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INTRODUCTION

A1

Emerging ideas to better understand and prevent stillbirths

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It is estimated that over 3.6 million babies are stillborn each year [1]. Although the majority of these occur in low-income countries, stillbirth continues to place a significant burden on maternity services in high-income settings where approximately 1 in 200 infants born after 24 weeks gestation is stillborn [1]. Despite advances in ultrasound detection of lethal fetal anomalies and widespread access to antenatal care, the stillbirth rate in many high-income countries has not decreased in over two decades. Stillbirth remains an enigma, in part due to lack of research investigation, but also due to a failure to accurately identify causes and understand how they lead to stillbirth. Recent meta-analyses resulting from international collaborations have highlighted the need to expand the understanding of stillbirth.

To this end, a meeting, the Stillbirth Summit, presented by the Star Legacy Foundation and supported by various organizations, was held in October 2011, Minneapolis, MN (USA) to discuss emerging ideas in the field of stillbirth research and management. In particular the focus was on the placenta, cord, infection and inflammation, reduced fetal movements and maternal sleep. Attendees were invited researchers, stillbirth advocates and parents.

The aim of this supplement is to briefly summarise the scientific aspects of the meeting.

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ORAL PRESENTATIONS

A2

Abnormalities of the placenta

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Normal placental structure and function is essential for a healthy pregnancy; the placenta is responsible for nutrient and oxygen transport, removal of waste products, protection from infection, modulation of the maternal immune system and hormone production to maintain pregnancy. The human placenta is structurally adapted to fulfil this role as it is haemomonochorial, minimising the distance between maternal and fetal circulations to maximise exchange. Disorders of the placenta including: FGR, pre-eclampsia, placental abruption and abnormal (velamentous) cord insertion are associated with over 50% of stillbirths and are frequently cited as the primary cause of death [1-3].

Abnormal placental structure and function significantly increases the risk of stillbirth. Levels of pregnancy associated plasma protein A (PAPP-A) in the lowest 5% and alpha fetoprotein (AFP) in the highest 5% increase the risk of stillbirth by 50-fold and 2.8-fold respectively [4,5]. In women at high-risk of pregnancy complications, abnormal placental structure and/or blood flow seen by ultrasound scan at 19-23 weeks preceded 15 out of 22 stillbirths [6]. There are few studies of microscopic placental structure in stillbirth. However, microscopic structure and cell turnover of the villous trophoblast are disrupted in FGR and pre-eclampsia [7-9]. Evidence from genetic analyses demonstrated that gene imprinting in the placenta is altered in pregnancy loss [10]. The importance of placenta genetics and epigenetics is supported by the observation of increased stillbirth and pregnancy loss in confined placental mosaicism where genetic abnormalities are only present in the placenta [11].

Due to its central role in determining pregnancy outcome, detailed examination of the placenta can give useful information about the cause of stillbirth and is recommended by the Royal College of Obstetricians and Gynaecologists (RCOG), American College of Obstetricians and Gynecologists (ACOG) and Perinatal Society of Australia and New Zealand (PSANZ) [12,13]. Examination of the placenta reduces the proportion of unexplained stillbirths [14]. Consequently, examination of the placenta is one of the most common investigations undertaken after a stillbirth and is one of the most valuable [2,15].

Despite the value of placental examination to identify conditions associated with stillbirth including: fetal thrombotic vasculopathy, chronic intervillositis, villitis, chorioamnionitis, funisitis, infarction, massive perivillous fibrin deposition, villous dysmaturity (increased syncytial knot formation), villous immaturity and cord lesions further research is needed to increase the understanding of placental pathology in stillbirth. This is reflected in the research priorities for high-income countries synthesised by an international panel of experts which mention need for repositories of well-phenotyped samples from stillbirths and from well-matched controls and the need to understand the pathophysiological pathways in common conditions associated with stillbirth including: diabetes, cigarette smoking and maternal obesity [16].

An important goal of translational medicine is to use the increased understanding of placental dysfunction to develop improved tests of pregnancy wellbeing. For example, factors derived from the placenta, such as human placental lactogen or placental growth factor may provide novel means to identify pregnancies at highest risk of stillbirth [17]. Discovery-based technologies such as proteomics or metabolomics offer the opportunity to analyse biofluids and tissue in hypothesis-generating studies

to provide a more holistic understanding of fetal and placental dysfunction. Better understanding of the role of the placenta in stillbirth offers the opportunity to develop strategies to identify placental dysfunction in pregnancies, in order that intervention may be targeted to prevent stillbirth.

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A3

Structural abnormalities in the placenta

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Genes regulate the development of fertilised egg into the inner cell mass (which will become the embryo, fetus and, eventually, baby) and the trophoblast (which will become the placenta). Defects in the genes that regulate these processes lead to a wide range of embryonic, fetal and neonatal defects, from minor cosmetic abnormalities, to such severe defects disasters that a pregnancy miscarries within a few days to weeks after fertilization. Since the placenta and fetus share the same genome, genetic defects in the fetus are often mirrored in the placenta as abnormal growth patterns. Abnormal growth pattern of the trophoblast layers, namely trophoblast invaginations, appear to be associated with genetic defects in the fetus. When these deep pits are cut in cross section they appear as trophoblast inclusions. Compared to the placentas from normal children there is a significantly increased frequency of trophoblast inclusions in cases of known chromosomal diseases, such as trisomy 21, 13 and 18, as well as triploidy.

