCH Research Ethics Committee at its April meeting. I have also received approval from Dr R Sweet for access of case notes. All matters have been addressed and final approval is given for the study to proceed.

I remind you approval is given subject to:

- immediate notification of any serious or unexpected adverse events to subjects;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Such changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of a brief annual report on the state of progress of the study, and a final report when it is completed.

Approval is given for a period of three (3) years only, and if the study is more prolonged than this, a new submission will be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

Yours sincerely

Peter Baghurst

PETER BAGHURST
A/CHAIR
WCH RESEARCH ETHICS COMMITTEE

Appendix Two: Hospital B HREC approval

The Royal Women's Hospital
132 Grattan Street, Carlton 3053
Australia

Mr. Arthur C. B. Hui
Administrative Officer
Research and Ethics Secretariat
Tel: (03) 9344 2759
Fax: (03) 9347 1761
E-mail: arthur.hui@rwh.org.au

25.8.04

Mrs J Warland
Department of Clinical Nursing
The University of Adelaide
23 Woodfield Ave
Fullarton SA 5063

Dear Mrs Warland,

Re: Project 03/41 - A retrospective case control study to determine if maternal hypotension and / or placental position are associated with stillbirth

Following our recent correspondence, I confirm the project is now approved.

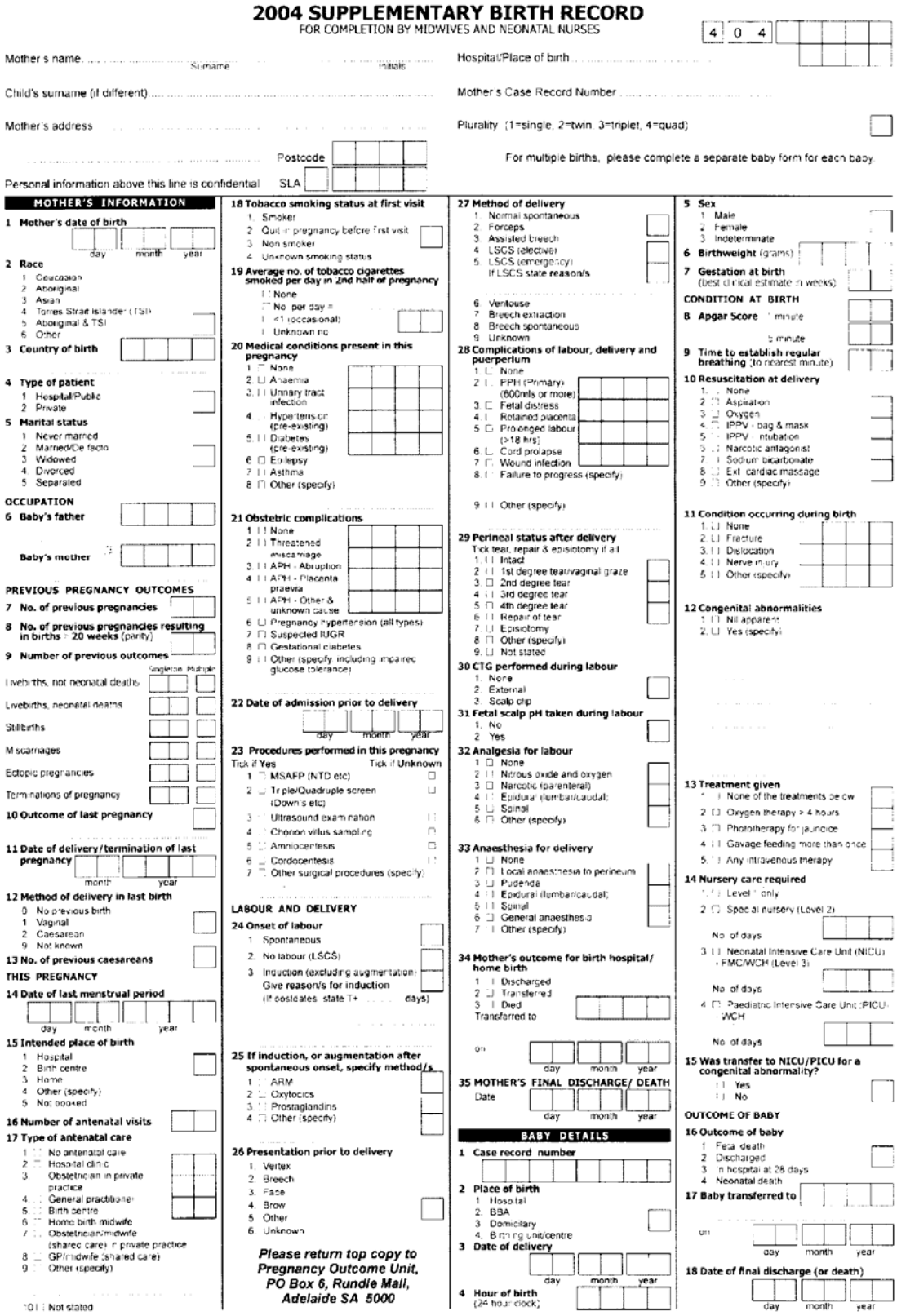
Enclosed please find Project Approval and Notification of Project Commencement Forms for your record. Please return the completed Notification of Project Commencement Form to me when the project begins.

