The Epidemiology of Stillbirth: The INTERGROWTH-21st Newborn Cross-Sectional Study

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M.SC THESIS AND ABSTRACT

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Abstract

Background. INTERGROWTH-21st is a prospective, multi-ethnic, population-based project exploring growth from early pregnancy to two years of age. The Newborn Cross-Sectional Study (NCSS) component of INTERGROWTH-21st was designed to evaluate the population characteristics and pregnancy outcomes for the 8 study sites included in the project. The INTERGROWTH-21st geographic areas were in: Pelotas, Brazil; Beijing, China; Nagpur, India; Torino, Italy; Nairobi, Kenya; Muscat, Oman; Oxford, United Kingdom; Seattle, United States.

Methods. Using the data gathered from the NCSS until the time that I completed my course work in Oxford, I attempted to identify potential risk factors for stillbirth in the INTERGROWTH-21st population. Stillbirth is defined as all foetal deaths occurring after at least 18 weeks gestation in order to capture stillbirths using the most inclusive definition. I also created the Foetal Death Supplementary Form to collect information on the causes of stillbirth that were not included in the original instrument according to Goldenberg et al.

Results/ Conclusions. I had available data from 6 study sites at the time of preparing this thesis. The population includes 43,078 pregnancies resulting in 43,781 total births. Of these, 295 were stillbirths representing an overall foetal death rate of 6.7 per 1000 births. Maternal education of primary school or lower [Odds ratio (OR): 2.10, 95% Confidence interval (CI): 1.45-3.04], maternal age >40 (OR: 2.52, 95% CI: 1.55-4.08), single marital status at parturition (OR: 1.70, 95% CI: 1.06-2.71) and maternal use of alcohol (OR: 4.60, 95% CI: 1.88-11.29), tobacco (OR: 1.83, CI: 1.18-2.83), or recreational drugs (OR: 4.27, CI: 1.57-11.63) during pregnancy independently increased the risk of stillbirth. Maternal medical conditions during pregnancy such as malaria (OR: 9.17, 95% CI: 3.69-22.76), HIV/AIDS (OR: 5.84, 95% CI: 2.72-12.54), and syphilis (OR: 7.11, 95% CI: 1.71-29.53) led to significantly higher stillbirth rates. Foetuses in breech presentation were at the greatest risk for stillbirth (OR: 5.00, 95% CI: 3.59-6.98). Caesarean delivery significantly reduced stillbirth risk (OR: 0.35, 95% CI: 0.27-0.47). The cause of death was unknown for 47% of stillbirths. Placental/cord complications, foetal genetic, structural, and karyotypic abnormalities, and maternal medical conditions accounted for 19%, 11%, and 9% of all stillbirths, respectively.

Conclusions. These analyses suggest a need for a more detailed stillbirth evaluation to understand the causes associated with half of all stillbirths. Expanding access to obstetric and antenatal care could reduce stillbirth, but this is a complex syndrome that requires multiple interventions for its prevention.

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Chapter I - Stillbirth: Definition, global burden, and its causes

Introduction

As neonatal and infant mortality rates continue to decline, stillbirth is gaining recognition as a pivotal public health concern (1). The aetiology of stillbirth is strongly associated with infant and maternal mortality/morbidity. Several pathologies that lead to infant death and illness, particularly where infant mortality rates are low, lie along the same aetiological pathways as causes of stillbirth (2, 3), and obstetric complications such as infection, intrauterine growth restriction, preeclampsia or obstructed labour lead to stillbirth and are related to maternal mortality and morbidity (4).

Stillbirth itself is also a major perinatal concern. According to estimations of the World Health Organization (WHO), there were overall 2.6 million stillbirths in 2009, or about 19 stillbirths per 1,000 births (5). This number, although lower than the approximately 3.6 million neonatal deaths that occur annually (26 per 1,000 births) (6), requires attention in public health programmes.

These stillbirth rates are, however, only estimates. In an effort to estimate the global burden of stillbirths in 190 countries, Stanton et al. (2006) found that only 33 countries published stillbirth data from vital statistics registries (7). For the remaining countries, statistical models based upon neonatal mortality data were used to estimate stillbirth totals, however it should be noted that these neonatal mortality statistics are also based upon statistical models, using under 5 child mortality data.

From 2004-2008, the WHO analysed stillbirth epidemiology from over 300,000 births at 373 randomly selected health facilities in the Americas, African, South-East Asia and Western Pacific WHO Regions, providing one of the more robust data sets on stillbirth in developing countries (8). These data demonstrate that among facility based

deliveries, the rates ranged from 4 stillbirths per 1,000 births in Vietnam and Thailand, to 71 per 1,000 births in Nigeria.

Efforts to improve stillbirth data collection and prevention have been met with contention, with many physicians and health policy leaders advocating that while neonatal death rates remain relatively higher, stillbirths should not be a primary public health focus (9). This is based upon the idea that, given the role of Caesarean deliveries and antenatal care in decreasing stillbirth rates, centring efforts on lowering neonatal and maternal mortality/morbidity by improving access to obstetric interventions will lower intrapartum foetal death rates as well (10). Improvements in the accessibility and quality of obstetric care have drastically reduced intrapartum foetal death rates, and antepartum foetal death to a lesser extent, in high-resource settings (11). However, in an analysis of 410 randomly selected facilities from 8 randomly selected Latin American countries, a proportional increase in rate of intrapartum foetal death with rises in rates of Caesarean deliveries, as opposed to a U-shaped relation, was found (12). Unexpected results such as this suggest that more research into the relationship between Caesarean rates and other obstetric interventions with stillbirth is required.

Even where there is strong support for stillbirth detailed data collection, practical complications have risen. Each country defines stillbirth in its own way, making data comparisons difficult or impossible, and perinatal mortality data have been previously demonstrated to consistently underreport antepartum mortality rates in high-income countries, leaving many stillbirths uncounted (13-15). The EURO-PERISTAT Project, assessing perinatal outcomes in 25 European Union member states and Norway, explains the limitations to stillbirth registry data in Europe (16). Along with the incompatibility of data from different countries, other stillbirth registry limitations include reports often coming from aggregate data, and inconsistent quality of data (16). In Cyprus, for example, national registry data in this study included only data mainly from

public institutions, as private hospitals were not mandated to provide statistics. This is often the case in larger countries as well.

As with all death, stillbirth is a complex, multi-causal syndrome. Although categorising the causes of stillbirth along aetiological pathways has proven to be difficult, to better understand and ultimately improve foetal outcomes, this is a necessary measure. In this chapter, I will outline the various definitions of stillbirth, assess timing as a main classification and aetiological factor of antepartum vs. intrapartum death, highlight the global burden of foetal death and trends observed in developed countries, categorize stillbirth by cause of death, and describe the known risk factors for stillbirth.

Definitions of stillbirth

There is no universal definition of stillbirth. Stillbirth is fundamentally any death prior to birth. The definition variation occurs according to the lower gestational age limit, the timing of the death and the use of birth weight lower limit. The separation between abortion/miscarriage and stillbirth also remains in the area of debate. The WHO recommends that stillbirths be identified using birth weight, followed by gestational age, and crown to heel length at minimum limits of 500 grams, 22 weeks, and 25 centimetres respectively (17). Those foetal deaths occurring below these limits are considered miscarriages by the WHO. However, for international comparison, the WHO suggests using minimums of 1000 grams, 28 weeks gestation, and 35 centimetres crown to heel length (17).

There are an array of different national systems of stillbirth data collection and registration. In the United States alone, there are 9 different definitions of stillbirth used, as registries are managed at the state level (18). In Europe, contrary to the WHO recommendations, stillbirth is typically assessed using primarily gestational age, not birth

weight, with the minimum gestational age for stillbirth ranging from 18-28 weeks (19). Using gestational age to delineate stillbirth is a problem in low-resource areas where gestational dating by ultrasound or LMP estimates at the first antenatal visit is often unavailable. However, birth weight has its limitations as well. Stillborn babies often lose weight in utero when foetal death occurs several days prior to delivery, leading to an underreporting of stillbirth rates at lower gestational ages. (20).

The lower bounds defining stillbirth are currently based upon viability of a newborn, thus medical capabilities. At 22 weeks gestation, few infants are viable in high-resource settings and at this age, bioethics committees do not recommend resuscitation (21). By 25 weeks gestation, most infants in developed countries will survive birth (21). Yet in most deliveries in low and middle-income countries, where 98% of stillbirths occur, few infants born at 28 weeks gestation or earlier will be viable due to lack of neonatal care, and most will survive once reaching 32 weeks gestational age (9). When possible, registries should aim to record all foetal deaths regardless of gestational age and birth weight. This would allow for better understanding of the condition, comparisons of national statistics, and more robust epidemiological data.

Timing is the major differentiation between types of stillbirth and should always be separated. Antepartum stillbirths are foetal deaths that occur before the onset of labour, while intrapartum stillbirths occur after the onset of labour but before delivery. Antepartum stillbirths are also referred to as macerated stillbirths because of the condition of the foetus after it is delivered. This of course depends on the time between the death and delivery and therefore will bias toward earlier gestational ages. Antepartum stillbirth in the United States has been reported to be as high as 67% of all stillbirths, and possibly even higher as timing of death data are missing in 20% of all stillbirths (22). As a general principle, the lower the overall stillbirth rate, then the more relevant is the antepartum component of stillbirth.

Conversely, a hospital-based cohort in the Gambia reported that 58% of all stillbirths were fresh, or intrapartum stillbirths (23). Worldwide, estimations describe approximately 2 million intrapartum-related deaths annually, with intrapartum stillbirths and neonatal deaths due to the same set of childbirth complications (24). The aetiological connectedness of intrapartum stillbirth and neonatal death leads to misclassification. Live born babies that are not breathing, requiring resuscitation, are often incorrectly labelled as stillborn (25).

Kramer et al. (2002) suggest that in low-resource settings, where birth asphyxia remains a common cause of intrapartum and neonatal death, it is often impossible for birth attendants to differentiate stillbirths from live births and the term perinatal mortality may be more appropriately applied (26). In high-resource settings, the prevalence of intrapartum stillbirth has been greatly reduced because the majority of intrapartum deaths occurred primarily due to sub-optimal care (10, 11, 27). The other major causes of intrapartum stillbirth are complications due to the placenta, umbilical cord, infection, and trauma (28).

Three points are important: first, intrapartum and antepartum deaths have to be always considered separately; second, some of the remaining intrapartum deaths could also be associated to undetected congenital conditions that may not improve by delivery care alone; and third, the pros and cons of reducing a small number of stillbirths versus increasing late preterm births have to be evaluated under different circumstances.

Global burden

According to WHO estimates, there were approximately 2.6 million stillbirths in 2008. Stillbirth was defined as any foetal death where birth weight was at least 1,000 grams or the gestational age was at least 28 weeks (5).
However these are estimations based on limited data and should be considered approximations.

Stillbirth rates vary significantly by global region. The highest rates of stillbirth are in Sub-Saharan Africa, where estimated stillbirth rates are 29 per 1,000 total births (9). Of these stillbirths, nearly 47% are intrapartum deaths. Nigeria, the most populous state in the region, is the greatest contributor of stillbirths in the region. This is due not only to Nigeria's population, but also to its extreme stillbirth rate: for instance the Katsina and Lagos provinces have stillbirth rates of 71 per 1,000 total births according to the WHO Global Maternal and Perinatal Health Survey (29).

In countries such as South Africa and Uganda, reported stillbirth rates are lower, at 15 stillbirths per 1,000 total births in both countries (30). Even within Western Africa, Ghana has a reported stillbirth rate of 11 per 1,000 total births according to WHO estimates (30). These reports suggest a significant underreporting of the condition.

In South Asia, stillbirth rates are lower than those of Sub-Saharan Africa. However, the absolute number of stillbirths in the region is the greatest in the world because of the size of the countries in that region. In a multicenter analysis to determine population based stillbirth rates, McClure et al. (2011) calculated a stillbirth rate of 32 per 1,000 births in Pakistan, a nation with over 170 million people (31). Stillbirth rates in India ranged from 18.5 in the Belgaum province to 29.5 in the Nagpur province. With a population of over 1.1 billion people in India alone, these high rates and large populations combined make South Asia the greatest contributor to the global burden of

stillbirth (31). Table 1 depicts stillbirth rates from the 2005 WHO Global Survey on Maternal and Perinatal Health from randomly selected countries in Africa, Asia, and Latin America (32).

The statistics for Africa and Asia are in stark contrast with the rates for stillbirth in high-income regions. In the United States, for example, foetal death at 20 weeks gestation or more occurred in only 6 per 1,000 total births, mostly antepartum stillbirth, according to the 2005 national vital statistics (33). Along with issues with sub-optimal care, the majority of stillbirths in high-income nations such as the United Kingdom are due to scattered and often unknown causes of death (10, 33). These variations suggest that the majority of the global burden of stillbirth could be eliminated by increasing access to quality antenatal care, early screening for congenital anomalies and the obstetric technologies and services that have diminished stillbirth in high-income countries.

This variation in stillbirth rates exists within countries as well, both in developed and developing nations. One major source of disparity is the rural and urban divide. In Sub-Saharan Africa and South Asia, where three quarters of the world's stillbirths occur, the stillbirth burden is more severe in under-developed urban centres (34-36). These urban centres must handle the added health burden that comes with high-density populations, such as increased infectious disease, without adequately addressing key urban issues like hygiene and sanitation systems. In more developed regions, the opposite is true. In high-income and Latin American countries, most stillbirths occur in rural settings, where poverty levels tend to be higher and access to healthcare facilities is often limited (9).

Socioeconomic disparities expressed in ethnic groups as in other medical conditions lead to stillbirth rate variations in heterogeneous nations. In the United States, for example, African-Americans suffer stillbirth rates of 11.1 per 1,000 total births, an

excessive rate for a population within a high-income country, while White Americans have stillbirth rates of 4.8 per 1,000 live births (37). Adjusting by income and other socio-demographic risk factors attenuates the relation between ethnic groups and stillbirth risk, though not completely. Ethnic disparities in stillbirth rates are often due to a collection of interrelated factors such as inequitable access to healthcare and/or antenatal care, a lack of education, poverty-related risk factors, and higher risk for other poor pregnancy outcomes such as preterm onset of labour (38).

These intra-national variations in stillbirth rates indicate that improving the quality of and access to health systems could prevent significant portions of the global burden of stillbirth. Bhutta et al. (2011) describe a basic healthcare package that could reduce the number of annual third trimester stillbirths by 1.1 million, or 45% of the annual total (27). The greatest opportunities for improvement exist in the realm of intrapartum stillbirth, with skilled care, basic emergency obstetric care, and comprehensive emergency obstetric care offering the most significant gains (11). For every 1% increase in rate of Caesarean sections, from 0-8%, intrapartum stillbirths decrease by 1.61 per 1,000 total births. This is equivalent to providing surgical services to hospitals. However there is a decreased effect when Caesarean sections are already at 8-15% and after Caesarean rates reach 15%, there is no additional effect on intrapartum stillbirth (10) or even side effects.

Trends in developed countries

In the past 100 years, stillbirth rates in high-income countries have fallen by more than 10 times (39). Most of the improvements in stillbirth have occurred in intrapartum stillbirths, with the vast majority of these advances having been made by 1980 (40). This has led some to believe that the progress in developed countries has reached a plateau,

with little room for improvement in the future (39). However, monitoring the data of individual high-income countries over the past 20 years shows that in nations such as Norway and the Netherlands, stillbirth rates have dropped by 50% and 40% respectively (40). Figure 1 shows the stillbirth trends at the John Radcliffe Hospital in Oxford, England from 1991-2010 recently obtained for this dissertation. Contrary to the declines seen in countries such as Norway and the Netherlands, stillbirth rates have not significantly declined in this referral large hospital that serves a geographic population but adds referrals for near-by towns, with a stillbirth rate per 1,000 births of 4.6 in 1991 and 5.0 in 2010. The vast majority of these stillbirths, over 75%, were attributable to antepartum foetal death (data not shown).