A4

Placental volume

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The relationship between placental size and pathology and risk of stillbirth is well recognised. Placental volume may predict birthweight and by association, outcome of pregnancy. The size of the placenta can be determined by two-dimensional sonography and volumetric mathematic modelling [1] and placental volume could be calculated at each ultrasound scan. We have developed a mathematical solution to accurately estimate intrauterine placental volume. Caregivers of pregnant women currently only track the growth of the fetus without any insight into the growth of the placenta, despite its importance in prenatal development. In situations where the placenta is significantly small or large for gestational age, a caregiver may not have any warning that the fetus is compromised or near death until it is too late. Fetal complications due to placental abnormalities occur in as many as 20% of pregnancies. Clinical intervention is possible with early detection. This invention allows for assessment of *in utero* placental volume using three basic measurements: width, height and thickness of the placenta. There are no alternative simple, reliable or convenient methods to determine the volume and/or weight of a placenta prior to delivery available today. We propose to use this method to generate normative data on a large population of pregnant women which can be used to automatically flag abnormal placental size. Such normative data will form the basis for the generation of tables which can be incorporated into future ultrasound devices. This will empower future caregivers to identify and intervene in cases where an intrauterine fetal death would have been the first indication of any problems.

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A5

Placental findings in cord accidents

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Many stillbirth cases are under- or completely un-investigated, for many reasons, including lack of consent for fetal autopsy. Placental examination is a non-invasive means, by which much information can be gained about adverse pregnancy outcomes, including stillbirth. Complete gross and histologic examination of the placenta can both point out and exclude multiple potential causes for stillbirth.

"Cord accident," defined by obstruction of fetal blood flow through the umbilical cord, is a common ante- or perinatal occurrence. Obstruction can be either acute, as in cases of cord prolapse during delivery, or subacute-to-chronic, as in cases of grossly abnormal umbilical cords (e.g. long cord, hypertwisting, cord with true knots, entangled cord, velamentous cord, etc). In the past, this diagnosis has relied on clinical history and has otherwise been one of exclusion for the pathologist, when, following a complete autopsy and placental examination, no other cause of death is

found. Since as many as 20% of normal livebirths are associated with a nuchal cord, clinical history by itself is not reliable for diagnosis of this entity. Over the past few years, we have studied the placenta in setting of cord accident, and have established histologic criteria for its diagnosis, which can identify this entity with high specificity [1,2].

Our initial study identified cord accident-related changes in large fetal vessels in the placenta [1]. These changes are all likely related to obstruction-induced vascular stasis, leading to dilated and thrombosed fetal vessels, most commonly found in the chorionic plate and large stem villous vessels [1,2]. These "minimal" criteria have a sensitivity of 62% and specificity of 79% [2]. The additional finding of fetal thrombotic vasculopathy (FTV) in sections of placental disc increases the specificity to 94%, albeit lowering the sensitivity (46%) [2]. FTV is defined by the diminuition of fetal vessels in terminal chorionic villi, leading early on to "villous stromal karyorrhexis," with fragmented red cells and cellular debris over the receding fetal vessels, and later on, by "avascular villi," characterized by fibrotic stroma and complete avascularity [3]. Originally suspected to be a marker for fetal and/or maternal thrombophilia, more recent studies have found it to be most commonly associated with grossly abnormal umbilical cords, which predispose to cord compression and compromise fetal blood flow [3]. Our own previous studies have shown that FTV is commonly seen in cases with gross abnormalities of the umbilical cord [4] as well as associated with fetal growth restriction, congenital heart abnormalities, and stillbirth, particularly those associated with umbilical blood flow compromise [5].

A few considerations regarding application of these criteria warrant mention here. First, these changes are characteristic of intermittent interruption of umbilical cord blood flow, and are therefore not useful in cases of acute cord accident (e.g. cord prolapse) [1]. Second, post-mortem changes in the chorionic villi can resemble changes of FTV, particularly when the placenta is retained over 48 hours following stillbirth [6]. In these settings, it is important to remember that FTV is a temporally heterogeneous lesion, while post-mortem change is uniform throughout the entire placental disc; therefore, the two are distinguishable in a careful histologic examination of the placenta [1,2,6]. Finally, due to the temporal heterogeneity of FTV, and the fact that focal FTV cannot be identified grossly, a more thorough sampling of the placental disc is warranted in the setting of stillbirth, particularly if cord accident is suspected. We routinely submit 4, instead of the usual 2, sections of the placental disc in the setting of stillbirth.