Yours sincerely,

A. C. B. Hui
Administrative Officer
Research and Ethics Secretariat

Encl:

Appendix Three: Supplementary Birth Record (SBR)



2004 SUPPLEMENTARY BIRTH RECORD
FOR COMPLETION BY MIDWIVES AND NEONATAL NURSES

4 0 4

Mother's name ... Surname ... Initials

Hospital/Place of birth ...

Child's surname (if different) ...

Mother's Case Record Number ...

Mother's address ...

Plurality (1=single, 2=twin, 3=triplet, 4=quad)

... Postcode

For multiple births, please complete a separate baby form for each baby.

Personal information above this line is confidential SLA

MOTHER'S INFORMATION

1 Mother's date of birth day month year

2 Race
1 Caucasian
2 Aboriginal
3 Asian
4 Torres Strait Islander (TSI)
5 Aboriginal & TSI
6 Other

3 Country of birth

4 Type of patient
1 Hospital/Public
2 Private

5 Marital status
1 Never married
2 Married/De facto
3 Widowed
4 Divorced
5 Separated

OCCUPATION

6 Baby's father

Baby's mother

PREVIOUS PREGNANCY OUTCOMES

7 No. of previous pregnancies

8 No. of previous pregnancies resulting in births ≥ 20 weeks (parity)

9 Number of previous outcomes

	Singleton	Multiple
Livebirths, not neonatal deaths		
Livebirths, neonatal deaths		
Stillbirths		
Miscarriages		
Ectopic pregnancies		
Terminations of pregnancy		

10 Outcome of last pregnancy

11 Date of delivery/termination of last pregnancy month year

12 Method of delivery in last birth
0 No previous birth
1 Vaginal
2 Caesarean
9 Not known

13 No. of previous caesareans

THIS PREGNANCY

14 Date of last menstrual period day month year

15 Intended place of birth
1 Hospital
2 Birth centre
3 Home
4 Other (specify)
5 Not booked

16 Number of antenatal visits

17 Type of antenatal care
1 No antenatal care
2 Hospital clinic
3 Obstetrician in private practice
4 General practitioner
5 Birth centre
6 Home birth midwife
7 Obstetrician/midwife (shared care) in private practice
8 GP/midwife (shared care)
9 Other (specify)

10 Not stated

18 Tobacco smoking status at first visit
1 Smoker
2 Quit in pregnancy before first visit
3 Non smoker
4 Unknown smoking status

19 Average no. of tobacco cigarettes smoked per day in 2nd half of pregnancy
0 None
No. per day =
1 <1 (occasional)
9 Unknown no

20 Medical conditions present in this pregnancy
1 None
2 Anaemia
3 Urinary tract infection
4 Hypertension (pre-existing)
5 Diabetes (pre-existing)
6 Epilepsy
7 Asthma
8 Other (specify)

21 Obstetric complications
1 None
2 Threatened miscarriage
3 APH - Abruption
4 APH - Placenta praevia
5 APH - Other & unknown cause
6 Pregnancy hypertension (all types)
7 Suspected IUGR
8 Gestational diabetes
9 Other (specify including impaired glucose tolerance)

22 Date of admission prior to delivery day month year

23 Procedures performed in this pregnancy

	Tick if Yes	Tick if Unknown
1 MSAFP (NTD etc)		
2 Triple/Quadruple screen (Down's etc)		
3 Ultrasound examination		
4 Chorion villus sampling		
5 Amniocentesis		
6 Cordocentesis		
7 Other surgical procedures (specify)		

LABOUR AND DELIVERY

24 Onset of labour
1 Spontaneous
2 No labour (LSCS)
3 Induction (excluding augmentation)
Give reason/s for induction
(if postdates state T+ ... days)

25 If induction, or augmentation after spontaneous onset, specify method/s
1 ARM
2 Oxytocics
3 Prostaglandins
4 Other (specify)

26 Presentation prior to delivery
1 Vertex
2 Breech
3 Face
4 Brow
5 Other
6 Unknown

Please return top copy to Pregnancy Outcome Unit, PO Box 6, Rundle Mall, Adelaide SA 5000