A wide range of stillbirth rates still exists among high-income countries, with rates as low as 2.1 per 1,000 total births in Finland, and 3.5 stillbirths per 1,000 total births in the Netherlands (41). This variation could be due to a number of potential explanations. As aforementioned, availability of elective terminations can greatly influence stillbirth rates. The proportion of stillbirths attributable to congenital anomalies in Poland, where termination policies are restrictive, is 30.4%, while in the United Kingdom, where termination policies are less restrictive, only 3.8% of stillbirths are attributed to congenital anomalies (42). Given the association of demographic characteristics and behaviour risk factors such as healthcare seeking habits, diet and prevalence of obesity, diabetes, and cardiovascular disease, and maternal use of tobacco during pregnancy with stillbirth, it is to be expected that differences in populations can lead to major differences in rates of stillbirth (43).

Yet even with these national differences in population demographics and behaviours, there is room for substantial improvements in perinatal outcomes in high-resource settings. In a Norwegian based study, 37% of foetal deaths were partly caused by sub-optimal care such as not identifying or mismanaging foetal growth restriction and

decreased foetal movement (44). Modifying behavioural risk factors such as poor diet, use of tobacco, alcohol, and/or illicit drugs during pregnancy presents a major opportunity for decreasing stillbirth. Better detection and management of maternal illness and improvement of maternal health prior to conception could significantly reduce rates of stillbirth in high-income nations.

High-income countries continue to under invest in the monitoring of, collecting of data on, and researching into stillbirth. Stillbirth research is severely limited by the inconsistencies across and within high-income nations with regards to data collection and vital statistics. More effort is needed to ensure that post-mortems are regularly conducted on stillborns, and that consent is actively sought from parents of stillborn babies to perform autopsies and placental pathologies (16, 45). Since Norway began conducting perinatal audits in 1986, perinatal mortality rates have fallen from 14 to 8 per 1,000 total births, and stillbirth rates dropped to among the lowest in the world (46).

While better data collection could improve epidemiological research, there are research gaps in discovery sciences as well that could lead to decreases in the rates of stillbirth, specifically antepartum stillbirth. Primary targets for research efforts include examining the effects of periconceptual environment on embryonic and foetal development, conducting phenotypical analyses of stillbirth cases with matched controls, investigating the pathophysiological pathways between maternal illness and stillbirth, and more (47). Last, research is needed to improve capabilities of systematically identifying the primary causes of stillbirth and associated risk factors, as reducing stillbirth rates in the future will require understanding ways to eliminate antepartum death, which is usually attributed to unknown causes of death or to causes of death that have not been demonstrated to be likely to cause foetal demise (48).

Classification systems

There is no widely accepted system for classifying stillbirth cases by cause of death. Classification systems are integral tools for designing preventative strategies and auditing measures for all causes of death and morbidity (49). The WHO published International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) serves as an international, comprehensive tool for identifying primary causes of death and associated problems (17). Acknowledging the complexity and multi-causal nature of death, the ICD-10 has created a separate classification list for infant death, which has a unique set of causes relative to death in adolescents and adults; however no such distinction has been made for stillbirth (17, 45). Stillbirth has a unique set of causes, and is linked with several maternal related causes of death and illness. The causes of death and related complications of stillbirths are difficult to assign, and are often poorly reported on stillbirth certificates (50).

In the past 50 years, 35 different classification systems have been published (9, 51). Relatively easy to apply and hierarchal classification models such as the Extended Wigglesworth and Amended Aberdeen systems are widely used, however these systems were rated amongst the worst in an assessment of classification systems based upon their retention of information about the cause of death, inter-observer agreement, and the proportion of unexplained stillbirths (52). Despite the limitations of current classification systems, there has been recent progress towards developing a system that adequately captures causes of stillbirth in both developing and developed settings with the publication of tools such as the Initial Causes of Foetal Death by the Stillbirth Collaborative Research Network and the Causes of death and associated conditions or CODAC system (28, 45, 52). The cause of death analyses in subsequent chapters will be based upon the Initial Causes of Foetal Death form as it is the most current tool that

relies on evidence-based probable causes for foetal death, using rigorous methodology to attempt to categorize stillbirths as follows: maternal medical conditions; obstetric complications; maternal or foetal hematologic conditions; foetal genetic, structural, and karyotypic abnormalities; placental infection, foetal infection, or both; and placental pathologic findings (48, 53).

Causes of stillbirth

Intrapartum factors:

Every year, there are 2 million intrapartum related perinatal deaths (24). Major discrepancies exist between countries based on resources available. In high-income countries, less than 10% of stillbirths are due to acute intrapartum events, as there have been major reductions in intrapartum stillbirth during the past century (27, 40). In low and middle-income countries, where only 46% of infants are delivered in the presence of a skilled birth attendant, intrapartum related stillbirth rates remain high (27). The risk for stillbirth in low and middle-income countries is 14 times the risk in high-income countries, and the risk in low-income countries is 17 times that observed in middle-income countries (54). However, intrapartum related deaths are rare in many developing nations as well. Latin American countries such as Chile and Argentina have reduced their total stillbirth rates to 5, and 8 stillbirths per 1,000 births, respectively, by significantly reducing intrapartum related perinatal deaths (31, 55). Intrapartum foetal deaths in Brazil, for example, have fallen by over 70% in some regions over the past two decades (56). Similar improvements have been made in Middle Eastern countries such as Qatar and Egypt (57, 58).

Intrapartum stillbirths account for approximately 60% of stillbirths in the United Nations defined South Asia region (Afghanistan, Bangladesh, Bhutan, India, Iran, the

Maldives, Nepal, Pakistan, and Sri Lanka), where a substantial proportion of infants are delivered without a skilled birth attendant, while in Latin American countries, where hospital deliveries are almost universal, only 23.1% of stillbirths are intrapartum related (5, 7).

Post-term pregnancy, defined as a pregnancy continuing beyond 41 weeks gestation, complicates 5-10% of pregnancies, and has been associated with increased risk of stillbirth. (59). Prolonged pregnancy leads to excess stillbirth by increasing the risk of labour complications due to foetal macrosomia, meconium aspiration, asphyxia, intrauterine infection, uteroplacental insufficiency, and anencephaly (59). Once labour begins, prolonged or obstructed labour complicates 3-6% of pregnancies (60). Cephalo-pelvic disproportion, malpresentation of the foetus, and multiple pregnancies can all lead to obstructed labour, causing stillbirth through foetal asphyxia and leading to maternal morbidity and mortality primarily through increased risk of infection and fistulas (60).

Preeclampsia and eclampsia may lead to severe complications, many mediated through IUGR, that threaten the lives of both the infant and mother, with the only known "treatment" being induction of labour, or Caesarean section (54). Preeclampsia and eclampsia contribute to both intrapartum and antepartum stillbirth. But preeclampsia also increases the risk for placental abruption, occurring in less than 1% of all pregnancies overall, which is the partial or complete separation of the placenta prior to delivery (61). Placental abruption is present in 10-20% of all foetal deaths if detailed examination is conducted. Abruption has only been demonstrated to significantly increase the likelihood of stillbirth when there is at least 50% placental separation (61).

Preeclampsia may also lead to stillbirth by restricting foetal growth and causing premature preterm rupture of membranes (PPROM), which is associated with greater risk for placental abruption in addition to posing its own threats for stillbirth by increasing the risk for foetal infection (62, 63).

Foetal/ maternal haemorrhage, where foetal blood cells are lost into maternal circulation, is a known stillbirth mediator for many of the aforementioned labour complications. In 5-14% of stillbirth cases, moderate to severe foetal/ maternal haemorrhage is reported (64). Foetal/ maternal haemorrhage could lead to foetal anaemia, red cell isoimmunisation, hydrops fetalis, and hypoxia, with the likelihood of foetal/ maternal haemorrhage causing an individual case of stillbirth being best assessed by determining the percentage of foetal blood in the maternal circulation (65). While trauma, placental abruption, and delivery complications can lead to foetal/ maternal haemorrhage, the cause of this bleeding is often of unknown origins, and a small amount of foetal blood is found in maternal circulation in most pregnancies (65).

The majority of the stillbirths due to acute intrapartum events among “healthy” term foetuses can be prevented because they are mostly due to a lack of resources, investment, and attention rather than to a lack of knowledge. This includes breech presentation for term and preterm foetuses. Breech presentation considerably increases the risk of intrapartum death. Caesarean delivery is recommended for preterm, breech presented infants, but this procedure is often not available, or onset of delivery begins before a Caesarean section can be performed.

Genetic/congenital factors:

Approximately 25% of all stillbirth cases have some sort of genetic causal component when all foetal structural malformations, including malformations secondary to foetal disruption or dysplasia, and chromosomal abnormalities are considered (66). In high-income settings, 6-17% of stillbirths are primarily caused by one or more chromosomal abnormalities (66). This prevalence is similar to that seen in low and middle-income countries. While the high levels of intrapartum stillbirth in low and middle-

income nations would seem to lead to a smaller proportion of total stillbirths due congenital anomalies in these regions relative to high-income countries, this is not the case. The higher accessibility to elective abortions in high-income countries artificially lowers the rates of stillbirths due to congenital abnormalities (67)

Only a small percentage of stillbirth cases will have reported aneuploidy. Among infants with noted abnormalities discovered via ultrasound or post-mortem examination, approximately 25% will have some form of aneuploidy (65). The common chromosomal abnormalities found in stillbirths parallel those found in the population of live born infants, as 23% of aneuploid stillborn infants will suffer from monosomy X, another 23% will be inflicted with trisomy 21, another 21% of cases being trisomy 18, and 8% trisomy 13 (66). However, these are likely to be underestimates, as karyotyping is often not assessed in cases of stillbirth, in both high and low-resource settings (65). Even in cases where karyotyping is attempted, the assessment is not always successful. In a cytogenic analysis of 750 foetal deaths in the Netherlands, only 28% of postpartum tissue analyses were successful, although invasive testing produced valid results in 85% of attempts (68). Also, the presence of a chromosomal abnormality clearly is not necessarily a cause of death. With cases of trisomy 18, for example, once the foetus survives to 20 weeks gestational age, only 1/3 or cases will lead to death (69).

The stillbirth mechanism for many of these genetic disorders is not well understood, as this topic is not well studied, nor are the genetic causes of stillbirth confined to a small number of disorders (65). Confined placental mosaicism is known to lead to poor pregnancy outcomes, including stillbirth, typically when aneuploid cells segregate entirely into the trophoblast and interfere, through a variety of pathways, with placental function (69). Several single gene and Mendelian disorders also contribute to the genetically attributed global burden of stillbirth. Haemoglobinopathies such as alpha thalassemia and glycogen storage disorders have been shown to cause stillbirth via

lethal foetal hydrops (66). Heritable thrombophilias have been associated with stillbirth through intrauterine stroke, but these thrombophilias are present in live births as well, and mothers testing positive for Factor V Leiden, Protein C deficiency, Protein S deficiency, Prothrombin Gene 20210A, and Antithrombin III deficiency assessments are all likely to give birth to healthy babies (70). Other known genetic pathways leading to stillbirth include metabolic diseases such as Smith-Lemli-Opitz syndrome, peroxisomal disorders, and amino acid disorders, all through a variety of mechanisms (66). The great number of pathways of genetic causes of stillbirth makes preventative efforts difficult, and provides little direction for areas of research and improvement. Still, as genetic disorders are associated with a significant proportion of stillbirths, identifying potential genetic risk factors, removing exposures that increase the likelihood of abnormalities, and more consistent screening could provide major opportunities for lowering rates of stillbirth in the future.

Infections:

In low and middle-income countries, an estimated 50% of stillbirths are associated with some form of infection, with another 10-25% of stillbirths in high-income countries being related to infection (71). It is important to understand that this association may not be causal in many cases. The greatest preventable contributors to the infection-related burden of stillbirth are syphilis and malaria (27). The acute effect of malaria infection during pregnancy significantly increases the risk of stillbirth in already at risk regions such as Sub-Saharan African and some areas of India (72, 73).

Wide ranges of organisms have been associated with stillbirth, including human cytomegalovirus, lymphocytic choriomeningitis virus, listeria monocytogenes, rubella, parvovirus B19, varicella zoster virus, and chorioamnionitis due to bacterial infection (74).

Other infectious agents such as human immunodeficiency virus, Chlamydia trachomatis, genital mycoplasmas, group B streptococci, influenza, and other organisms have been suggested to lead to stillbirth and are associated with increased risk of foetal death (75).

This wide range of infections leads to an equally diverse pool of mechanisms for causing stillbirths. At the most basic level, any infection that leads to systemic maternal illness can cause stillbirth if severe enough. For a vulnerable mother, a severe case of influenza can lead to both foetal and maternal death (76). However the mother and foetus are not typically affected equally by these infections. Infections such as rubella and human cytomegalovirus can have mild effects on the mother, but lead to stillbirth via severe congenital abnormalities in the infant (77). Common infections such as malaria and syphilis are rarely fatal for healthy, adult mothers, but both can lead to stillbirth by infecting the placenta and the vital organs of the developing foetus, with even greater effects when these infections are contracted during the pregnancy (78-80).

There are also a wide variety of organisms that lead to maternal infection of the genital tract, contributing to preterm birth and stillbirth. While typically harmless to the mother, bacteria in the genital tract can often ascend and lead to inflammation of the chorion and/or amnion, with the worst outcomes occurring during very early or late gestation because of the increased risk of a foetal inflammatory response (81). The significantly higher rates of chorioamnionitis discovered in stillborn babies relative to live births have not been causally linked, as live, healthy babies are not assessed for chorioamnionitis regularly (81, 82, 82). This is also true of other infectious organisms, which are often present in healthy mothers, such as parvovirus B19, listeria monocytogenes, human cytomegalovirus, and *Toxoplasma gondii* (71, 74, 75). In order to better understand the role of infections in the causes of stillbirths, it is therefore necessary to assess the presence of these infectious agents in healthy babies as well as stillborn and preterm infants in either prevalence or prospective studies.

Foetal growth restriction/size at birth:

Growth restriction or small for gestational age at birth is often listed as a cause of stillbirth. A more accurate use of growth restriction in terms of stillbirth is as an associated cause, as restricted growth, when leading to death, is a result of another upstream disorder (65). A distinction must be made between small for gestational age infants (SGA) and intrauterine growth restriction. SGA infants are newborns with smaller weight at birth than expected for a given gestational age, while growth restricted infants require evidence of intrauterine growth alterations in several parameters e.g. stunted growth by velocities by ultrasound, which are seldom documented (83). Clinical Doppler velocimetry of the umbilical artery, when routinely used for screening, enables physicians and pathologists to consider if the causes of growth restriction are related to a reduced placental transfer to the foetus rather than other mechanisms (84). Pooled results from 16 studies investigating the clinical effects of the use of Doppler velocimetry found a 29% reduction in perinatal mortality rates (Relative Risk: 0.71, 95% Confidence Interval: 0.52-0.98) when Doppler velocimetry of umbilical and foetal arteries in high-risk pregnancies was combined with the appropriate interventions (84).

As with many aspects of stillbirth, an insufficient number of studies have been conducted using controls to analyze the clinical significance of placental and umbilical cord abnormalities (85). Several cord complications exist in both healthy, live births, and in poor outcome births, including stillbirth. These complications include forms of cord obstruction such as true knots, torsions, strictures, cord prolapses, and length and coiling abnormalities, all which exist in completely healthy babies, making causality difficult to ascertain (86). The same is true of umbilical thrombosis (86). Umbilical cord insertion abnormalities such as velamentous cord insertion and vasa praevia have

clearer links to stillbirth, but are also present in normal births (87). Abnormal villous parenchyma of the placenta also may lead to restricted growth and subsequent stillbirth. These abnormalities are due to developmental malformations, and infarcts due to maternal conditions such as preeclampsia, maternal diabetes mellitus, and systemic erythematosus lupus (65).