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A6

Cord around the neck syndrome

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A nuchal cord (or Cord-Around-the Neck (CAN)) occurs when the umbilical cord becomes wrapped around the fetal neck 360 degrees. Nuchal cords are very common, the incidence of nuchal cord increases with advancing gestation from 12% at 24 to 26 weeks to 37% at term [1]. Most are not associated with perinatal morbidity and mortality. In some fetuses and newborns CAN may cause problems, especially when the cord is tightly wrapped around the neck. The cluster of cardiorespiratory and neurological signs and symptoms associated with unique physical features that occur secondary to tight cord-round-the-neck has been referred to as 'tCAN syndrome' (tight Cord Around the Neck Syndrome) [2]. A small number of studies have shown that nuchal cord and or tCAN can affect the outcome of delivery and may have long-term effects on the infant [3] and but as a causative factor for stillbirth it is debatable [4,5]. However, some case reports of postmortem findings on stillbirths show negative pathology reports and tight cord around the neck being the only cause of death [6].

It is the unique physical features of tCAN syndrome that distinguishes it from birth asphyxia even though there are many similarities between these two conditions. Umbilical cord abnormalities are considered as one of the causative factor for birth asphyxia. The manifestation of tCAN symptomatology seems to happen both in the presence of normal and depressed AGPAR scores [7]. Umbilical cord compression due to tCAN may cause obstruction of blood flow first in thin walled umbilical vein, while infant's blood continues to be pumped out of baby through the thicker walled umbilical arteries thus causing hypovolemia and hypotension resulting in acidosis [8]. Anemia [9] and mild respiratory distress may occur. Some of these infants may also have facial and conjuctival petechiae [10] and rarely petechiae of the neck and upper part of the chest and skin abrasion of neck [11] where the cord was tightly wrapped and facial suffusion [12], all of which can also be seen in some postmortem findings of stillbirth infants who had tCAN [Archana Bargaje, personal communication]. If born alive, some of these infants may also be somewhat obtunded with a low tone and have transient feeding difficulties. These findings raise the possibility of transient encephalopathy, which may lead to long-term complications.

A stillbirth attributed to a cord problem should have evidence of cord obstruction or circulatory compromise. Other potential causes of stillbirth need to be excluded prior to labelling cord abnormalities as the causative factor, since cord abnormalities seen in more than a third of all normal live births.

The tCAN Syndrome may conceptually be similar to strangulation which may result in non lethal problems or death. The pathophysiological mechanisms of strangulation injuries (lethal and non lethal) involves venous, arterial obstruction (arterial spasm due to carotid pressure) in the neck and vagal collapse (increased parasympathetic tone) [13]. This can lead to cerebral stagnation, hypoxia, and unconsciousness, which, in turn, produces loss of muscle tone. The same pathophysiology of strangulation may possibly be applicable to tCAN syndrome in neonates. A study on potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight showed evidence of association of tCAN in children with quadriplegia [14].

Intermittent umbilical cord occlusion in preterm and near term sheep caused a decline in pO_2 and pH, and higher PCO_2 and altered brain protein synthesis/degradation [6]. Whether human fetal intermittent strangulation by tCAN have similar brain protein alterations and thus long-term effects remains to be seen. Using specific placental histologic criteria for umbilical blood flow restriction in unexplained stillbirth Parast et al [4] showed significant correlation of placental changes of "minimal histologic criteria" with cord accidents (as tCAN is part of cord accidents). Nuchal cords showed highest rates of thrombosis-related placental histopathology and fetal thrombotic vasculopathy and thrombosis seems to be highly specific for cord related stillbirths [4,5].

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A7

Umbilical cord accidents

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The Stillbirth Collaborative Research Network recently reported on the probable or possible cause of death of 512 stillbirths whose mothers consented to complete postmortem examination [1]. Umbilical cord accidents (UCA) represented 10% of stillbirths [1]. In Caucasians the UCA associated stillbirth rate was 13% and 4% in non-Hispanic black. 9% of stillbirths were due to hypertension and 8% due to other maternal medical disorders. A literature review places the UCA associated stillbirth rate at 15% [2]. These data bases do not include stillbirth due to several UCA pathologies such as: torsion, multiple cord entanglement and abnormal placental cord insertion. The main reason for these absences is the belief by some that these abnormalities do not cause actual death or recurrent stillbirth.

One of the first published accounts of an UCA in western medical writings was by William Smellie his Treatise on Midwifery in 1750, London, England: a nuchal cord associated stillbirth. One of the first published drawings of an UCA was by Andrew Bell in the Encyclopedia Britanica 1st edition 1769 Edinburgh, Scotland, depicting a fetal death with a combination of one nuchal cord, a body loop and a true knot (currently on the cover of the Royal College of Obstetricians and Gynaecologists (UK) brochure).

As UCA is a significant cause of death, JC argues it is now time for the focus to be on screening for UCA, managing UCA prenatally and delivery of the baby in distress defined by the American Congress of Obstetricians and Gynecologists as a heart rate of 90 beats per minute for 1 minute on a recorded non-stress test. The ability of ultrasound and magnetic resonance imaging (MRI) to visualize UCA is well documented. The 18-20 week ultrasound review should include the umbilical cord, its characteristics and description of its placental and fetal attachment. The American Association of Ultrasound Technologists has defined these parameters for umbilical cord abnormalities:

- Abnormal insertion
- Vasa previa
- Abnormal composition
- Cysts, hematomas and masses
- Umbilical cord thrombosis
- Coiling, collapse, knotting and prolapse

Umbilical cord evaluation with sonography includes the appearance, composition, location and size of the cord [3]. A normal cord has a single vein and 2 arteries that have a twisted, rope-like appearance. Absence of twisting often is associated with a decrease in fetal movement and a poor pregnancy prognosis.