27 Method of delivery
1 Normal spontaneous
2 Forceps
3 Assisted breech
4 LSCS (elective)
5 LSCS (emergency) If LSCS state reason/s
6 Ventouse
7 Breech extraction
8 Breech spontaneous
9 Unknown

28 Complications of labour, delivery and puerperium
1 None
2 PPH (Primary) (600mls or more)
3 Fetal distress
4 Retained placenta
5 Prolonged labour (>18 hrs)
6 Cord prolapse
7 Wound infection
8 Failure to progress (specify)
9 Other (specify)

29 Perineal status after delivery
Tick tear, repair & episiotomy if all
1 Intact
2 1st degree tear/vaginal graze
3 2nd degree tear
4 3rd degree tear
5 4th degree tear
6 Repair of tear
7 Episiotomy
8 Other (specify)
9 Not stated

30 CTG performed during labour
1 None
2 External
3 Scalp clip

31 Fetal scalp pH taken during labour
1 No
2 Yes

32 Analgesia for labour
1 None
2 Nitrous oxide and oxygen
3 Narcotic (parenteral)
4 Epidural (lumbar/caudal)
5 Spinal
6 Other (specify)

33 Anaesthesia for delivery
1 None
2 Local anaesthesia to perineum
3 Pudenda
4 Epidural (lumbar/caudal)
5 Spinal
6 General anaesthesia
7 Other (specify)

34 Mother's outcome for birth hospital/ home birth
1 Discharged
2 Transferred
3 Died
Transferred to
on day month year

35 MOTHER'S FINAL DISCHARGE/ DEATH
Date day month year

BABY DETAILS

1 Case record number

2 Place of birth
1 Hospital
2 BBA
3 Domiciliary
4 Birthing unit/centre

3 Date of delivery day month year

4 Hour of birth (24 hour clock)

5 Sex
1 Male
2 Female
3 Indeterminate

6 Birthweight (grams)

7 Gestation at birth (best clinical estimate in weeks)

CONDITION AT BIRTH

8 Apgar Score 1 minute
5 minute

9 Time to establish regular breathing (to nearest minute)

10 Resuscitation at delivery
1 None
2 Aspiration
3 Oxygen
4 IPPV - bag & mask
5 IPPV - intubation
6 Narcotic antagonist
7 Sodium bicarbonate
8 Ext. cardiac massage
9 Other (specify)

11 Condition occurring during birth
1 None
2 Fracture
3 Dislocation
4 Nerve injury
5 Other (specify)

12 Congenital abnormalities
1 Nil apparent
2 Yes (specify)

13 Treatment given
1 None of the treatments below
2 Oxygen therapy > 4 hours
3 Phototherapy for jaundice
4 Gavage feeding more than once
5 Any intravenous therapy

14 Nursery care required
1 Level 1 only
2 Special nursery (Level 2)
No. of days
3 Neonatal Intensive Care Unit (NICU) - FMC/WCH (Level 3)
No. of days
4 Paediatric Intensive Care Unit (PICU) - WCH
No. of days

15 Was transfer to NICU/PICU for a congenital abnormality?
1 Yes
2 No

OUTCOME OF BABY

16 Outcome of baby
1 Fetal death
2 Discharged
3 In hospital at 28 days
4 Neonatal death

17 Baby transferred to
on day month year

18 Date of final discharge (or death) day month year

Appendix Four: Data collection proforma

Year of birth

BABY DETAILS

1.Placental Location

1.Fundal
2.Posterior
3.Anterior
4.Lateral :
5. Praevia:
6. Other
7. Unknown

2.Cause of death

1. Unexplained
2. Preterm
3. IUGR
4. Infection
5. Hypertension
6. Intrapartum Asphyxia
7. Maternal Disease
8. APH
9. Fetal Abnormality
10. Other
11. Not stated

3. Autopsy

1. Yes
2. No

4. Contributing factors (autopsy)

1. Nil Noted
2. Signs of infection
3 Signs of asphyxia
4. IUGR
5. Two or more of above
6 Other (state)

5. Gender

1. Male
2. Female
3. Indeterminate

6. Weight

gms

7. Condition of baby

1. Macerated
2. Fresh
3 Not Noted

8. Liquor colour

1. Clear
2. MSL
3 MSL/BSL
4. PSL
5. BSL
6. Not noted

9. Nuchal Cord ?

1. Yes
2. No
3. Not Noted

10. Estimated time of death

1. Antepartum
2. Intrapartum
3. Unknown

11 Gestational age by dates

Dates agree with scan? Y/N

12 EBL (mls)

1. Min
2. 200-499
3. 500-999
4. 1000+
5. Not recorded

Appendix Five: Data collection proforma

Project Number:

Maternal Details

13. Blood Pressure

a.Systolic	b. Diastolic	c. Weeks

14. Race

1. Caucasian
2. Aborigirial / TSI
3. Asian
4. Other

15. Previous Spontaneous loss

1. Yes
2. No
3 Unknown

G P

16. Last Pregnancy Outcome

1. Nil
2. Livebirth
3. Neonatal deaths
4. Stillbirths
5. Miscarriages
6. Ectopic Pregnancies
7. Termination of pregnancy
8. Multiple pregnancy

17. No. of antenatal visits

18. Tobacco smoking @ 1st visit

1. Smoker
2. Quit smoking before first visit
3. Non Smoker
4. Unknown

19. Medical Condition present

1. None
2. Anaemia
3. Urinary tract infection
4. Hypertension (essential)
5. Diabetes (pre-existing)
6. Epilepsy
7. Asthma
8. Other
9. 2 or more of the above

20. Obstetric Complications

1. None
2. TMC
3. APH - abruption
4. APH- Placenta Praevia
5. APH- other /unknown
6. PIH
7. Suspected IUGR
8. Gestational Diabetes
9. Other
10. Two or more of the above

21. Hospital admissions

22. Maternal weight

kg

23. Height

cm

24.Hb Booking / Third Trimester

25. Blood group

1. A+ 5. A-
2. B+ 6. B-
3 O+ 7. O-
4. AB+ 8. AB- 9. Not noted

26.Maternal age

Appendix Six: Whitfield/ PSANZ comparison

Obstetric Cause-specific classification of perinatal deaths (Amended Whitfield)
The only sub-categories shown is 'other')

1.	**Spontaneous Preterm** < 37 weeks, normally formed, appropriately grown
2.	**Intrauterine Growth Restriction (IUGR)** < 10th percentile for gestational age
3.	**Unexplained Intrauterine Death** Normally formed fetuses without IUGR where fetal death is known to have preceded labour in the absence of any other primary complication
4.	**Birth Trauma** >1,500g with evidence of lethal trauma at autopsy even when labour and delivery were not complicated by mechanical difficulty
5.	**Intrapartum Asphyxia** >1,500g with evidence of intrapartum hypoxia and confirmed by hypoxic changes at autopsy
6.	**Hypertension**
7.	**Maternal Disease**
8.	**Antepartum Haemorrhage (APH)**
9.	**Fetal Abnormality**
10.	**Haemolytic Disease**
11.	**Infection** Pathological evidence of infection required. Infections occurring as primary factors including deaths with chorioamnionitis or congenital pneumonia preceding membrane rupture
12	**Other**
	12.1 Non-immune hydrops 12.2 Feto-maternal haemorrhage 12.3Twin-twin transfusion 12.4 Accident, poising or violence (postnatal) 12.5 SIDS 12.8 Unknown/ unexplained 12.9 Other

Perinatal Society of Australia and New Zealand- Perinatal Death Classification (PSANZ-PDC) (sub-categories not shown other than specific perinatal conditions)

1.	**Congenital Abnormality**
2.	**Perinatal Infection**
3.	**Hypertension**
4.	**Antepartum Haemorrhage (APH)**
5.	**Maternal Condition**
6.	**Specific Perinatal Conditions**
	6.1 Twin-Twin transfusion 6.2 Fetomaternal haemorrhage 6.3 Antepartum cord complications e.g. cord haemorrhage; true knot with evidence of occlusion. 6.4 Uterine Abnormalities e.g. bicornuate uterus , cervical incompetence 6.5 Birth trauma (typically infants < 24 weeks gestation or < 600g birthweight) 6.6 Alloimmune disease 6.7 Idiopathic Hydrops 6.8 Other specific perinatal condition (includes iatrogenic conditions such as rupture of membranes after amniocentesis. Termination of pregnancy for suspected but unconfirmed congenital abnormality)
7.	**Hypoxic Peripartum Death** (typically infants < 24 weeks gestation or < 600g birthweight)
8.	**Fetal Growth** Restriction (FGR)
9.	**Spontaneous Preterm (< 37 weeks gestation)**
10.	**Unexplained Antepartum Death**
11.	**No Obstetric Antecedent**

Appendix Seven: Hypotensive symptoms questionnaire.

Please indicate on the scales below how often you experience the following:

Tiredness

Never _____Fairly often_____ All the time

Cold hands and feet

Never _____Fairly often_____ All the time

Headache

Never _____Fairly often_____ All the time

Dizzy spells

Never _____Fairly often_____ All the time

Numbness in hands and feet

Never _____Fairly often_____ All the time

Visual disturbances including sudden, temporary darkening of vision or double vision

Never _____Fairly often_____ All the time

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