Multiple pregnancies are more likely to suffer from growth restriction and complications (88). Twin-to-twin transfusion syndrome, also known as Twin Oligohydramnios, Polyhydramnios Sequence, occurs when, with the shared placenta of twin foetuses, blood supplies become interconnected in such a way that one foetus serves as a donor, in essence, to the other foetus, resulting in restricted growth and in severe cases, stillbirth and neonatal death (89).

It is relatively easy to associate a stillbirth to small weight, however this is not a cause of death but a symptom of a number of disorders. It is therefore pivotal to attempt to understand the underlying causes of restricted growth and subsequent foetal demise when assessing the causes of stillbirth. Categorizing stillbirth based on known and proven aetiological mechanisms for foetal death will be key for directing research. The lumping of unrelated causes of death into the insufficiently descriptive category of low weight at birth does little to advance efforts to understand and reduce the rates of stillbirth. For growth restriction to play a role in stillbirth classification systems, it will need to be combined with adequate testing for disorders that may explain the restricted growth, rather than serving as a quick alternative to a thorough post-mortem workup (9).

Unknown:

In contrast with the often preventable intrapartum stillbirths, the causes of the majority of antepartum stillbirths are unknown, with the cause of death for a quarter of all

stillbirths being identified as unknown (9, 90). However these statistics may be misleading. Only 5% of stillbirths are indentified as unknown after a complete autopsy and placental investigation, indicating that most stillbirths attributed to unknown causes have not been duly investigated with a proper workup (47). The proportion of stillbirths of unknown causes is also dependent upon the classification system being used to assess the cause of death (47). Although some systems may appear to produce less unknown causes than others, it must be noted that several systems include symptoms such as restricted growth as a cause of death, and require no assessment of severity of a particular disorder so as to assign reliable and clinically plausible causes of death (48). Placental abnormalities and umbilical cord complications without clinical confirmation of placental insufficiency or decreased arterial flow say little about the cause of a particular stillbirth case, as these anomalies can be found in the placentas and cords of healthy babies as well (45). Maternal risk factors, while informative and useful for preventative and research purposes, are not sufficient explanations for stillbirth without assessing the severity of the risk factor, and the likelihood of stillbirth occurring due to such a factor (48).

Risk factors

It is important to consider while evaluating the association between standard risk factors to perinatal outcomes that most of these are generic risk factors for many outcomes including stillbirth, and that is difficult to make concrete causal links between these exposures and specific outcomes. Caution should be exercised when interpreting this section.

Maternal illness:

Though not necessarily the direct cause of the foetal death, 10% of stillbirths after 20 weeks gestation are related to maternal illnesses (91). Hypertension, diabetes mellitus, and obesity are some of the more common stillbirth risk factors. Hypertensive disorders include preeclampsia, eclampsia, pregnancy induced hypertension, and haemolysis, elevated liver enzymes, and low-platelet count (HELLP) syndrome (92). These risk factors may progress to a severity where they become causes of stillbirth, however with adequate management of these hypertensive disorders, pregnancies can progress normally. There have been major improvements in the management of hypertensive disorders in high-income regions, but in low-resource areas, the necessary treatments are often unavailable. Still, greater use of low cost treatments such as aspirin and magnesium sulphate for preeclampsia could significantly lower stillbirth rates in low-resource settings (93). The difficulties with managing diabetes mellitus are similar to those pregnancy complications due to hypertensive disorders. When left uncontrolled, diabetes mellitus can lead to hyperglycaemia, which can cause stillbirth through foetal anaerobic metabolism with hypoxia and acidosis (94). Depending on how the mismanagement of diabetes mellitus is manifested, stillbirth can be mediated through

growth restriction or macrosomia (94). When defined as a body mass index of ≥ 30 kg/m^2, 20-40% of women of reproductive age in North America are obese, with upward trends throughout the world (91). Obese women have 2.5-3.0 times the risk for stillbirth relative to women with body mass indexes < 30 kg/m^2, with no relation between maternal weight gain during pregnancy and stillbirth (91). This excess risk of stillbirth in obese women is in part explained by their greater risk for hypertensive disorders, diabetes mellitus, and gestational diabetes, relative to non-obese mothers, although these factors do not completely attenuate the relation between maternal obesity and stillbirth (95). The pathway between maternal obesity and stillbirth thus remains incompletely understood. As a preventable risk factor, obesity is a key target for reducing stillbirth rates globally.

Other maternal illnesses, although less common than the aforementioned disorders, significantly increase the risk of stillbirth. Systemic lupus erythematosus, an autoimmune disorder that affects the skin, joints, kidneys, brain, and other organs, leads to stillbirth rates of 40-150 deaths per 1,000 total births in high-income countries (96). The wide range is attributable to increased mortality risk when the onset of systemic lupus erythematosus is during pregnancy, compared to when the onset is prior to conception. Foetal demise occurs in 3% of cases where onset is prior to conception, compared to 18% when onset is during pregnancy (97). Chronic renal disease, while rare, can have an even more devastating influence on stillbirth risk when not properly managed (98). Intrahepatic cholestasis of pregnancy increases risk for stillbirth as well, and in regions where pregnancy cannot be induced due to a lack of resources and facilities, the outcomes are even more grave (96). Thyroid disorders, when properly managed, present little risk to pregnant mothers. However, pregnancy does cause changes in thyroid function, which when left uncontrolled, can lead to thyrotoxicosis or overt hypothyroidism, and subsequent stillbirth (99). Identifying and properly managing

these maternal illness risk factors can significantly reduce stillbirth in settings of all resource-levels.

Sociodemographic and behaviour risk factors:

Sociodemographic risk factors for stillbirth extend well beyond income. While income is certainly an important risk factor and strongly correlated with many other social risk factors, income alone does not explain the disparities in risk for stillbirth (100). It is equally important to understand what goods income is used to purchase. Access to quality of care in some regions is nearly impossible at most income levels. The availability of adequate preconception care varies greatly from region to region, and within countries (42). Quality prenatal care allows health care workers and physicians to screen for congenital anomalies, monitor and manage maternal illnesses, and manage foetal complications during pregnancy (42). Pregnancy history also affects risk for stillbirth, as previous poor pregnancy outcomes, including a prior foetal death, primiparity, and previous spontaneous losses all increase the risk of subsequent stillbirth, and these mothers require additional monitoring during pregnancy (101). Both before and during pregnancy, access to a balanced and nutritious diet has tremendous benefits for the mother and the foetus, with diet often being dictated by the availability of healthy foods, culture, and education, as well as income (102).

Other social risk factors for stillbirth include maternal level of education and maternal marital status. Mothers with less than 10 years of formal education have twice the risk for stillbirth relative to mothers with 10 years of education or more, although this effect varies greatly across populations (103). And while the mechanism is unclear, and

not completely explained by socioeconomic status, giving birth out of wedlock increases the risk for stillbirth by 25% (104).

At either extreme, maternal age is well-established risk factor for stillbirth. Due to increased health risks such as hypertension, gestational diabetes, congenital anomalies, and the effects of technology-assisted reproduction, including multiple gestation, mothers aged 35 years or more face significantly higher risk for stillbirth than younger mothers, with the effect most profound in women about 40 years of age (105). Young mothers face increased risk for stillbirth as well. Attributed mostly to issues with maternal size and socioeconomic status, mothers below 15 years of age face significantly higher risk for stillbirth than those aged 15 years or greater (106).

Maternal substance abuse is a severe health risk for the mother and infant. The risk for stillbirth is double for mothers with a history of drug addiction relative to drug-free mothers (101). When compared to non-smokers, mothers smoking 10 or more cigarettes per day during the 3 months prior to pregnancy were 50% more likely to have a stillborn child than non-smokers, with that risk increasing when mothers continue to use tobacco during pregnancy (101). Maternal consumption of alcohol during pregnancy has a dose-dependent effect on stillbirth risk that is magnified when alcohol abuse occurs during early-pregnancy (107).

Worldwide, there are intranational, ethnic variations for stillbirth rates and related poor pregnancy outcomes. In Australia, indigenous populations are twice as likely to experience a stillbirth than white Australians, and in the United States, African-Americans also face double the stillbirth risk observed among white Americans (47). Studies of stillbirth rates in the Netherlands found that ethnic minorities suffered 30-80% increased risk for stillbirth, a finding that can be found in several other countries (47). These ethnic variations in stillbirth are unlikely to be due to genetic factors alone, and are better explained by ethnic associations with diseases and characteristics that

predictors of stillbirth (108). Socioeconomic status contributes to these ethnic disparities in stillbirth rates through its association with access to adequate antenatal care, care seeking behaviours, and ability to obtain quality medical care (96). Other factors such as stress have been hypothesized to lead to ethnic disparities in stillbirth and other poor pregnancy outcomes, but the difficulty in defining and measuring stress across populations creates limitations for such studies (109-112).

INTERGROWTH-21st Project

The epidemiological and aetiological analyses of stillbirth in the subsequent chapters have been conducted within the Newborn Cross-Sectional Study (NCSS) of the INTERGROWTH-21st Project. INTERGROWTH-21st is a prospective, longitudinal, multi-ethnic, population-based project exploring growth from early pregnancy to two years of age (113-118). The INTERGROWTH-21st protocol was conceptually based upon the WHO Multicentre Growth Reference Study protocol (119). The purpose of the INTERGROWTH-21st Project is to develop new 'prescriptive' standards describing normal foetal growth and newborn nutritional status, and the epidemiological characteristics of the preterm birth and impaired foetal growth syndromes in eight geographically diverse populations and to relate these standards to neonatal health risk (114). The eight study sites are located in: Pelotas, Brazil; Beijing, China; Nagpur, India; Torino, Italy; Nairobi, Kenya; Muscat, Oman; Oxford, United Kingdom; and Seattle, Washington, United States (120-127). All sites were selected to serve low risk populations for impaired foetal growth, with a LBW rate of less than 10%, a mean birth weight of greater than 3,100 grams, an altitude below 1,600 meters, a perinatal mortality rate of less than 20 per 1,000 live births, basic educational attainment of local mothers, and a lack of significant exposure to environmental hazards. Large (>1,000 deliveries a year) private or corporate hospitals were selected, covering at least 80% of all deliveries in the local target population (114). Mothers attending antenatal care in these institutions were required to have plans to deliver in that or a similar hospital located in the same region.

Beyond these basic characteristics, institutions were selected that were identified locally as private or corporation hospitals, or hospitals serving the upper-socioeconomic sector of the region. Developed country sites were required to serve the general

population of a region, covering at least 80% of all deliveries in the target population. This was not a requirement of developing country sites. All sites were required to be large institutions with at least 1,000 deliveries a year.

There is an epidemiological component to the INTERGROWTH-21st Project with the goal to "investigate in this multi-ethnic, population based sample the determinants of low birth weight and its components (preterm delivery, impaired foetal growth) under current healthcare conditions" (114). Along with two longitudinal activities, the INTERGROWH-21st Project also includes the Newborn Cross-Sectional Study (NCSS), where in addition to comprehensive pregnancy and delivery data, height, weight, and length anthropometric measurements were taken from all of the approximately 56,000 deliveries at the 8 sites over a fixed time-period (114).

Upon delivery, for all women giving birth at the respective sites during a specified time period, a Pregnancy and Delivery Form (*Appendix I*) was completed using maternal medical records. When the necessary information was not available in the maternal medical records, maternal reporting was used instead.

Given the connectedness of intrauterine growth restriction, preterm birth and stillbirth risk factors, the INTERGROWTH-21st Project readily lends itself to an epidemiological analysis of stillbirth. The exhaustive list of variables collected in the NCSS Pregnancy and Delivery Form to identify intrauterine growth restriction risk can be used to investigate the epidemiology of stillbirth at the INTERGROWTH-21st sites. Foetal growth restriction is a proxy for foetal complications such as placental and cord insufficiency, congenital anomalies, and hypertensive disorders, all major contributors to the global burden of stillbirth (128-130). There is therefore significant overlap in the socio-demographic risk factors for growth restriction used in the INTERGROWTH-21st study, and the potential risk factors for stillbirth.

In this thesis, I present the findings and analyses on the socio-demographic risk factors, maternal pre-existing illnesses ad pregnancy related health complications, and the reported causes of stillbirth in the INTERGROWTH-21st Project. I created the Foetal Death Supplementary Form to retrospectively determine the causes and risk factors of stillbirth using maternal medical records, gaining insight not collected during the INTERGROWTH-21st NCSS. The goal of this thesis is to describe the stillbirth risk for mothers giving birth at the INTERGROWTH-21st sites and the causes of stillbirth. As aforementioned, the INTERGROWTH-21st sites were selected to be high-performing hospitals and institutions with relatively low population health risks. Developing country sites in particular are in no way representative of these countries. I defined stillbirth in this thesis as all cases of foetal death occurring after at least 18 weeks gestation. Gestational age limits for stillbirth are typically set nationally according to state defined limits of viability of a foetus. In order to capture the most stillbirths and enable the INTERGROWTH-21st team to compare these findings with any national or hospital cohorts, I chose to define stillbirth using the least restrictive age limits set by any national government. In this same sense, multiple pregnancies are included in these analyses as well. Given that the goal of this thesis was to identify stillbirth risk factors for all mothers included in the INTERGROWTH-21st Project, not to investigate stillbirth risk to singelton pregnancies, I found it appropriate to include these mothers here.

In Chapter II, I will calculate prevalence statistics on stillbirth in the INTERGROWTH-21st NCSS, and identify all socio-demographic exposures associated with stillbirth risk. In Chapter III, I will assess the relation between maternal medical conditions occurring both before and during the index pregnancy and stillbirth risk among this cohort. In Chapter IV, I will calculate the prevalence of certain pregnancy, delivery, and birth outcome statistics among the INTERGROWTH-21st NCSS and

assess their influence on stillbirth risk. Finally in Chapter V, I will categorize all stillbirths collected in the INTERGROWTH-21st NCSS by plausible causes of death.

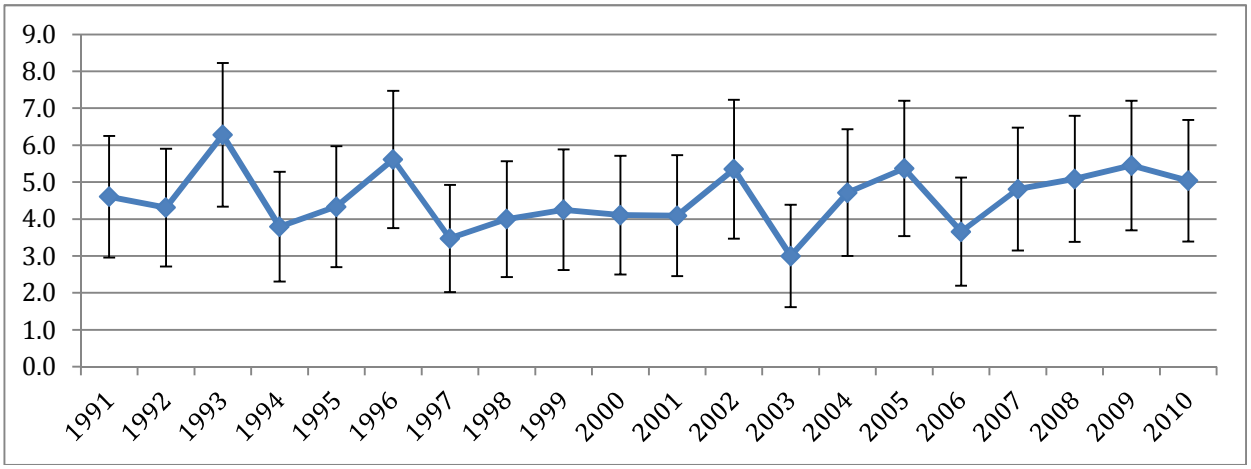
Tables/ Figures

Table 1. Stillbirth rates from the 2005-2009 WHO global survey on maternal and perinatal health.