Umbilical cord pathology is separate from placental pathology [4]. Developmentally the umbilical cord is fetal in origin not placental [5]. The umbilical cord originates from the "primitive ridge" of the embryo. There are paternal genetic elements influencing growth and development. To date there have been no reports of mosaicism in the human umbilical cord. The Human Genome Project has not reviewed cord genetics. There are eight different umbilical cord designs. None of these issues have been incorporated into a detailed prospective study of pregnancy and outcomes. Our current knowledge of the human umbilical cord and its influence on the fetus is limited. Interactions between the fetus and umbilical cord are becoming apparent due to studies of fetal behavior.

Hyperactivity is a fetal response associated with umbilical cord compression risk factors [6]. This fetal behavior may be related to intrauterine umbilical blood flow disturbance which stimulate the fetus to react reflexively and excessively. Animal studies (in rats and sheep) have reproduced forms of hyperactivity with cord compression. Hyperactivity may be a prenatal behavior capable of repositioning the fetus and relieving the compression. In the rat model, umbilical cord compression triggered lateral trunk curls, head tosses and foreleg extensions. In the sheep model intermittent umbilical cord compression triggered fetal hiccups. Hiccups occurring daily after 28 weeks, and greater than 4 times per day requires fetal evaluation. UCA should be looked for no matter how trivial it seems on ultrasound.

Fetal body movements have been studied with ultrasound over 24 hour periods [7]. These movements are unique between midnight and 6 a.m. Time of fetal behavioral observation (bedtime and midnight to 6 a.m.) may need to be included in any future stillbirth study. Fetal jerking movements and fetal hiccups may also be related to fetal blood flow disturbances especially cord compression. These maternal observations should be taken seriously and prompt an ultrasound review of the fetus looking for UCA.

Recent research into circadian rhythms may help explain why UCA stillbirth is an event between 2 a.m. and 4 a.m. Melatonin has been described as stimulating uterine contractions through the M2 receptor [8]. Melatonin secretion from the pineal gland begins around 10 p.m. and peaks to 60 pg at 3 a.m. Serum levels decline to below 10 pg by 6 a.m. Uterine stimulation intensifies and may be overwhelming to a compromised fetus, especially one experiencing intermittent umbilical cord compression due to UCA. Pregnancy Institute has documented over 1000 UCA stillbirths through patient interview that occurred during maternal sleep.

UCA are an important cause of stillbirth. It is now possible to identify UCA on ultrasound and test for the compromised fetus. As with gestational hypertension, screening for UCA is needed to possibly avoid thousands of stillbirths worldwide. If UCA is detected, the mother should be hospitalized and evaluated with ultrasound and fetal heart rate monitoring for at least 24 hours. If fetal behavior or the fetal heart rate is abnormal, the observation period should be extended and if necessary deliver the baby.

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A8

Infection and inflammation

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Potentially preventable maternal infections are increasingly recognized as being a cause of fetal death or stillbirth. McClure and Goldenberg maintain that infection causes 20% to 40% of fetal deaths in developed and developing countries respectively [1]. Infection causes embryonic, fetal, and perinatal death by multiple mechanisms including:
1) direct, blood borne placental infection (via maternal blood stream),
2) ascending vaginal infection through the cervix,
3) iatrogenic infection (such as amniocentesis and "membrane stripping"), and
4) persistent uterine infection already present during implantation [2].
More recently recognized mechanisms include:
1) combined viral and microbial infections, in which placental viral infection sensitizes to the effects of bacterial lipopolysaccharide [3],
2) "graft vs. host" immunologic phenomena in which ongoing or preceding infections may potentiate maternal and/or fetal inflammatory rejection mechanisms, and
3) "sterile inflammation" considered to be due to innate immune or "autophagic" mechanisms which are required to remove dead cells caused by "senescence" or apoptosis [4].
The types of microbes causing stillbirth vary by location, population, and occupational factors. These include all taxa of microbes: bacteria, mycoplasmas, viruses (entero and herpes viruses), fungi (yeasts), rickettsia (Q-fever and Rocky Mountain spotted fever), parasites (toxoplasmosis), and possibly nematodes and transposons or prions.
Infection-caused stillbirth or septic miscarriage occurs when invasive microorganisms either overwhelm embryonic or fetal innate and adaptive immune host defense mechanisms or cause sufficient cell and tissue death to result in the death of the entire placenta and embryo or fetus. Less extensive intrauterine infections or inflammation can also damage the developing embryo or fetus causing lifetime disability. We now understand that host immune cells and tissue pathophysiologic "death mechanisms" can stimulate necrosis (death of internal cell organelles) or apoptosis (due to "death programming") cell signalling [5]. Both processes may cause considerable organ damage in vulnerable organs, especially the central nervous system and special sense organs (retina, hearing organs) without causing "cardiac death" clinically recognizable by loss of heartbeat. As an example, Group B streptococcus (GBS) is widely recognized to cause lifelong brain injury from meningoencephalitis or systemic "FIRS" (fetal inflammatory reaction syndrome.) Infection-caused stillbirth may occur as isolated cases (syphilis) or in epidemics (Q-fever or foodborne Listeria infection.)
Successful programs prevent prevalent causes of infection-caused stillbirth depend upon:
1) recognition of the problem,
2) means to identify the agent, and
3) effective means to treat intrauterine infections.
Prevention of GBS infection is an example of programmatic primary prevention of septic stillbirth through identification and treatment of GBS urinary tract infection or asymptomatic bacteriuria with penicillin followed by test of cure (TOC) [6].
Other successful examples of secondary prevention are anti-syphilis and anti-HIV programs which unite maternal screening and indicated treatments.
Primary prevention (before maternal infection) of infection-causing reproductive loss depends on the knowledge of the epidemiology and pathophysiology of the particular infectious agents. Examples include preventing rubella and varicella by vaccinations, listeriosis via milk pasteurization, and malaria by using mosquito netting. Prevention of more recently understood causes, such as ascending *in utero* infection due to GBS, BV, or associated vaginal microflora, will require new care practice strategies including expanded screening and maternal vaccination. Such prenatal programmatic change will require a concerted and organized effort.
In Germany, weekly vaginal pH screening using a *sensitive* indicator (increased vaginal pH over 4.7) has been used to indicate the need for *specific* microbial testing and treatment. Other approaches to preventing ascending vaginal infection include specific screening for prevalent abnormal microflora (vaginitis, GBS, or sexually transmitted infections) in populations at risk.