Region Country (all births)	Total Stillbirths	Stillbirths per 1,000 births
Africa (n=83,351)	**3054**	**37**
Algeria	403	25
Angola	207	32
Democratic Republic of Congo	297	33
Niger	324	38
Nigeria	651	71
Kenya	723	36
Uganda	449	32
Latin America (n=97,996)	**981**	**10**
Argentina	87	8
Brazil	151	14
Cuba	137	11
Ecuador	108	9
Mexico	178	8
Nicaragua	47	8
Paraguay	58	16
Peru	215	13
Asia (n=104,910)	**1816**	**17**
India	1083	43
Nepal	202	24
Sri Lanka	84	6
Thailand	42	4
Cambodia	87	15
China	72	5
Philippines	193	14
Vietnam	53	4

Global survey on maternal and perinatal health crude tabulations database [Internet]. Naples, Italy: WHO; 2009; cited April 2012]. Available from: http://www.who.int/reproductivehealth/topics/best_practices/GS_Tabulation.pdf.

Figure 1. Stillbirth rate[1] per 1,000 births with 95% confidence intervals at the John Radcliffe Hospital in Oxford, UK and surrounding units[2], 1991-2010.



[1]Stillbirth defined as foetal death at ≥24 weeks gestation age
[2]This excludes the Horton Hospital in Banbury due to insufficient data

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Chapter II - Maternal demographic, socioeconomic, and nutritional characteristics and stillbirth risk

Introduction

In this chapter, I will use the risk factors considered in *Section 1: Demographic, socioeconomic, and nutritional characteristics* and *Section 7: Nutritional Supplements/Medication* of the Pregnancy and Delivery form to assess the risk factors for stillbirth at INTERGROWTH-21st sites. The objectives of this chapter are to describe the distribution of these demographic, socioeconomic, and nutritional characteristics across populations, and to assess the association between these characteristics and stillbirth risk.

For a more detailed description of the INTERGROWTH-21st study protocol, please consult the INTERGROWTH-21st Study Protocol and Manual (www.intergrowth21.org.uk) (1).

Methods

Data:

The data on all births were obtained from the 7 INTERGROWTH-21st sites that had enrolled at least 5,000 participants into the NCSS between January 2009 and June 2012: Pelotas, Brazil; Beijing, China; Nagpur, India; Torino, Italy; Nairobi, Kenya; Muscat, Oman; Oxford, United Kingdom. The Seattle, USA site will have completed the NCSS by March 2013. At the time of analysis, the Torino, Italy site had not yet entered information

on many of the stillbirths occurring at the site into the INTERGROWTH-21st database. Pregnancies in Torino, Italy were therefore excluded from this analysis. Work has since been done to complete the NCSS in Italy.

The primary outcome of the present analysis was stillbirth, defined as foetal death at a gestation age of 18 weeks or more. Gestational age was calculated using crown to rump length from early ultrasound examinations whenever possible. In cases without early ultrasound pregnancy dating, maternal reported last menstrual periods were used to estimate gestational age. As the Foetal Growth Longitudinal Study arm of the INTERGROWTH-21st Project requires 6 ultrasound images to be taken throughout the pregnancy for all participating mothers, all study sites were selected only if they had a policy of checking for gestational age with early dating ultrasound scans in place prior to their participation in the study. These policies were reinforced during the NCSS collection period. This has ensured a high level of ultrasound dating, relative to dating via last menstrual period, among NCSS mothers as well.

Secondary outcomes of foetal death and perinatal death were included as well. Foetal death is defined here as any case of foetal demise occurring before birth, regardless of gestational age. It should be noted that early miscarriages were not included in this figure, given the difficulty in counting miscarriages. Perinatal death is defined here as any stillbirth or early neonatal death (an infant death occurring within the first week of life). Foetal death and perinatal death are included here to provide information about the overall pregnancy outcomes for the study population, providing context for the stillbirth rates being reported. Further in-depth analyses of foetal death and perinatal death are outside of the scope of this thesis, and only stillbirth will be included in the present analysis.

All exposures of interest were assessed using *Section 1: Demographic, socioeconomic, and nutritional characteristics* and *Section 7: Nutritional*

Supplements/Medication of the Pregnancy and Delivery form. Exposures include the following maternal characteristics and demographics: age (<20 years, 20-34 years, 35-39 years, ≥40 years); height (<155 cm, 155-169.9 cm, ≥170 cm); weight (<50 kg, 50-79.9 kg, 80-99.9 kg, ≥100 kg); body mass index (<18.5 kg/m^2, 18.5-30.0 kg/m^2, ≥30.0 kg/m^2); marital status (single, married/cohabiting, widowed, separated/divorced); highest level of education (primary school, secondary school, professional/technical, university); occupational status (housework, manager/professional/technical, clerical support, services or sales, skilled manual work, unskilled manual work, other); high risk occupation and/or vigorous or contact sport during pregnancy as defined in *Appendix II* (yes, no); use of tobacco during pregnancy (none, 1-5 cigarettes per day, > 5 cigarettes per day); 5 or more units of alcohol per week during pregnancy (yes, no); use of recreational drugs during pregnancy (yes, no); special diet during pregnancy such as a vegetarian diet with no animal products (this does not include vegetarian diets limiting only meat and fish), gluten-free diets, or weight-loss reduction programmes (yes, no); routine use of iron supplements during pregnancy (yes, no); routine use of folic acid supplements during pregnancy (yes, no); routine use of calcium supplements during pregnancy (yes, no); routine use of food supplements during pregnancy (yes, no); routine use of multi-vitamin/mineral supplements during pregnancy (yes, no); routine use of any supplements during pregnancy (yes, no).

The study complies with the International Ethical Guidelines for Biomedical Research Involving Human Subjects at the appropriate international, national, local, and individual levels.

Analysis:

First, I calculated univariate statistics, including stillbirth rate per 1,000 total births, foetal death rate per 1,000 total births, perinatal mortality rate per 1,000 total births and prevalence of the exposures of interest by site, and antepartum contribution to total stillbirth numbers in order to describe the population samples, and calculated 95% confidence intervals for all rates.

Second, I calculated crude odds ratios and fit an adjusted multivariable logistic regression model of pregnancy outcome (any stillbirth vs. live birth) to assess the contribution of all maternal demographic, socioeconomic, and nutritional characteristics found to be associated with stillbirth in bivariate analyses. In the multivariable logistic regression model, I only included exposures that were independently associated with stillbirth risk in chi-squared tests for heterogeneity ($p < 0.050$, data not shown).

In each analysis, all mothers are used as a baseline measure, rather than controls, in order to gain insight into prevalence, given the feasibility of gathering NCSS data for all participants.

STATA 11 was used to carry out all statistical analyses (2).

Results

There were 43,781 births occurring between 2009-2012 at the 6 sites included in this analysis, with 295 resulting in stillbirths. Of these births, 39 births were excluded because the mother was lost to follow up during pregnancy, and did not deliver at one of the 6 study sites included in this analysis. Therefore, 43,742 births are included in this analysis, with a total of 43,078 pregnancies. One additional birth was excluded, as the mother, grieving from the stillbirth of her infant, was too distraught to provide any

information about her pregnancy and refused to consent to any further investigations. This pregnancy will be included in all prevalence analyses but excluded from those analyses relying upon data gathered from interviews and maternal medical records. Thus, there are 294 stillbirths to 289 mothers included in the demographic, social, and nutritional characteristics analyses from.

Table 1 shows descriptive statistics for foetal death (all foetal death), perinatal death (all foetal death occurring after at least 18 weeks gestation and any infant death occurring in the first week of life), and stillbirth (foetal death occurring after at least 18 weeks gestation) rates per 1,000 total deliveries by site. The overall foetal death and perinatal death rates were 7.3 and 9.9 per 1,000 total deliveries, respectively, with an overall stillbirth rate of 6.7 per 1,000 births. The foetal death rates for the sites in Brazil, China, India, Kenya, Oman, and the United Kingdom were as follows: 10.1, 5.1, 3.6, 15.9, 3.6, and 5.0 per 1,000 births, respectively. Perinatal death rates were 18.0, 5.4, 4,4, 19.9, 5.5, and 6.3 per 1,000 births, respectively. Stillbirth rates were 10.0, 5.1, 2.2, 14.7, 3.2, and 4.9 per 1,000 births, respectively. The percentage of antepartum stillbirths ranged from 96.9% antepartum stillbirths in Brazil, down to 64.9% antepartum stillbirths in Kenya.

Table 2 shows the prevalence of maternal demographic, socioeconomic, and nutritional characteristics among all mothers and mothers of stillborn infants. There were significant differences between mothers of live born infants and mothers of stillborn infants in maternal age ($p=0.003$), maternal height ($p=0.023$), maternal weight ($p=0.005$), marital status ($p<0.001$), level of education ($p=0.002$), use of tobacco during pregnancy ($p<0.001$), use of 5 or more units of alcohol per week during pregnancy ($p=0.001$), use of recreational drugs during pregnancy ($p=0.008$), routine iron supplements during pregnancy ($p<0.001$), folic acid supplements during pregnancy ($p<0.001$), routine calcium supplements during pregnancy ($p<0.001$), food supplements during pregnancy

(p<0.001), and routine maternal use of any supplements during pregnancy (p<0.001). There were no significant differences between mothers of live born infants and mothers of stillborn infants in maternal body mass index (p=0.233), occupational status (p=0.482), high risk occupation and/or vigorous or contact sport during pregnancy (p=0.268), maternal special diet (p=0.299), and routine maternal use of multi-vitamin/mineral supplements during pregnancy (p=0.953).

Table 3 shows the stillbirth rates per 1,000 births for given demographic, socioeconomic, and nutritional characteristics (along with antepartum stillbirth and intrapartum stillbirth rates), and chi-squared tests for heterogeneity. The stillbirth rate for mothers below 15 years of age was 26.3 (95% CI: 0.0-77.9) per 1,000 births. The stillbirth rate among mothers ≥40 years of age was 15.0 per 1,000 births (95% CI: 8.1-21.9), manifested through a higher rate of antepartum stillbirth (11.7) relative to other age categories. Mothers with missing maternal height values had significantly higher stillbirth rates than mothers with reported heights (p=0.004). The stillbirth rate for mothers weighing 80-99.9 kg was 9.9 per 1,000 births (95% CI: 6.9-12.9), with a rate of 6.0 (95% CI: 0.7-11.3) for mothers weighing ≥100 kg. The stillbirth rates for single (10.8, 95% CI: 5.9-15.6) and separated/divorced (31.8, 95% CI: 3.9-59.8) mothers were elevated due to significantly higher rates of antepartum stillbirth (p=0.001). For mothers with only primary school levels of education, the stillbirth rate was 10.7 per 1,000 births (95% CI: 7.6-13.9), with 10.3 antepartum stillbirths per 1,000 births (p<0.001). High-risk occupations and/or vigorous or contact sport during pregnancy led to an antepartum stillbirth rate of 14.5 per 1,000 births, however this did not reach statistical significance (p=0.087). The stillbirth rate for mothers using 1-5 cigarettes per day during pregnancy was 11.6 per 1,000 births (95% CI: 6.7-16.4), however there were no stillbirths for mothers using >5 cigarettes per day during pregnancy (p<0.001). Maternal use of 5 or more units of alcohol per week during pregnancy led to a stillbirth rate of 29.6 per 1,000

births (95% CI: 3.7-55.5). Maternal use of recreational drugs during pregnancy led to antepartum stillbirth rates of 27.8 per 1,000 births (p=0.001). Failure to use iron supplements (11.4), folic acid supplements (14.8), calcium supplements (8.6), or food supplements (7.6) during pregnancy led to elevated stillbirth rates (p<0.001). The stillbirth rate for infants born to mothers not using any supplement during pregnancy was 21.4 per 1,000 births (95% CI: 17.1-25.6). There was no significant difference in stillbirth rates between mothers using multi-vitamin/mineral supplements during pregnancy and those who did not (p=0.963).

Table 4 shows univariate and multivariate logistic regression models of the association between maternal demographic, socioeconomic, and nutritional characteristics, and stillbirth. In crude, univariate models, there was significant excess risk of stillbirth among mothers ≥40 years of age (Odds ratio (OR) = 2.52, 95% confidence interval (CI): 1.55-4.08), mothers weighing 80-99.9 kg (OR = 1.42, 95% CI: 1.01-1.99), single mothers (OR = 1.70, 95% CI: 1.06-2.71), separated/divorced mothers (OR = 5.13, 95% CI: 2.09-12.61), mothers with only primary levels of education (OR = 2.10, 95% CI: 1.45-3.04) or professional/technical training (OR = 1.54, 95% CI: 1.09-2.18), maternal use of 1-5 cigarettes per day (OR = 1.83, 95% CI: 1.18-2.83), maternal use of 5 or more units of alcohol per week during pregnancy (OR = 4.60, 95% CI: 1.88-11.29), and maternal use of recreational drugs during pregnancy (OR = 4.27, 95% CI: 1.57-11.63). Routine maternal use of iron (OR = 0.43, 95% CI: 0.34-0.54), folic acid (OR = 0.33, 95% CI: 0.26-0.41), calcium (OR = 0.52, 95% CI: 0.40-0.67), and food supplements (OR = 0.29, 95% CI: 0.17-0.48) during pregnancy were associated with lower risk of stillbirth, as well as maternal weight of <50 kg (OR = 0.57, 95% CI: 0.36-0.88). Routine maternal use of any supplements during pregnancy was also associated with lower risk of stillbirth (OR = 0.24, 95% CI: 0.19-0.31). In the multivariable analysis, mothers weighing 80-99.9 kg (OR = 1.26, 95%CI: 0.90-1.79), single mothers (OR = 1.23,

95% CI: 0.74-2.04), separated/divorced mothers (OR = 2.78, 95% CI: 0.86-8.99), mothers with primary level of education (OR = 1.47, 95% CI: 0.97-2.23), mothers using of 1-5 cigarettes per day (OR = 1.01, 95% CI: 0.67-1.83), mothers using 5 or more units of alcohol per week during pregnancy (OR = 2.60, 95% CI: 0.96-7.05), and mothers using recreational drugs during pregnancy (OR = 1.81, 95% CI: 0.58-5.65) no longer faced statistically significant excess risk for a stillbirth occurring during their pregnancy. Calcium no longer significantly reduced the risk for stillbirth (OR = 0.96, 95% CI: 0.71-1.29).

Discussion

In this analysis of 43,742 births between 2009-2012, 295 infants were stillborn, resulting in a stillbirth rate of 6.7 per 1,000 total births. Of these 295 stillbirths, 75.9% were antepartum, or macerated, stillbirths. There were several demographic, socioeconomic, and nutritional characteristics that were associated with stillbirth, including maternal age, maternal weight, marital status, highest level of maternal education, maternal use of tobacco during pregnancy, maternal consumption of 5 or more units of alcohol per week during pregnancy, maternal use of recreational drugs during pregnancy, and routine use of iron, folic acid, calcium, or food supplements during pregnancy. In the multivariable logistic regression model, only maternal age ≥40, maternal consumption of 5 or more units of alcohol per week during pregnancy, and routine use of iron, folic acid, or food supplements during pregnancy remained significantly associated with stillbirth.

The stillbirth rate of 6.7 per 1,000 total births is similar to rates calculated in previous studies of populations with access to full hospital and emergency services (3).

As expected, given the catchment differences, stillbirth rates varied from site to site. Referral centres such as the site in Nairobi, Kenya, and locations with diverse socioeconomic populations such as Pelotas, Brazil, had greater stillbirth rates than sites serving only relatively affluent populations, such as the Muscat, Oman site. We did not attempt to assess the contribution of the demographic, socioeconomic, and nutritional characteristics by site given the low number of stillbirths at each particular site.

In previous analyses of stillbirth risk factors, maternal education, age, BMI, marital status, substance abuse, diet, and micronutrient supplementation have all been associated with stillbirth (4-8). The findings of this study are similar to these results.

Extreme maternal age has been associated with increased stillbirth risk. As with prior studies (5, 7), I found that among women below the age of 15 years, the stillbirth rate was approximately 4 times that of the overall population (not statistically significant), while the rate among mothers 40 years old or greater was more than twice the overall rate. The multivariable regression model suggests that maternal age operates largely outside of the aetiological pathway of the other demographic, socioeconomic, and nutritional characteristics.

Maternal BMI was not associated with significantly higher risk of stillbirth in this study. Maternal weight of 80-99.9 kg was associated with a 40% increased risk of stillbirth, however there was no significantly increased risk of stillbirth among mothers weighing greater than or equal to 100 kg. Relative to places such as England, where 26% of the population has a BMI of 30 kg/m^2 (8), there are few obese mothers in this study (13.5%). Obesity may be more of a contributor to stillbirth risk in populations where obesity is more widespread. This study, however, does not have the statistical power to examine such a hypothesis.

Aside from the above maternal demographics, several socioeconomic factors were also associated with stillbirth. The stillbirth rate among single mothers has been

shown to be higher than that among mothers married during parturition, linked primarily to lesser access to and use of antenatal care and lower socioeconomic status (4). The results from this study add support to this hypothesis. In the multivariable logistic regression analysis, the excess risk of stillbirth among unwed mothers was largely explained by the other demographic, socioeconomic, and nutritional characteristics included in the model. However, the stillbirth rate among separated/divorced mothers was 31.8 per 1,000 births. To my knowledge, no previous studies have shown such excess risk of stillbirth among divorced/separated mothers. Given the complexity of socioeconomic status and the issues related to marital status, it is difficult to explain the pathway from divorce/separation to stillbirth. The effect shown here, however, is not due solely to educational/occupational status, or maternal age. Antenatal care could play a role, as this variable was not included in the NCSS Pregnancy and Delivery Form.

Little formal education was associated with increased risk of stillbirth. Relative to mothers with university level education, those mothers with only primary levels of education were twice as likely to experience a stillbirth. Mothers reaching secondary school were not exposed to such excess risk. Those mothers with professional or technical training were 50% more likely to experience a stillbirth than mothers who had attended university. The types of professions that mothers with professional/technical training chose could explain this finding. Women working in the medical professions, for example, have been shown to have greater stillbirth risk relative to women not working in the medical field due to exposure to work hazards such as radiation (9). Beauticians, dentists, and other professions have also been linked to stillbirth risk (9, 10). The results of this study do not suggest that manager/professional/technical levels of occupation contribute to excess stillbirth risk, although stillbirth risk among women working in skilled manual labour was 40% greater than that among mothers doing only housework (results not significant).

Maternal use of 10 or more cigarettes per day has been shown to significantly increase the risk of stillbirth (11). In our study, however, there was very little reported use of cigarettes and tobacco products among this study population. Only 0.6% of the population reported using more than 5 cigarettes per day, and no women reported using 10 or more cigarettes per day (data not shown). Despite the low use of tobacco, mothers using 1-5 cigarettes per day were 83% more likely to have a stillborn infant compared to non-smokers. This relation, however, was attenuated in the multivariable model to non-significance.

As with tobacco, very few women reported consuming alcohol frequently. Just 0.4% of the overall population reported consuming 5 or more units of alcohol per week. But among these women, the stillbirth rate was 4-5 times that of women drinking little or no alcohol during pregnancy. In the multivariable model, use of 5 or more units of alcohol remained the strongest predictor of stillbirth among all demographic, socioeconomic, and nutritional characteristics. In univariate analyses, maternal use of recreational drugs also led to stillbirth rates 4-5 times those of non-drug using mothers, although mothers using recreational drugs only comprised 0.3% of the overall population. The relation was not significant in the multivariable model. This could be due to the significant correlation between use of alcohol, tobacco, and recreational drugs ($p<0.001$).

Routine maternal use of iron, folic acid, and food supplements was protective against stillbirth. Supplementation has long been proven to protect against poor pregnancy outcomes, with some mechanisms being well explained, such as the relation between neural tube defects and folic acid deficiencies, and others not so well understood (12, 13). However, given the association between supplements and general access to and use of antenatal care, the relation between supplements and decreased risk of stillbirth may not be causal. For folic and iron, 71% and 80%, respectively of all women received supplementation. But for food and calcium, only 16% and 46%,

respectively, of women received supplements. This indicated that both supplements commonly suggested for antenatal care and those not generally recommended to pregnant women had protective effects. Also, multi-vitamins/minerals, which 19% of women used during pregnancy, had no effect on stillbirth rates, further supporting the hypothesis that the added benefit from these supplements as a whole is not merely an effect of maternal use of antenatal care, and bias towards women placing more emphasis on their health. Still, in the multivariable logistic regression model, calcium was no longer associated with stillbirth. In multivariable models with only these nutritional supplements, calcium again was no longer associated with stillbirth, indicating that it is perhaps not protective against stillbirth on its own, and more likely indicative of antenatal care status.

There are several limitations that must be considered when interpreting the results of this study. First, the study relies on maternal reporting of stigmatized topics such as use of tobacco, alcohol, and recreational drugs during pregnancy. Along with the typical limitations of retrospectively gathering information through surveys, this also may have led to an artificially low prevalence of these behavioural characteristics. Still, there is no reason to suspect a difference in the level of underreporting among mothers of stillborn infants relative to mothers of live born infants. Second, it was not possible to analyse the effects of these demographic, socioeconomic, and nutritional characteristics by site, given the low number of stillbirths at each individual site. However, the aim of this study is not to provide regional analyses, but to investigate the general effects of these potential stillbirth risk factors. Third, for several variables, stillborn infants were significantly more likely to have missing data than live born infants. Mothers of stillborn infants often receive or seek less antenatal care, providing less available access points to her, and distressed mothers of stillborn infants are often not pursued for additional information about their loss and prior medical history (14).

In subsequent chapters, I will attempt to relate the socioeconomic, demographic, and nutritional characteristics associated with stillbirth here to the relevant clinical risk factors.

Tables/ Figures

Table 1. Stillbirth prevalence by site, 2009-2012.

	Total deliveries	Foetal deaths per 1,000 total births	Perinatal deaths per 1,000 total births	Stillbirths per 1,000 total births	Percent antepartum stillbirths
Pelotas, Brazil	6,503	10.1	18.0	10.0	96.9
Beijing, China	7,399	5.1	5.4	5.1	71.1
Nagpur, India	6,317	3.6	4.4	2.2	71.4
Nairobi, Kenya	7,740	15.9	19.9	14.7	64.9
Muscat, Oman	7,578	3.6	5.5	3.2	83.3
Oxford, United Kingdom	8,205	5.0	6.3	4.9	75.0
Overall	**43,742**	**7.3**	**9.9**	**6.7**	**75.9**

Table 2. Maternal demographic, socioeconomic, and nutritional characteristics, and stillbirth, 2009-2012.

	All mothers % n=43,077	Mothers of stillborn infants % n=289
Maternal age (years)		
< 15	0.1	0.4
15-19	3.9	3.8
20-34	81.8	76.1
35-39	11.5	13.5
≥ 40	2.7	6.2
Missing	0.0	0.0
Maternal height (cm)		
< 155	21.6	16.6
155-169.9	70.3	74.4
≥ 170	7.6	7.6
Missing	0.5	1.4
Maternal weight (kg)		
< 50	13.3	7.6
50-79.9	74.0	74.7
80-99.9	9.7	13.8
≥ 100	1.9	1.7
Missing	1.1	2.1
Maternal body mass index (kg/m^2)		
< 18.5	6.1	4.2
18.5-30.0	79.0	78.6
≥ 30.0	13.5	14.9
Missing	1.4	2.4
Marital Status		
Single	4.0	6.6
Married/Cohabiting	95.3	91.7
Separated/Divorced	0.4	1.7
Widowed	0.1	0.0
Missing	0.2	0.0
Highest level of education		
Primary	9.8	15.6
Secondary	29.4	29.4
Professional/Technical training	16.9	19.7
University	34.6	26.3
Missing	9.3	9.0
Occupational Status		
Housework	45.9	41.2
Manager/Professional/Technical	27.0	28.0
Clerical support, service or sales	14.9	14.9
Skilled manual work	2.5	3.1
Unskilled manual work	2.5	3.1
Other	6.3	8.0
Missing	1.0	1.7
High risk occupation and/or vigorous or contact sport during pregnancy?		
No	99.3	98.6
Yes	0.6	1.4
Missing	0.0	0.0
Maternal use of tobacco during pregnancy		
None	95.0	91.7
1-5 cigarettes per day	4.3	7.6
> 5 cigarettes per day	0.6	0.0
Missing	0.1	0.7
5 or more units of alcohol per week during pregnancy?		
No	99.6	98.3
Yes	0.4	1.7
Missing	0.0	0.0
Maternal use of recreational drugs during pregnancy		
No	99.6	98.6
Yes	0.3	1.4
Missing	0.0	0.0
Maternal special diet?		

No	98.8	97.9
Yes	1.1	2.1
Missing	0.0	0.0
Routine maternal use of iron supplements during pregnancy		
No	28.6	48.1
Yes	71.4	51.9
Missing	0.0	0.0
Routine maternal use of folic acid supplements during pregnancy		
No	19.7	42.6
Yes	80.3	57.4
Missing	0.0	0.0
Routine maternal use of calcium supplements during pregnancy		
No	54.3	69.6
Yes	45.7	30.5
Missing	0.0	0.0
Routine maternal use of food supplements during pregnancy		
No	84.0	94.8
Yes	15.9	5.2
Missing	0.0	0.0
Routine maternal use of multi-vitamin/mineral supplements during pregnancy		
No	81.0	80.6
Yes	19.0	19.4
Missing	0.0	0.0
Routine maternal use of any supplements during pregnancy		
No	10.4	32.2
Yes	89.6	67.8
Missing	0.0	0.0

Table 3. Maternal demographic, socioeconomic, and nutritional characteristics, and stillbirth rates per 1,000 total births by timing of death and chi-squared tests for heterogeneity, 2009-2012.

	Stillbirth rate per 1,000 births (95% CI)	p-values	Antepartum rate per 1,000 births	p-values	Intrapartum rate per 1,000 births	p-values
Overall	**6.7 (6.0 - 7.5)**		**5.1**		**1.6**	
Maternal age (years)		0.006		0.014		0.571
< 15	26.3 (0.0 - 77.9)		26.3		--	
15-19	6.5 (2.6 - 10.3)		5.3		1.2	
20-34	6.3 (5.5 - 7.1)		4.8		1.5	
35-39	7.7 (5.3 - 10.1)		5.5		2.2	
≥ 40	15 (8.1 - 21.9)		11.7		3.3	
Missing	--		--		--	--
Maternal height (cm)		0.004		0.426		<0.001
< 155	5.2 (3.8 - 6.7)		4.3		1.0	
155-169.9	7.1 (6.1 - 8.0)		5.4		1.7	
≥ 170	6.8 (4.0 - 9.6)		4.8		2.1	
Missing	24.3 (3.0 - 45.5)		9.7		14.6	
Maternal weight (kg)		0.004		0.033		0.129
< 50	4 (2.3 - 5.6)		2.9		1.0	
50-79.9	6.7 (5.8 - 7.6)		5.2		1.5	
80-99.9	9.9 (6.9 - 12.9)		6.8		3.1	
≥ 100	6 (0.7 - 11.3)		4.8		1.2	
Missing	12.4 (2.5 - 22.3)		10.3		2.1	
Maternal body mass index (kg/m^2)		0.120		0.299		0.202
< 18.5	4.6 (2.0 - 7.1)		3.4		1.1	
18.5-30.0	6.7 (5.8 - 7.5)		5.0		1.6	
≥ 30.0	7.4 (5.2 - 9.6)		6.1		1.4	
Missing	12.8 (3.9 - 21.7)		8.0		4.8	
Marital Status		0.001		0.001		0.652
Single	10.8 (5.9 - 15.6)		9.1		1.7	
Married/Cohabiting	6.5 (5.7 - 7.2)		4.9		1.6	
Separated/Divorced	31.8 (3.9 - 59.8)		25.5		6.4	
Widowed	-- --		--		--	
Missing	-- --		--		--	
Highest level of education		0.001		<0.001		0.020
Primary	10.7 (7.6 - 13.9)		10.3		0.5	
Secondary	6.7 (5.3 - 8.1)		5.1		1.6	
Professional/Technical training	8 (6.0 - 10.0)		5.3		2.7	
University	5.1 (3.9 - 6.2)		3.9		1.2	
Missing	6.4 (3.9 - 8.8)		4.2		2.2	
Occupational Status		0.439		0.770		0.042
Housework	6 (4.9 - 7.1)		4.8		1.1	
Manager/Professional/Technical	6.9 (5.4 - 8.4)		5.1		1.8	
Clerical support, service or sales	6.9 (4.9 - 9.0)		4.8		2.2	
Skilled manual work	9.2 (3.5 - 14.8)		7.3		1.8	
Unskilled manual work	8.1 (2.8 - 13.4)		5.4		2.7	
Other	8.4 (5.0 - 11.8)		6.9		1.5	
Missing	11.9 (1.5 - 22.4)		4.8		7.2	
High risk occupation and/or vigorous or contact sport during pregnancy?		0.271		0.087		0.794
No	6.7 (5.9 - 7.4)		5.1		1.6	
Yes	14.5 (0.3 - 28.8)		14.5		--	
Missing	--		--		--	
Maternal use of tobacco during pregnancy		<0.001		<0.001		0.922
None	6.5 (5.7 - 7.3)		4.9		1.6	
1-5 cigarettes per day	11.6 (6.7 - 16.4)		10.0		1.6	
> 5 cigarettes per day	--		--		--	
Missing	45.5 (0.0 - 108.5)		45.5		--	
5 or more units of alcohol per week during pregnancy?		<0.001		0.003		0.368
No	6.6 (5.9 - 7.4)		5.1		1.6	
Yes	29.6 (3.7 - 55.5)		23.7		5.9	
Missing	--		--		--	
Maternal use of recreational drugs during pregnancy		0.008		0.001		0.882
No	6.7 (5.9 - 7.4)		5.0		1.6	
Yes	27.8 (0.6 - 55)		27.8		--	

Missing	--		--	--	
Maternal special diet?		0.319		0.285	0.961
No	6.7 (5.9 - 7.4)		5.1	1.6	
Yes	12.1 (2.4 - 21.8)		10.1	2.0	
Missing	--		--	--	
Routine maternal use of iron supplements during pregnancy		<0.001		<0.001	<0.001
No	11.4 (9.6 - 13.3)		8.6	2.8	
Yes	4.8 (4.1 - 5.6)		3.7	1.1	
Missing	--		--	--	
Routine maternal use of folic acid supplements during pregnancy		<0.001		<0.001	<0.001
No	14.8 (12.2 - 17.4)		11.6	3.3	
Yes	4.7 (4.0 - 5.5)		3.6	1.2	
Missing	--		--	--	
Routine maternal use of calcium supplements during pregnancy		<0.001		<0.001	0.054
No	8.6 (7.5 - 9.8)		6.6	2.0	
Yes	4.4 (3.5 - 5.4)		3.3	1.1	
Missing	--		--	--	
Routine maternal use of food supplements during pregnancy		<0.001		<0.001	0.236
No	7.6 (6.7 - 8.5)		5.9	1.7	
Yes	2.1 (1.1 - 3.2)		f	0.9	
Missing	--		--	--	
Routine maternal use of multi-vitamin/mineral supplements during pregnancy		0.963		0.902	0.767
No	6.7 (5.9 - 7.6)		5.1	1.7	
Yes	6.7 (5.0 - 8.5)		5.4	1.3	
Missing	--		--	--	
Routine maternal use of any supplements during pregnancy		<0.001		<0.001	<0.001
No	21.4 (17.1 - 25.6)		16.3	5.1	
Yes	5 (4.3 - 5.7)		3.8	1.2	
Missing			--	--	

Table 4. Crude and multivariate logistic regression models of the associations between maternal demographic, socioeconomic, and nutritional characteristics, and risk of a stillbirth occurring during this pregnancy, 2009-2012.