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A9

Low blood pressure

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The link between high maternal blood pressure and poor pregnancy outcome is well established. Similarly the causal relationship between acute maternal hypotension and acute fetal distress is well recognised. The link between poor pregnancy outcome and persistent maternal hypotension is less well known.
McClure Brown [1] was the first to report an increase in perinatal mortality in the presence of persistent maternal hypotension. In a prospective trial involving more than 7,000 primigravid women conducted in the 1960s he noticed a "curious" association between low initial (first visit) systolic and diastolic blood pressure and increased risk of stillbirth. Nearly 20 years later Friedman and Neff [2] also found a similar level of risk in a population based study of more than 38,000 women who presented with persistently low (over 4 visits) diastolic hypotension and poor pregnancy outcome. A number of German studies conducted in the 1980s also variously reported findings suggesting a relationship between maternal hypotension and poor pregnancy outcome such as FGR and stillbirth. For example, a retrospective study comparing hypotensive pregnant women with their normotensive peers found there was an increased risk of preterm birth, IUGR and complications such as meconium stained liquor and post partum hemorrhage in the hypotensive group [3]. There were seven stillbirths in total in their study, four in the hypotensive and three in the normotensive groups, but the study was underpowered to detect any statistically significant difference on this rare outcome. Zhang and Klebanoff [4] further investigated the "paradox" of hypotension. Using the same data bank as Friedman and Neff they found the lower the baseline the higher the risk of poor pregnancy outcome. They suggested that the mechanism for this finding may be poor placental perfusion in the hypotensive group, also implicated in several of the German studies. In another large population based study Steer et al [5] described higher risk of low birth weight and increased risk of perinatal mortality in their hypotensive group. Although Chen [6] pointed out that this finding may be due to failure to take into account gestational length, in a case-control study matched for gestational age [7] still found an association between hypotension and stillbirth.
It is problematic that previously reported studies have defined maternal hypotension differently. However, Warland [7] attempted to address this by including all previously used definitions as well as mean arterial pressure (MAP). Diastolic hypotension and low MAP seemed more "dangerous" than systolic hypotension and this supports findings from earlier German studies which suggest that the casual mechanism for hypotension on poor pregnancy outcome is poor placental perfusion.

In summary, there is a small body of research which has consistently demonstrated the negative effect of persistent maternal hypotension on poor pregnancy outcome including stillbirth. These studies have been conducted using a range of approaches including prospective cohort, retrospective case-control and population based data bank analysis. Many questions remain unanswered, including the definition of hypotension, the level at which hypotension becomes problematic, and how best to manage maternal hypotension in pregnancy.

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A10

Reduced fetal movements

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The association between a reduction in fetal movements (RFM) and stillbirth has been noted for at least 450 years. This was formalised from the 1970s onwards in a series of studies that noted the increased incidence of stillbirth and FGR in women presenting with RFM, which in some cases preceded intrauterine fetal death by several days. Interpretation of the literature relating RFM to stillbirth and FGR is complicated by differences in studies' definitions of RFM and FGR [1]. Nevertheless, the association between RFM and stillbirth remains, irrespective of the definitions used. Recently, the Auckland Stillbirth Study confirmed that women who had a RFM were 2.4 times (95% CI 1.29-4.35) more likely to have a late stillbirth [2], which is strikingly similar to a UK-based study which found a 3-fold increase in stillbirth after one presentation with RFM [3]. RFM, FGR and stillbirth are thought to be related by placental insufficiency, with RFM representing fetal compensation to restriction of nutrients and oxygen *in utero* [4,5]. This hypothesis is supported by evidence of abnormal placental structure and amino acid transport in women with RFM, even in the absence of a small-for-gestational age fetus [6].