	Univariate		Multivariable		p-values
	OR	95% CI	AOR	95% CI	
Maternal age (years)					
< 15	4.42	0.60-32.38	2.85	0.37-21.76	0.309
15-19	1.04	0.56-1.90	0.68	0.35-1.29	0.299
20-34	ref	ref	ref	ref	ref
35-39	1.26	0.90-1.78	1.11	0.78-1.56	0.183
≥ 40	2.52	1.55-4.08	2.00	1.22-3.28	0.002
Maternal height (cm)					
< 155	0.73	0.53-0.99	0.90	0.65-1.24	0.704
155-169.9	ref	ref	ref	ref	ref
≥ 170	0.95	0.61-1.47	0.82	0.52-1.29	0.107
Maternal weight (kg)					
< 50	0.57	0.36-0.88	0.77	0.49-1.21	0.201
50-79.9	ref	ref	ref	ref	ref
80-99.9	1.42	1.01-1.99	1.26	0.90-1.79	0.116
≥ 100	0.90	0.37-2.20	0.82	0.33-2.00	0.791
Maternal body mass index (kg/m^2)					
< 18.5	0.69	0.38-1.23			
18.5-30.0	ref	ref			
≥ 30.0	1.11	0.80-1.54			
Marital Status					
Single	1.70	1.06-2.71	1.23	0.74-2.04	0.416
Married/Cohabiting	ref	ref	ref	ref	ref
Separated/Divorced	5.13	2.09-12.61	2.78	0.86-8.99	0.088
Widowed	--	--	--	--	
Highest level of education					
Primary	2.10	1.45-3.04	1.47	0.97-2.23	0.074
Secondary	1.32	0.97-1.80	1.27	0.93-1.74	0.195
Professional/Technical training	1.54	1.09-2.18	1.47	1.04-2.08	0.041
University	ref	ref	ref	ref	ref
Occupational Status					
Housework	ref	ref			
Manager/Professional/Technical	1.16	0.87-1.53			
Clerical support, service or sales	1.12	0.79-1.58			
Skilled manual work	1.40	0.71-2.76			
Unskilled manual work	1.37	0.69-2.70			
Other	1.42	0.91-2.22			
High risk occupation and/or vigorous or contact sport during pregnancy?					
No	ref	ref			
Yes	2.21	0.82-5.97			
Maternal use of tobacco during pregnancy					
None	ref	ref	ref	ref	ref
1-5 cigarettes per day	1.83	1.18-2.83	1.11	0.67-1.83	0.652
> 5 cigarettes per day	--	--	--	--	
5 or more units of alcohol per week during pregnancy?					
No	ref	ref	ref	ref	ref
Yes	4.60	1.88-11.29	2.60	0.96-7.05	0.051
Maternal use of recreational drugs during pregnancy					
No	ref	ref	ref	ref	ref
Yes	4.27	1.57-11.63	1.81	0.58-5.65	0.565
Maternal special diet?					
No	ref	ref			
Yes	1.86	0.83-4.21			
Routine maternal use of iron supplements during pregnancy					
No	ref	ref	ref	ref	ref
Yes	0.43	0.34-0.54	0.63	0.47-0.84	0.001
Routine maternal use of folic acid supplements during pregnancy					
No	ref	ref	ref	ref	ref
Yes	0.33	0.26-0.41	0.50	0.38-0.66	<0.001
Routine maternal use of calcium supplements during pregnancy					

No	ref	ref	ref	ref	ref
Yes	0.52	0.40-0.67	0.96	0.71-1.29	0.693
Routine maternal use of food supplements during pregnancy					
No	ref	ref	ref	ref	ref
Yes	0.29	0.17-0.48	0.50	0.28-0.87	0.025
Routine maternal use of multi-vitamin/mineral supplements during pregnancy					
No	ref	ref			
Yes	1.03	0.77-1.37			
Routine maternal use of any supplements during pregnancy					
No	ref	ref			
Yes	0.24	0.19-0.31			

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Chapter III – Maternal medical conditions and stillbirth risk

Introduction

Maternal medical conditions arising prior to and during pregnancy provide direct aetiological links from the risk factors mentioned in Chapter II to stillbirth. The additional risk of stillbirth seen in obese mothers, for example, found in other studies is partially explained by the increased risk for hypertensive disorders and diabetes associated with obesity (1). Environmental exposure to tobacco smoke and maternal use of tobacco lead to increased risk of hypertension and maternal immunity disorders, which may in turn be responsible for the increased risk of stillbirth due to tobacco exposure (2, 3).

Any severe medical condition that compromises maternal health can theoretically lead to stillbirth. Maternal medical illnesses such as diabetes, hypertension, and chronic renal disease accounted for 10% of all foetal deaths (4). Those medical illnesses that contribute to foetal growth restriction through placental insufficiency (1, 2), autoimmunity complications leading to foetal hydrops and thrombosis (5), and infections acting through a range of aetiological pathways are the best understood (6). A significant portion of the stillbirths attributable to maternal medical conditions is due to suboptimal care and mismanagement of disorders known to lead to pregnancy complications (4). Better management of these illnesses during pregnancy could have major health benefits. Further research explaining the magnitude of the stillbirth risk associated with these maternal medical illnesses could help identify improvement areas, and indicate the importance of disease management in pregnancy.

Several other medical conditions have been associated with stillbirth risk, although the causal pathways are poorly understood. Severe maternal psychiatric conditions, for example, were shown to increase the risk of stillbirth due to nearly all

cause of death categories in a Danish national cohort study, but few studies have investigated this relationship (7).

Further investigation into the relation between maternal medical conditions and risk of stillbirth is therefore of epidemiological and clinical need. *Section 2: Medical Conditions* and *Section 5: Clinical Conditions* in the INTERGROWTH-21st Pregnancy and Delivery Form assess maternal clinical conditions acquired prior to and during pregnancy, respectively. In this chapter, I will explore the prevalence of various maternal medical conditions occurring before and during pregnancy and analyse the effect of these diseases on stillbirth risk.

Methods

Data:

The data on 43,781 births was obtained from the 6 INTERGROWTH-21st sites that have enrolled at least 5,000 participants into the NCSS between 2009-2012. Data from the Torino, Italy and Seattle, USA sites were not available at the time of this analysis.

The primary outcome was stillbirth, defined as foetal death at a gestation age of 18 weeks or more. Gestational age was calculated using crown to rump length from early ultrasound examinations whenever possible. In cases without early ultrasound pregnancy dating, maternal reported last menstrual periods were used to estimate gestational age.

All exposures of interest were assessed using *Section 2: Medical history* and *Section 5: Clinical conditions* of the INTERGROWTH-21st Pregnancy and Delivery Form. Exposures include the following maternal medical conditions occurring prior to the

pregnancy of interest: diabetes (yes, no); thyroid disease or other endocrinological conditions including Addison's disease, adrenal gland disorders, hypothyroidism, and hyperthyroidism (yes, no); cardiac disease (yes, no); hypertension/chronic hypertension (yes, no); proteinuria, kidney disease or chronic renal disease (yes, no); lupus erythematosus (yes, no); epilepsy (yes, no); malaria (yes, no); tuberculosis (yes, no); Crohn's disease, coeliac disease, ulcerative colitis, or any severe malabsorption condition (yes, no); any type of malignancy/cancer (yes, no); any haematological condition including sickle cell anaemia or leukaemia (yes, no); HIV or AIDS (yes, no); any congenital abnormality or genetic disease such as cystic fibrosis or congenital heart defects, but excluding mild abnormalities (yes, no); any other clinically relevant conditions as judged by the attending staff requiring special care (yes, no). The following maternal medical conditions diagnosed or treated during pregnancy were also included as exposures: cardiac disease (yes, no); chronic respiratory disease including chronic asthma but excluding mild asthma not requiring treatment or seasonal allergy induced difficulties (yes, no); malaria (yes, no); mental illnesses, including depression, bipolar disorder, schizophrenia, and general anxiety disorder but not including mild depression (yes, no); epilepsy (yes, no); thyroid disease or any other endocrinological condition (yes, no); lower urinary tract infections requiring antibiotic treatment (yes, no); pyelonephritis or inflammation of the kidney and upper urinary tract from non-contagious bacterial infection of the bladder and other urinary infections (yes, no); respiratory tract infection requiring antibiotic/antiviral treatment (yes, no); any other infections requiring antibiotic/antiviral treatment (yes, no); positive syphilis test (yes, no); HIV or AIDS (yes, no); any sexually transmitted infections such as Chlamydia, gonorrhoea, or herpes (yes, no); any type of malignancy or cancer (yes, no); any other medical/surgical condition requiring treatment or referral (yes, no). All exposures were derived from maternal medical records and maternal self-reporting.

The study complies with the International Ethical Guidelines for Biomedical Research Involving Human Subjects at the appropriate international, national, local, and individual levels.

Analysis:

First, I calculated univariate statistics, including prevalence of the maternal medical illnesses prior to the pregnancy of interest, in order to describe the population sample, and calculated 95% confidence intervals for all rates.

Second, I calculated univariate odds ratios and fit an adjusted multivariable logistic regression model of pregnancy outcome (stillbirth vs. live birth) to assess the contribution of all maternal medical history found to be associated with stillbirth in bivariate analyses. In the multivariable logistic regression model, I only included exposures that were independently associated with stillbirth risk in chi-squared tests for heterogeneity ($p < 0.050$, data not shown). I also included the socio-demographic risk factors shown to be independently associated with stillbirth ($p < 0.050$).

Third, I repeated the above analyses using maternal medical conditions diagnosed or treated during the pregnancy of interest as exposures.

STATA 11 was used to carry out all statistical analyses (8).

Results

There were 43,781 births occurring between 2009-2012 at the 6 sites included in this analysis, with 295 resulting in stillbirths. Of the 43,781 births, 39 births were excluded because the mother was lost to follow up during pregnancy, with the mother not delivering at one of the 6 sites. Therefore, 43,742 births are included in this analysis, with a total of 43,078 pregnancies. One additional birth was excluded, as the mother, grieving from the stillbirth of her infant, was too distraught to provide any information about her pregnancy and refused to consent to any further investigations. This pregnancy will be included in all prevalence analyses but excluded from those analyses relying upon data gathered from interviews and maternal medical records. Thus, there are 294 stillbirths to 289 mothers included in the maternal medical conditions analyses.

Table 1 shows the prevalence of maternal medical conditions diagnosed prior to this pregnancy (clinical history) among all mothers and mothers of stillborn infants. There were significant differences in the prevalence of hypertension/ chronic hypertension ($p<0.001$) and HIV or AIDS ($p<0.001$) among mothers of stillborn infants relative to mothers of live born infants. For all other maternal medical conditions arising prior to this pregnancy, there were no significant differences in the prevalence of the condition among mothers of stillborn infants relative to mothers of live born infants ($p>0.050$).

Table 2 shows the stillbirth rates per 1,000 births for given maternal medical conditions diagnosed prior to pregnancy (along with antepartum stillbirth and intrapartum stillbirth rates) and chi-squared tests for heterogeneity. Mothers with hypertension/chronic hypertension experienced stillbirth at a rate of 31.6 per 1,000 births (95% CI: 18.4-44.8). The antepartum stillbirth rate for mothers with hypertension/chronic hypertension was 30.2 per 1,000 births, while intrapartum stillbirths were not affected by the disorder ($p=0.989$). Infants born to mothers diagnosed with HIV or AIDS had a

stillbirth rate of 37.7 per 1,000 births (95% CI: 7.5-67.9). The antepartum stillbirth rate for mothers with HIV or AIDS was 31.4 per 1,000 births. The intrapartum stillbirth rate for these mothers was 6.3 per 1,000 births, although this was not statistically significantly greater than the 1.6 intrapartum stillbirths per 1,000 births among mothers without HIV or AIDS (p=0.332). No other maternal medical condition diagnosed prior to pregnancy led to significantly higher stillbirth, antepartum stillbirth, or intrapartum stillbirth rates (p>0.050).

Table 3 shows univariate logistic regression models of the associations between maternal medical history and stillbirth, as well as a multivariable logistic regression model adjusting for maternal demographic and socioeconomic characteristics shown to predict stillbirth in Chapter II. In the univariate models, there was excess stillbirth risk for mothers with hypertension/chronic hypertension (OR = 4.98, 95% CI: 3.17-7.81) and HIV or AIDS (OR = 6.03, 95% CI: 2.64-13.74). There was no significantly higher stillbirth risk among mothers with any other medical condition diagnosed before pregnancy (data not shown). In the multivariable analysis including demographic and socioeconomic characteristics shown to be associated with stillbirth in Chapter II (maternal age, maternal weight, marital status, highest level of maternal education, maternal use of tobacco during pregnancy, maternal use of 5 or more units of alcohol per week during pregnancy, and maternal use of recreational drugs during pregnancy), the excess stillbirth risks among mothers with hypertension/chronic hypertension (OR = 3.87, 95% CI: 2.40-6.24) and mothers with HIV or AIDS (OR = 4.52, 95% CI: 1.93-10.56), although partially attenuated, remained statistically significant. Maternal weight and maternal use of tobacco during pregnancy no longer predicted stillbirth in the multivariable model. Maternal use of recreational drugs during pregnancy remained associated with excess risk of stillbirth, although this association was no longer statistically significant (OR = 2.30, 95% CI: 0.75-7.04). The excess stillbirth risk among single mothers (OR = 1.33,

95% CI: 0.79-2.22) and separated/divorced mothers (OR = 2.91, 95% CI: 0.98-8.61) were no longer statistically.

Table 4 shows the prevalence of maternal medical conditions diagnosed or treated during the index pregnancy among all mothers, and mothers of stillborn infants. There were statistically significant differences in the diagnosis or treatment of malaria ($p<0.001$), lower urinary tract infection requiring antibiotics ($p=0.001$), syphilis ($p<0.001$), and HIV or AIDS ($p<0.001$) between mothers of stillborn infants and mothers of live born infants. The difference between the prevalence of mental illness among mothers of stillborn infants and that of mothers of live born infants approached statistical significance ($p=0.087$). No other medical conditions diagnosed or treated during pregnancy were associated with significant risk of stillbirth ($p>0.050$).