Despite the association between RFM and stillbirth, RFM is frequently suboptimally managed clinically. Of 422 stillbirths reviewed in a confidential enquiry, 16.4% of cases had suboptimal care related to RFM, including: not communicating the importance of RFM to mothers and a failure to act on RFM [7]. Reasons for clinicians' behaviour have been explored by two related questionnaire studies, one in the UK and one in Australia and New Zealand. Both of these studies found significant variations in the definitions of RFM applied to clinical practice and varied knowledge of the association between RFM, FGR and stillbirth. As a consequence clinical management of women with RFM varied significantly, with cardiotocography being used in 80-90% of cases and ultrasound assessment of fetal growth, liquor volume and umbilical artery Doppler in approximately 20% of cases [8,9].

Due to the association between RFM, FGR and stillbirth, ultrasound assessment of fetal growth, liquor volume and umbilical artery Doppler may be useful screening tests to identify placental insufficiency [10]. Norwegian studies have suggested that asking women to be more aware of fetal movements did not increase the number of attendances with RFM. Importantly, the implementation of an associated quality-improvement programme was associated with increased use of ultrasound, but a reduction of stillbirth from 4.2% to 2.4% [11], strongly suggesting that appropriate identification of, and intervention following, RFM may decrease the incidence of stillbirth. The management of RFM may be improved by more sensitive tests to specifically identify placental dysfunction, including measurement of placentally-derived factors such as human placental lactogen or placental growth factor [12,13].

The use of RFM as a screening tool for stillbirth prevention needs to be developed; it has the advantages that it is free and does not significantly increase the burden on the antenatal service. However, the best management protocol after women present with RFM has yet to be determined. To date there have been no randomised controlled trials of the management of RFM, despite calls from the World Health Organisation to improve the quality of evidence regarding stillbirth prevention [14]. Therefore, a high-quality trial is needed to evaluate whether intervention (delivery) directed by appropriate investigations after RFM can reduce the incidence of late stillbirth, without significantly increasing maternal and perinatal morbidity.

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A11

Sleep disruption and adverse pregnancy outcomes

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A recent meta-analysis reported the most important and potentially modifiable risk factors for stillbirth [1]. Approximately half of these risk factors are likely influenced by maternal sleep disruption. Poor sleep occurs for many reasons although the most common sleep problems include:

• sleep restriction (short sleep duration), which is often self-imposed because of busy lifestyles;

• sleep-disordered breathing (SDB), a term which describes a spectrum of breathing problems during sleep from habitual snoring to obstructive sleep apnea, resulting in oxygen desaturation and sleep fragmentation; and

• poor sleep quality.

Emerging literature now suggests that sleep disruption during pregnancy is associated with poor pregnancy outcomes for both mother and infant [2]. There are emerging associations between maternal sleep and several major risk factors for stillbirth: maternal obesity, gestational hypertension/ pre-eclampsia, gestational diabetes, and intra-uterine growth restriction (IUGR).

In recent years, sleep duration has drastically fallen and has been paralleled by a rise in the prevalence of obesity. Chronic sleep restriction (such as self-imposed short sleep duration) plays a pivotal role in the pathophysiology of overweight and obesity via the modulation of neuroendocrine function. Sleep disruption, including short sleep duration and sleep fragmentation, has emerged as a major determinant of metabolic health, independently of weight and is implicated in poor glucose control [3] and possibly gestational diabetes.

Of note, approximately half of all Western women of childbearing age are overweight or obese and obesity can lead to increased risk for sleep disorders such as SDB. Habitual snoring is the main symptom of SDB and its frequency reaches a peak in the third trimester, affecting approximately one third of pregnant women in general, and the majority of those with pre-eclampsia. Habitual snoring is independently associated with gestational hypertension and pre-eclampsia [4]. Although the pathogenesis of pre-eclampsia is not completely understood, the biological pathways include endothelial dysfunction, oxidative stress, and inflammation. The pathogenic process likely originates in the placenta during early pregnancy with abnormal implantation and vasculature development. This leads to oxidative stress and inflammation with subsequent release of anti-angiogenic factors and widespread endothelial dysfunction. Sleep disruption, including poor sleep quality, in early pregnancy has been suggested to adversely impact implantation [5] which has the potential to accelerate the cascade of inflammation and oxidative stress described above. Notably, the mechanisms of sleep disruption that affect cardiovascular morbidity are remarkably similar to the biological pathways for pre-eclampsia.

Poor sleep quality during pregnancy is already evident in the first trimester and has been associated with increased risk for longer labors and Caesarean section delivery [6], as well as preterm delivery [5], likely via its impact on neuroendocrine, metabolic, and inflammatory pathways. In women with SDB, case reports have shown that maternal obstructive apneas are associated with fetal heart rate decelerations, perhaps due to uteroplacental hypoperfusion, a mechanism implicated in intrauterine growth restriction (IUGR).

In summary, maternal sleep disruption is emerging as a significant factor in adverse pregnancy outcomes. Future research should consider maternal sleep when investigating stillbirth.