Table 5 shows the stillbirth rates per 1,000 births for given maternal medical conditions diagnosed or treated during pregnancy (as well as antepartum stillbirth and intrapartum stillbirth rates) and chi-squared tests for heterogeneity. The stillbirth rate among mothers diagnosed or treated with malaria during pregnancy was 54.9 per 1,000 births (95% CI: 6.8-103.1). The antepartum stillbirth rate for mothers in this group was 44.0 ($p<0.001$), while the intrapartum stillbirth rate was 11.0 per 1,000 births. The intrapartum stillbirth rate for mothers diagnosed or treated with malaria was not significantly greater than the rate of 1.6 for mothers without a malaria episode ($p=0.080$). The stillbirth rate among women with lower urinary tract infections requiring antibiotics was 9.9 per 1,000 births (95% CI: 7.1-12.8), which was significantly greater than that of women who did not experience a lower urinary tract infection during pregnancy ($p=0.003$). This excess risk was mediated through the elevated antepartum stillbirth rate of 8.5 per 1,000 births ($p<0.001$), and the significant relation held when women with missing data were excluded (data not shown). The antepartum stillbirth rate among women with a positive syphilis test during pregnancy was 43.5 per 1,000 births (95% CI:

0.0-103.7)). For women diagnosed or treated for HIV or AIDS, the stillbirth rate was 36.5 per 1,000 births ($p<0.001$). Both antepartum (26.0, $p<0.001$) and intrapartum (10.4, $p=0.009$) stillbirth rates per 1,000 births were elevated in these mothers. While the overall stillbirth rate for women with mental illnesses was not significantly higher than that of healthy mothers ($p=0.095$), the antepartum stillbirth rate for women with mental illnesses was significantly higher ($p=0.014$). Mothers with infections (excluding respiratory and lower urinary tract infections) requiring antibiotic/antiviral treatment did not have a significantly higher rate of stillbirth ($p=0.169$), however they were at increased risk for intrapartum stillbirth relative to mothers without infections ($p=0.039$). Diagnosis of other medical/surgical conditions requiring treatment led to an antepartum stillbirth rate of 9.4 per 1,000 births ($p=0.002$).

Table 6 shows univariate logistic regression models of the associations between maternal medical conditions diagnosed or treated during pregnancy and stillbirth, as well as a multivariable logistic regression model adjusting for maternal demographic and socioeconomic shown to predict stillbirth in Chapter II. In the univariate models, diagnosis or treatment of malaria (OR = 9.17, 95% CI: 3.69-22.78), mental illness (OR = 2.42, 95% CI: 1.07-5.46), lower urinary tract infection requiring antibiotics (OR = 1.50, 95% CI: 1.09-2.07), a positive syphilis test (OR = 7.11, 95% CI: 1.71-29.53), HIV or AIDS (OR = 5.84, 95% CI: 2.72-12.54), and other medical/surgical conditions requiring treatment or referral (OR = 1.49, 95% CI: 1.01-2.18) were all associated with increased risk of stillbirth. Maternal diagnosis or treatment for any infection (excluding respiratory and lower urinary tract infections) requiring antibiotic/antiviral treatment led to increased risk of stillbirth that approached significance (OR = 1.81, 95% CI: 0.93-3.53). There were no other significant associations between maternal medical conditions diagnosed or treated during pregnancy (data not shown). In the multivariable analysis including demographic and socioeconomic characteristics shown to be associated with stillbirth in

Chapter II, the excess risks of stillbirth among mothers diagnosed or treated for mental illness (OR = 1.44, 95% CI: 0.61-3.37), lower urinary tract infections requiring antibiotics (OR = 1.20, 95% CI: 0.85-1.70), HIV/AIDS (OR = 2.36, 95% CI: 0.85-6.56), any infection (excluding respiratory and lower urinary tract infections) requiring antibiotic/antiviral treatment (OR = 1.53, 95% CI: 0.78-3.02), and any other medical/surgical condition requiring treatment or referral (OR = 1.24, 95% CI: 0.83-1.84) were no longer statistically significant. The associations between diagnosis or treatment of malaria (OR = 8.98, 95% CI: 3.58-22.51), and a positive syphilis test (OR = 5.09, 95% CI: 1.16-22.80) and stillbirth were partially attenuated in the multivariable analysis.

Discussion

There were 43,742 births at the 6 collaborating sites between 2009-2012 included in this analysis. Among medical conditions existing prior to pregnancy, only hypertension/chronic hypertension and HIV/AIDS independently increased the risk for stillbirth (5 and 6 times, respectively) relative to mothers without these diseases. Malaria, mental illness, lower urinary tract infections requiring antibiotics, any other infection requiring antibiotic/antiviral treatment, positive syphilis tests, HIV or AIDS, and any other medical/surgical condition requiring treatment or referral were all independently associated with increased risk for stillbirth. Malaria, syphilis, and HIV/AIDS increased the risk for stillbirth by approximately 9, 7, and 6 times, respectively.

In this study population, 1.6% of all mothers suffered from hypertension/chronic hypertension. The stillbirth rate among hypertensive mothers was 31.6 per 1,000 births, consisting primarily of macerated stillbirths. Much of the excess stillbirth occurring because of hypertension/chronic hypertension has been shown to be largely preventable through improved disease management and prevention (9). The findings in this study support this hypothesis. The excess stillbirth due to hypertension/chronic decreased by

over 20% in the multivariable logistic regression model adjusting for demographic and socioeconomic characteristics, including use of alcohol, tobacco, and other substance abuse.

Although less prevalent amongst this cohort than hypertensive disorders, pre-existing HIV/AIDS increased stillbirth risk more than any other independent clinical history. Previous studies have shown that women with HIV/AIDS were significantly more likely to give birth to a stillborn infant than were seronegative mothers, with the effect greater in developing countries (10). In more current studies, there is evidence that the proper use of highly active antiretroviral therapy and modern HIV/AIDS treatment eliminates this excess risk (11). Today, those mothers with higher HIV plasma loads remain more likely to experience a stillbirth than seronegative mothers and mothers with relatively low plasma loads (12). Given that the women in this analysis did not receive treatment for HIV/AIDS during the index pregnancy, it is likely that their increased risk for stillbirth was due to a lack of antiretroviral therapy.

Other maternal illnesses existing prior to pregnancy such diabetes, proteinuria, kidney disease or chronic renal disease, and malaria, which have been previously shown to increase the risk for stillbirth when occurring during pregnancy, did not lead independently to significantly higher stillbirth rates here. This is likely a reflection of adequate management of these disorders, independently, and an absence of significant relapses during pregnancy. When diagnosed or treated during pregnancy, malaria, for example, becomes a major risk factor for stillbirth, leading to a stillbirth rate of 54.9 per 1,000 births.

Infections, when occurring during pregnancy, also posed significant threats to the foetuses in this analysis. Lower urinary tract infections requiring antibiotics, occurring in 11% of the pregnancies in this study, led to a 50% increase in stillbirth risk. Syphilis and HIV/AIDS, although far less common than urinary tract infections, drastically increased

the rates of stillbirth when a woman was diagnosed or treated during pregnancy to 43.5 and 36.5 per 1,000 births. Malaria, even less prevalent than syphilis and HIV/AIDS, led to a stillbirth rate of 54.9 per 1,000 births when diagnosed or treated during pregnancy. The effect of these infections on the global burden of stillbirth should be of concern. While lower urinary tract infections do not increase stillbirth rates to the levels of the aforementioned infections, its high prevalence makes lower urinary tract infections a serious risk to populations. As the relation between urinary tract infections and stillbirth was no longer significant in the multivariable model, it is likely that stillbirth due to these infections is over-represented amongst women of low socioeconomic status, and preventable. Although somewhat attenuated, the relation between Syphilis, HIV/AIDS, and malaria and stillbirth all remained statistically significant, independently. These infections were fortunately rare in this cohort, but in some communities, they are endemic. In such regions, these infections can have devastating effects on pregnancy outcomes, given the extreme stillbirth rates associated with these infections. Moreover, as antepartum stillbirth rates are mainly affected, prophylactic measures should be of high priorities in these regions given the paucity of treatments for the foetus once the death mechanism for these infections has begun.

Mental illness was the only individual non-communicable disease that increased the risk of stillbirth when occurring during pregnancy in this study. A previous national registry cohort study in Denmark from 1973-1998 found strong associations between mental illnesses and stillbirth risk as well, with the evidence suggesting that the increased risk for stillbirth was mediated through the inconsistent use of antenatal care and unhealthy lifestyles associated with these mental disorders, rather than occurring as a direct effect of the mental illnesses themselves (13). The findings in this study support this hypothesis, as the relation between mental illness and stillbirth was attenuated to

non-significance by adjusting for the demographic and socioeconomic characteristics, including substance abuse, shown to increase stillbirth risk in Chapter II.

There are several limitations that should be considered when interpreting the findings of this study. First, the primary aim of the INTERGROWTH-21st Project is not to investigate the effects of maternal illness on pregnancy outcomes. Thus, the populations in this study were selected because they are generally healthy. There is therefore lower statistical power to observe small increases in stillbirth risk, or excess stillbirth risk due to these low prevalence disorders. The study does, however, provide insight into the effect of clinically relevant episodes and pre-existing illness in general on stillbirth outcomes, as well as identifying strong stillbirth risk factors.

Second, the effects of these maternal medical conditions were not assessed by site. It is plausible that there are significant variations in the prevalence and quality of management/treatment of these medical conditions at the different collaborating institutions. However the hospitals included in the INTERGROWTH-21st Project have been selected for their standards of care, and the overall relative health of the populations they serve. Third, the severity of these medical conditions is not assessed. It is likely that more severe cases of these disorders could lead to increased stillbirth risk. This sort of analysis, given the already low cases of disorders and stillbirths, would require a significantly larger cohort, or, more appropriately, a case-control study design approach.

In the next chapter, I will attempt to explain the stillbirth risk associated with certain pregnancy, delivery, and birth characteristics, as well as certain pregnancy related medical complications. In this upcoming chapter, I will also explore how maternal demographic, socioeconomic, and nutritional characteristics relate to these pregnancy and delivery variables to further develop the stillbirth aetiological pathways.

Tables/ Figures

Table 1. Prior maternal medical illnesses and stillbirth, 2009-2012.

	All mothers % n=43,077	Mothers of stillborn infants % n=289
Diabetes		
No	99.3	99.0
Yes	0.7	1.0
Missing	0.0	0.0
Thyroid disease or other endocrinological condition		
No	97.9	98.3
Yes	2.1	1.7
Missing	0.0	0.0
Cardiac disease		
No	99.3	99.3
Yes	0.7	0.7
Missing	0.0	0.0
Hypertension/Chronic hypertension		
No	98.4	92.7
Yes	1.6	7.3
Missing	0.0	0.0
Proteinuria, kidney disease or chronic renal disease		
No	98.9	99.3
Yes	1.1	0.7
Missing	0.0	0.0
Lupus erythematosus		
No	99.9	100.0
Yes	0.1	0.0
Missing	0.0	0.0
Epilepsy		
No	99.6	99.7
Yes	0.4	0.4
Missing	0.0	0.0
Malaria		
No	99.4	99.3
Yes	0.6	0.7
Missing	0.0	0.0
Tuberculosis		
No	99.8	99.7
Yes	0.2	0.4
Missing	0.0	0.0
Crohn's disease, coeliac disease, ulcerative colitis or any severe malabsorption condition		
No	99.6	100.0
Yes	0.4	0.0
Missing	0.0	0.0
Any type of malignancy/cancer		
No	99.8	100.0
Yes	0.2	0.0
Missing	0.0	0.0
Any haematological condition		
No	98.7	98.6
Yes	1.3	1.4
Missing	0.0	0.0
HIV or AIDS		
No	99.6	97.9
Yes	0.4	2.1
Missing	0.0	0.0
Any congenital abnormality		
No	99.7	99.7
Yes	0.2	0.4
Missing	0.0	0.0
Other clinically relevant conditions		
No	91.0	92.4

Yes	9.0	7.6
Missing	0.0	0.0

Table 2. Maternal medical history and stillbirth rates per 1,000 total births by timing of death and chi-squared tests for heterogeneity, 2009-2012.

	Stillbirth rate per 1,000 births (95% CI)	p-values	Antepartum rate per 1,000 births	p-values	Intrapartum rate per 1,000 births	p-values
Overall	**6.7 (6.0 - 7.5)**		**5.1**		**1.6**	
Diabetes		0.742		0.906		0.079
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	10.3 (0.0 - 21.9)		3.4		6.8	
Thyroid disease or other endocrinological condition		0.873		0.972		0.470
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	5.5 (0.7 - 10.2)		5.5		--	
Missing	--		--		--	
Cardiac disease		0.970		0.895		0.785
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	6.9 (0.0 - 16.4)		6.9		--	
Missing	--		--		--	
Hypertension/Chronic hypertension		<0.001		<0.001		0.989
No	6.3 (5.6 - 7.1)		4.7		1.6	
Yes	31.6 (18.4 - 44.8)		30.2		1.4	
Missing	--		--		--	
Proteinuria, kidney disease or chronic renal disease		0.799		0.955		0.683
No	6.7 (6 - 7.5)		5.1		1.6	
Yes	4.3 (0.0 - 10.3)		4.3		--	
Missing	--		--		--	
Lupus erythematosus		0.856		0.888		0.964
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	--		--		--	
Missing	--		--		--	
Epilepsy		0.961		0.620		0.403
No	6.7 (6.0 - 7.5)		0.5		1.6	
Yes	5.6 (0.0 - 16.6)		--		5.6	
Missing	--		--		--	
Malaria		0.961		0.925		0.684
No	6.7 (5.9 - 7.5)		0.5		1.6	
Yes	7.4 (0.0 - 17.6)		0.4		3.7	
Missing	--		--		--	
Tuberculosis		0.776		0.613		0.934
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	13 (0.0 - 38.4)		13.0		--	
Missing	--		--		--	
Crohn's disease, coeliac disease, ulcerative colitis or any severe malabsorption condition		0.544		0.630		0.866
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	--		--		--	
Missing	--		--		--	
Any type of malignancy/cancer		0.732		0.789		0.929
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	--		--		--	
Missing	--		--		--	
Any haematological condition		0.957		0.767		0.632
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	7.2 (0.1 - 14.3)		7.2		--	
Missing	--		--		--	
HIV or AIDS		<0.001		<0.001		0.332
No	6.6 (5.8 - 7.4)		5.0		1.6	
Yes	37.7 (7.5 - 67.9)		31.4		6.3	
Missing	--		--		--	
Any congenital abnormality		0.924		0.814		0.912
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	9.3 (0.0 - 27.7)		9.3		--	
Missing	--		--		--	
Other clinically relevant conditions		0.626		0.732		0.851
No	6.8 (6.0 - 7.7)		5.2		1.6	
Yes	5.6 (3.2 - 7.9)		4.3		1.3	

Table 3. Crude and multivariable logistic regression models of the associations between maternal medical history and risk of a stillbirth occurring during this pregnancy, 2009-2012.

	Univariate		Multivariable		p-values
	OR	95% CI	OR	95% CI	
Hypertension/Chronic hypertension					
No	ref	ref	ref	ref	ref
Yes	4.98	3.17-7.81	3.87	2.40-6.24	<0.001
HIV or AIDS					
No	ref	ref	ref	ref	ref
Yes	6.03	2.64-13.74	4.52	1.93-10.56	0.012
Maternal age (years)					
< 15	4.42	0.60-32.38	3.23	0.42-24.71	0.255
15-19	1.04	0.56-1.90	0.79	0.41-1.51	0.513
20-34	ref	ref	ref	ref	ref
35-39	1.26	0.90-1.78	1.13	0.80-1.60	0.175
≥ 40	2.52	1.55-4.08	1.96	1.19-3.23	0.005
Maternal weight (kg)					
< 50	0.57	0.36-0.88	0.61	0.39-0.94	0.025
50-79.9	ref	ref	ref	ref	ref
80-99.9	1.42	1.01-1.99	1.24	0.88-1.76	0.162
≥ 100	0.90	0.37-2.20	0.69	0.28-1.71	0.461
Marital Status					
Single	1.70	1.06-2.71	1.33	0.79-2.22	0.257
Married/Cohabiting	ref	ref	ref	ref	ref
Separated/Divorced	5.13	2.09-12.61	2.71	0.83-8.87	0.100
Widowed	--	--	--	--	
Highest level of education					
Primary	2.10	1.45-3.04	1.67	1.11-2.51	0.012
Secondary	1.32	0.97-1.80	1.33	0.98-1.82	0.098
Professional/Technical training	1.54	1.09-2.18	1.55	1.09-2.18	0.013
University	ref	ref	ref	ref	ref
Maternal use of tobacco during pregnancy					
None	ref	ref	ref	ref	ref
1-5 cigarettes per day	1.83	1.18-2.83	1.20	0.72-1.98	0.755
> 5 cigarettes per day	--	--	--	--	
5 or more units of alcohol per week during pregnancy?					
No	ref	ref	ref	ref	ref
Yes	4.60	1.88-11.29	2.91	0.98-8.61	0.054
Maternal use of recreational drugs during pregnancy					
No	ref	ref	ref	ref	ref
Yes	4.27	1.57-11.63	2.30	0.75-7.04	0.309

Table 4. Maternal medical conditions diagnosed or treated during this pregnancy and stillbirth, 2009-2012.