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A12

Sleep position and risk of late stillbirth

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Obesity is an established risk factor for stillbirth, however the reason for this is not known. There are several possible mechanisms which have not previously been investigated, such as maternal and fetal hypoxia from adverse maternal sleep position or sleep disordered breathing (SDB). We hypothesised:

1. that obesity is an independent risk factor for stillbirth,
2. that after adjustment for established risk factors for stillbirth, the higher rates in Maori and Pacific Island babies are no different to that of European babies, and
3. that sleep disordered breathing is a risk factor for stillbirth, and that this (at least in part) explains the increased risk with obesity.

The Auckland stillbirth study was a case control study conducted in Auckland, New Zealand between 2006 and 2009 [1]. In this study, we explored potentially modifiable risk factors for late stillbirth, including maternal position on going to sleep [2]. We found that maternal non-left position on going to sleep (on the last night prior to stillbirth, or prior to interview) was associated with a two fold increase in late stillbirth adjusted odds ratio (aOR) 2.0 (95% confidence interval (CI): 1.2 to 3.3) [2]. The greatest effect was when the mother went to sleep on her back (aOR 2.5, 95% CI: 1.0 to 6.2) and intermediate when on the right (aOR 1.7 95% CI: 1.0 to 3.0). These findings remained significant after adjustment for known confounders such as maternal body mass index, age and smoking. Although we could not establish an association between SDB (measured using self reported snoring and daytime sleepiness) and risk of stillbirth, these symptoms are common in pregnancy and may not identify true SDB.

This is the first time that an association between maternal sleeping position and risk of late stillbirth has been described and therefore the finding should be interpreted with some caution until further studies have confirmed or refuted it. There is, however, some evidence that may support the biological plausibility of such an association, as maternal body position has been found to impact on maternal and fetal physiological parameters. Specifically it has been shown that maternal cardiac output in late pregnancy is greatest in the left lateral position, intermediate in the right lateral position and lowest when the mother is supine [3]. Similar graded effects have been found between fetal oxygenation in labour and maternal position, with optimum oxygen levels recorded with the mother on her left side [4]. This is speculated to be due to the anatomy of the lower abdomen and the potential compression of the aorta and inferior vena cava caused by the weight of the uterus and growing fetus when the woman is in either the supine position or in the right lateral position.

The absolute risk of late stillbirth for women who went to sleep on their left side was 1.96/1000 and was 3.93/1000 for women who did not go to sleep on their left. This study identified a potentially modifiable risk factor for stillbirth, but confirmatory studies are needed before public health recommendations can be made.

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A13

Sleep practices and risk of stillbirth: implications for prevention and research

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Stillbirth research is hindered by a lack of a uniform definition and a lack of an internationally agreed protocol for the investigation of a death. However, the major issue is that not all stillbirths have an autopsy [1], and many are not investigated at all.

Mortality reviews (case series) are descriptive and hypothesis generating. In New Zealand the Perinatal and Maternal Mortality Review Committee reviews all deaths from 20 weeks gestation to 28 completed days after birth, or weighing at least 400g if gestation is unknown [2]. In 2009 the stillbirth rate was 6.3/1000 births. 25% were unexplained, and half of these occurred at term. 22% were not investigated. Maori and Pacific mothers were at higher risk and rates were increased in the most deprived socioeconomic quintile. Teenage mothers and those 40+ years were also at higher risk. Maternal obesity, multiple pregnancy and maternal medical conditions were also associated with risk of stillbirth. Only 15% of stillbirths were potentially avoidable. Although much can be learnt from examining national mortality databases, these do not allow examination of risk factors which are operating close to the demise of the fetus.

Case control studies are an efficient way to examine such risk factors. A small number of studies have been completed [3,4] or are still collecting data. The Auckland Stillbirth Study, a three year case-control study, had a particular focus on modifiable risk factors, including that related to maternal sleep [3]. We found an increased risk of stillbirth with non-left sleep position, regular sleep during day-time, more than 8 hours of night-time sleep and getting up to the toilet once or less per night [5]. The prevalence of non left sided sleep position in this study was 57.3% and the population attributable risk for non-left sided sleep position was 37%. Therefore, if there is a causative pathway between maternal sleep position and late stillbirth, over a third of late stillbirths (in high income countries) could be attributable to maternal sleep position. Further studies need to be conducted as soon as possible to determine whether this finding is reproducible and if confirmed, it would then be appropriate to instigate public health campaigns to encourage women to go to sleep on their left side in late pregnancy.

Research is needed to show how best to implement the findings. One testable hypothesis is that sleeping on the left side of the bed encourages mothers to sleep on their left side. A survey in Auckland is currently underway to examine this.

Furthermore, physiological studies of the pregnant mother and the fetus are required, such as examining the effect of maternal body position on cardiac output, uterine blood flow and on fetal wellbeing. There needs to be sleep studies of normal pregnant mothers in late pregnancy as well as longitudinal studies over the last trimester and possibly beginning at 20 weeks gestation.

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A14

Concluding remarks

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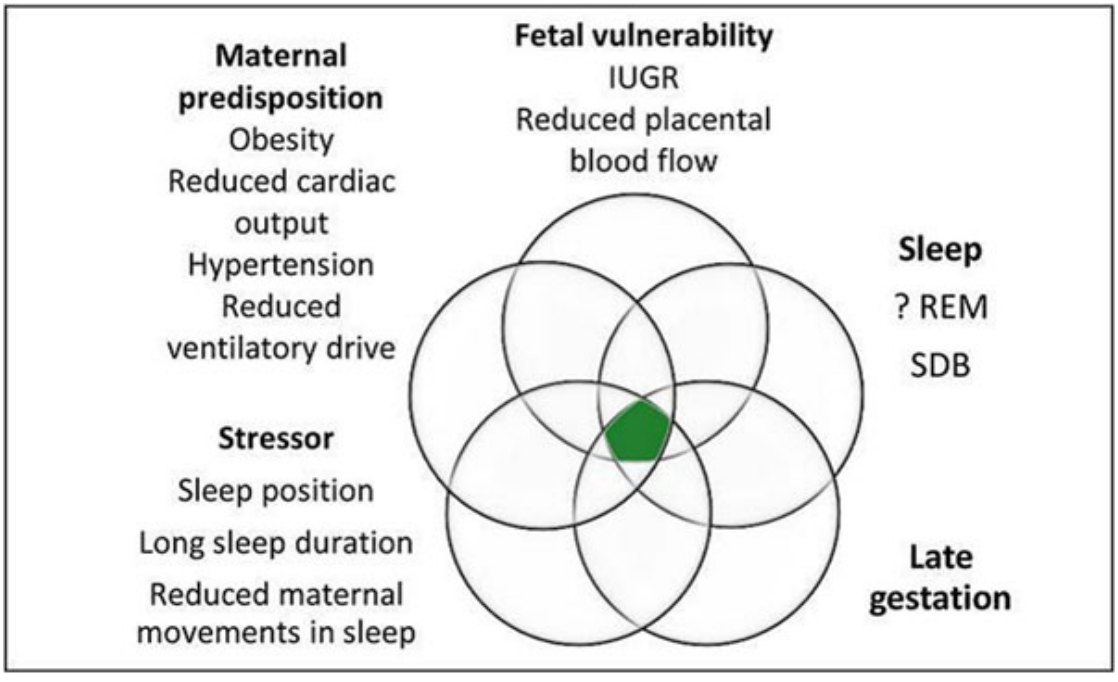

Figure 1(abstract A14) Conceptual model for the mechanism of stillbirths (developed by EM).

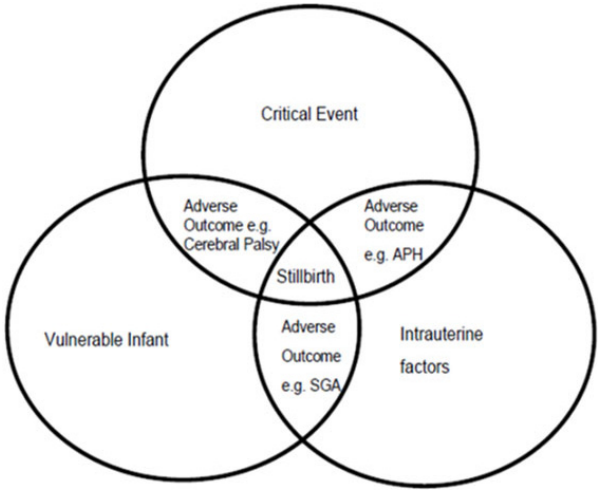

Figure 2(abstract A14) Conceptual model for the mechanism of stillbirths (developed by JW) [2] and adapted from Rognum and Saugstad [3].

This forum allowed for the discussion and exploration of a number of issues relating to stillbirth that have either been given minimal attention, or are emerging hypotheses. Research has identified many risk factors that may contribute or are associated with stillbirth. These risk factors have odds ratios between 2 and 3 indicating that it is unlikely that any of these are the definitive cause of stillbirth, rather they might be additive or interact together resulting in a stillbirth particularly if the fetus is somehow vulnerable. Two of the authors (EM & JW) presented conceptual models at the conference which were adapted from the SIDS triple risk model (Figure 1 and 2 respectively) [1-3]. Both models are more applicable to unexplained stillbirths rather than when there is a single clear cut cause. These show that that stillbirth may occur when there are prevailing risk factors, especially intrauterine or maternal disposition, accompanied by a stressor or critical event if the fetus is vulnerable.

These conceptual models were endorsed by the researchers, and suggestions for improving them were made, including adding specific risk factors such as maternal diabetes, placental abruption, maternal smoking and maternal age.

There was healthy and robust debate, both between the presenters and the attendees and between the researchers themselves, which brought a richness to the meeting. Alongside the energy and passion to see a real change in the devastating number of babies that die before birth, there was a moderating voice from a number of the researchers for the need for robust, peer reviewed evidence to be generated before significant recommendations for change in practice, or public health campaigns are launched.

Acknowledgement: We thank the Star Legacy Foundation who organised and funded the meeting. We also sincerely thank the many parents who attended. They ensured the meeting had energy and focus, and reminded us that stillbirths cause so much grief. Professor Ed Mitchell is supported in part by Cure Kids.

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Organising committee: Sherokee Ilse, Shauna Libsack and Lindsey Wimmer

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Cite abstracts in this supplement using the relevant abstract number, e.g.: Mitchell: Concluding remarks. *BMC Pregnancy and Childbirth* 2012, **12 (Suppl 1)**:A14