	All mothers % n=43,077	Mothers of stillborn infants % n=289
Cardiac disease		
No	99.6	99.7
Yes	0.4	0.4
Missing	0.0	0.0
Chronic respiratory disease		
No	99.1	99.3
Yes	0.9	0.7
Missing	0.0	0.0
Malaria		
No	99.8	98.3
Yes	0.2	1.7
Missing	0.0	0.0
Mental illness		
No	99.1	97.9
Yes	0.9	2.1
Missing	0.0	0.0
Epilepsy		
No	99.8	100.0
Yes	0.2	0.0
Missing	0.0	0.0
Thyroid disease or any other endocrinological condition		
No	98.6	97.9
Yes	1.4	2.1
Missing	0.0	0.0
Lower urinary tract infection requiring antibiotics		
No	89.0	84.1
Yes	11.0	15.6
Missing	0.0	0.4
Pyelonephpritis		
No	99.5	99.3
Yes	0.4	0.7
Missing	0.0	0.0
Respiratory tract infection requiring antibiotic/antiviral treatment		
No	98.2	99.7
Yes	1.8	0.4
Missing	0.0	0.0
Any other infection requiring antibiotic/antiviral treatment		
No	98.2	96.9
Yes	1.8	3.1
Missing	0.0	0.0
Positive syphilis test		
No	99.9	99.0
Yes	0.1	0.7
Missing	0.0	0.4
HIV or AIDS		
No	99.5	97.6
Yes	0.4	2.4
Missing	0.0	0.0
Any sexually transmitted infection		
No	99.5	100.0
Yes	0.5	0.0
Missing	0.0	0.0
Any type of malignancy or cancer		
No	100.0	100.0
Yes	0.0	0.0
Missing	0.0	0.0
Any other medical/surgical condition requiring treatment or referral		
No	93.0	90.0
Yes	7.0	10.0
Missing	0.0	0.0

Table 5. Maternal medical conditions diagnosed or treated during this pregnancy and stillbirth rates per 1,000 total births by timing of death and chi-squared tests for heterogeneity, 2009-2012.

	Stillbirth rate per 1,000 births (95% CI)	p-values	Antepartum rate per 1,000 births	p-values	Intrapartum rate per 1,000 births	p-values
Overall	**6.7 (6.0 - 7.5)**		**5.1**		**1.6**	
Cardiac disease		0.964		0.956		0.871
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	6.2 (0.0 - 18.4)		6.2		--	
Missing	--		--		--	
Chronic respiratory disease		0.863		0.720		0.910
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	4.8 (0.0 - 11.5)		2.4		2.4	
Missing	--		--		--	
Malaria		<0.001		<0.001		0.080
No	6.6 (5.9 - 7.4)		5.0		1.6	
Yes	54.9 (6.8 - 103.1)		44.0		11.0	
Missing	--		--		--	
Mental illness		0.095		0.014		0.727
No	6.6 (5.9 - 7.4)		5.0		1.6	
Yes	15.7 (3.1 - 28.2)		15.7		--	
Missing	--		--		--	
Epilepsy		0.776		0.824		0.942
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	--		--		--	
Missing	--		--		--	
Thyroid disease or any other endocrinological condition		0.648		0.579		0.990
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	9.6 (1.9 - 17.3)		8.0		1.6	
Missing	--		--		--	
Lower urinary tract infection requiring antibiotics		<0.001		<0.001		0.951
No	6.3 (5.5 - 7.1)		4.7		1.6	
Yes	9.9 (7.1 - 12.8)		8.5		1.5	
Missing	66.7 (0.0 - 197.3)		66.7		--	
Pyelonephpritis		0.779		0.563		0.848
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	10.5 (0.0 - 25)		10.5		--	
Missing	--		--		--	
Respiratory tract infection requiring antibiotic/antiviral treatment		0.169		0.313		0.527
No	6.8 (6.0 - 7.6)		5.2		1.6	
Yes	1.3 (0.0 - 3.8)		1.3		--	
Missing	--		--		--	
Any other infection requiring antibiotic/antiviral treatment		0.214		0.827		0.039
No	6.6 (5.9 - 7.4)		5.1		1.5	
Yes	11.8 (4.1 - 19.5)		6.6		5.2	
Missing	--		--		--	
Positive syphilis test		<0.001		0.001		<0.001
No	6.7 (5.9 - 7.4)		5.1		1.6	
Yes	43.5 (0.0 - 103.7)		43.5		--	
Missing	62.5 (0.0 - 185)		--		62.5	
HIV or AIDS		<0.001		<0.001		0.009
No	6.6 (5.8 - 7.4)		5.0		1.6	
Yes	36.5 (9.4 - 63.5)		26.0		10.4	
Missing	--		--		--	
Any sexually transmitted infection		0.493		0.584		0.846
No	6.8 (6.0 - 7.5)		5.1		1.6	
Yes	--		--		--	
Missing	--		--		--	
Any type of malignancy or cancer		0.925		0.942		0.982
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	--		--		--	
Any other medical/surgical condition requiring treatment or referral		0.059		0.002		0.388
No	6.5 (5.7 - 7.3)		4.8		1.7	
Yes	10.1 (6.5 - 13.6)		9.4		0.6	

Table 6. Crude and multivariable logistic regression models of the associations between maternal medical conditions diagnosed or treated during pregnancy and risk of a stillbirth occurring during this pregnancy, 2009-2012.

	Univariate		Multivariable		p-values
	OR	95% CI	OR	95% CI	
Malaria					
No	ref	ref	ref	ref	ref
Yes	9.17	3.69-22.78	8.98	3.58-22.51	<0.001
Mental illness					
No	ref	ref	ref	ref	ref
Yes	2.42	1.07-5.46	1.44	0.61-3.37	0.737
Lower urinary tract infection requiring antibiotics					
No	ref	ref	ref	ref	ref
Yes	1.50	1.09-2.07	1.20	0.85-1.70	0.366
Any other infection requiring antibiotic/antiviral treatment					
No	ref	ref	ref	ref	ref
Yes	1.81	0.93-3.53	1.53	0.78-3.02	0.154
Positive syphilis test					
No	ref	ref	ref	ref	ref
Yes	7.11	1.71-29.53	5.09	1.16-22.28	0.016
HIV or AIDS					
No	ref	ref	ref	ref	ref
Yes	5.84	2.72-12.54	2.36	0.85-6.56	0.098
Any other medical/surgical condition requiring treatment or referral					
No	ref	ref	ref	ref	ref
Yes	1.49	1.01-2.18	1.24	0.83-1.84	0.199
Maternal age (years)					
< 15	4.42	0.60-32.38	2.41	0.31-18.79	0.37
15-19	1.04	0.56-1.90	0.75	0.39-1.44	0.451
20-34	ref	ref	ref	ref	ref
35-39	1.26	0.90-1.78	1.18	0.83-1.66	0.096
≥ 40	2.52	1.55-4.08	2.17	1.32-3.55	0.002
Maternal weight (kg)					
< 50	0.57	0.36-0.88	0.60	0.38-0.93	0.022
50-79.9	ref	ref	ref	ref	ref
80-99.9	1.42	1.01-1.99	1.45	1.01-2.07	0.043
≥ 100	0.90	0.37-2.20	0.86	0.35-2.11	0.849
Marital Status					
Single	1.70	1.06-2.71	1.33	0.80-2.22	0.271
Married/Cohabiting	ref	ref	ref	ref	ref
Separated/Divorced	5.13	2.09-12.61	3.83	1.52-9.63	0.045
Widowed	--	--	--	--	
Highest level of education					
Primary	2.10	1.45-3.04	1.66	1.09-2.52	0.022
Secondary	1.32	0.97-1.80	1.34	0.98-1.83	0.121
Professional/Technical training	1.54	1.09-2.18	1.53	1.08-2.17	0.016
University	ref	ref	ref	ref	ref
Maternal use of tobacco during pregnancy					
None	ref	ref	ref	ref	ref
1-5 cigarettes per day	1.83	1.18-2.83	1.14	0.68-1.90	0.739
> 5 cigarettes per day	--	--	--	--	
5 or more units of alcohol per week during pregnancy?					
No	ref	ref	ref	ref	ref
Yes	4.60	1.88-11.29	2.83	1.06-7.54	0.044
Maternal use of recreational drugs during pregnancy					
No	ref	ref	ref	ref	ref
Yes	4.27	1.57-11.63	1.97	0.63-6.14	0.475

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Chapter IV – Pregnancy, delivery, and birth characteristics and stillbirth risk

Introduction

While better management of maternal medical illness may prevent some stillbirth, seemingly healthy mothers often deliver stillborn infants. The cause of death in many of these cases is unknown, but the mothers are at increased risk of having a stillborn infant in subsequent pregnancies. Frias et al. (2004) reported that of 232 women with prior foetal deaths, of their subsequent 721 pregnancies, only 24% resulted in live births (1). Other poor pregnancy outcomes predict risk of stillbirth as well. In a population-based cohort study in New South Wales, Australia, Gordon et al. (2012) found that among mothers previously delivering an SGA infant, stillbirth hazard ratio in the subsequent pregnancy was nearly double that of healthy controls, and stillbirth hazard ratio increased almost 6-fold in mothers delivering a preterm infant in the previous pregnancy (2). More research is needed to understand the relation between prior pregnancy history and stillbirth to better identify and care for these at risk mothers.

Known pregnancy complications such as HELLP, pre-labour rupture of membranes, and pre-eclampsia/eclampsia contribute to some of the aforementioned recurrent foetal deaths (3). There have been improvements in recent decades in the management of preeclampsia and eclampsia throughout pregnancy, mainly by carefully monitoring the progression of the disorder during antenatal care visits, in order to appropriately time induction of labour or Caesarean delivery. However, in low-income and/or low-resource settings, sub-optimal care and the failure to use low-cost treatments such as aspirin and magnesium sulphate have led to elevated stillbirth risk in some populations (4, 5). A better understanding of the risks associated with these pregnancy

complications and the effectiveness of their respective treatments could have significant positive influences on stillbirth prevention efforts.

Once the foetus of a complicated or high-risk pregnancy reaches the point of viability, subsequent management of the pregnancy and decisions about labour induction will become key predictors of the ultimate pregnancy outcome. Caesarean sections have been used to prevent countless perinatal deaths over the past century, but excess use of the surgical procedure has also led to increased risk of stillbirth and maternal/infant mortality/morbidity (6, 7). Labour induction agents such as misoprostol have also had profound impacts on reducing intrapartum stillbirth rates, but come with additional risks such as rupture of the unscarred uterus (8).

Given the limited resources available in settings with high stillbirth rates, both in absolute and relative terms, there is a need to understand which pregnancy complications bear the most risk for stillbirth, and which procedures could best lower overall rates.

In this Chapter, using data collected from *Section 3: Gynaecological history*, *Section 4: Obstetric history*, *Section 6: Pregnancy specific conditions*, *Section 7: Nutritional supplements/ medications*, *Section 8: Delivery*, *Section 9: Newborn outcomes and care*, and *Section 10: Newborn anthropometry* of the INTERGROWTH-21st NCSS Pregnancy and Delivery Form, I will assess the relation between pregnancy characteristics, complications, and outcomes and stillbirth risk.

Methods

Data:

The data on 43,781 births was obtained from the 6 INTERGROWTH-21st sites that have enrolled at least 5,000 participants into the NCSS between 2009-2012. Data from the Torino, Italy and Seattle, USA sites were not available at the time of this analysis.

The primary outcome was stillbirth, defined as foetal death at a gestational age of 18 weeks or more. Gestational age was calculated using crown to rump length from early ultrasound examinations whenever possible. In cases without early ultrasound pregnancy dating, maternal reported last menstrual periods were used to estimate gestational age.

The following pregnancy, delivery, and birth characteristics were included as exposures of interest: parity (0, 1, 2-3, 4-5, >5); previous preterm birth (yes, no); previous birth weight below 2.5 kg or above 4.5 kg (yes, no); any previous miscarriage (yes, no); previous miscarriage in both of last 2 consecutive pregnancies (yes, no); previous stillbirth, defined as foetal death at 24 weeks gestation or more, or neonatal death, defined as infant death within 28 days of life to a live born infant of at least 24 weeks gestational age (yes, no); plurality (singleton, twins, triplets, four or more); pregnancy conceived with fertility treatment (yes, no); regular menstrual cycle in 3 months prior to pregnancy (yes, no); use of hormonal contraceptives or breastfeeding in the 2 months prior to this pregnancy (yes, no); premature rupture of membranes (yes, no); mode of delivery (vaginal spontaneous, vaginal assisted (e.g. forceps, vacuum), assisted breech or breech extraction); foetal presentation (cephalic, breech, other); gestational age (extremely preterm – less than 28 weeks gestation, very preterm – 28 to 31 6/7 weeks gestation, preterm – 32 to 36 6/7 weeks gestation, term – 37 to 41 6/7

weeks gestation, postterm – 42 weeks gestation or more); birth weight (extremely low birth weight – less than 1000 grams, very low birth weight – 1000 to 1499 grams, low birth weight – 1500 to 2499 grams, normal birth weight 2500 to 3999 grams, high birth weight 4000 grams or more); foetal distress in the antepartum period (yes, no); suspected impaired foetal growth or SGA (yes, no).

In addition, the following pregnancy specific medical conditions were included as exposures of interest: severe vomiting requiring hospitalization (yes, no); gestational diabetes (yes, no); vaginal bleeding before 15 weeks gestation (yes, no); vaginal bleeding at 15-27 weeks gestation (yes, no); vaginal bleeding after 27 weeks gestation (yes, no); pregnancy induced hypertension, defined as high blood pressure of 140/90 or greater developing after 20 weeks gestation in a previously normotensive pregnancy (yes, no); preeclampsia, defined as high blood pressure of 140/90 or greater or an increase of 30 mmHg systolic or 15 mmHg diastolic over baseline values on at least two occasions six or more hours apart developing after 20 weeks gestation in a previously normotensive pregnancy, with proteinuria (yes, no); severe preeclampsia/eclampsia /HELLP syndrome, with severe preeclampsia occurring when blood pressures are ≥160 mmHg systolic and/or ≥110 mmHg diastolic on two occasions, at least 4 hours but not more than 168 hours apart, or if the first measurement was immediately followed by treatment with an antihypertensive, with proteinuria, eclampsia defined as the occurrence of convulsions and/or coma unrelated to maternal cerebral conditions in women with signs and symptoms of preeclampsia, and HELLP syndrome defined as a group of symptoms that occur in pregnant women who have preeclampsia or eclampsia and who also show signs of liver damage and abnormalities in blood clotting (yes, no); rhesus disease, or RH- isoimmunisation (yes, no); any other pregnancy related condition requiring treatment or referral (yes, no). Exposures for maternal use of the following medications during the pregnancy of interest were also included: routine aspirin (yes,

no); any antibiotics or antivirals not used for PROM (yes, no); antibiotics used for PROM (yes, no); non-steroidal anti-inflammatories (yes, no); insulin (yes, no); prophylactic steroids for preterm labour (yes, no); any other treatment (yes, no). All exposures were derived from maternal medical records and maternal self-reporting.

The study complies with the International Ethical Guidelines for Biomedical Research Involving Human Subjects at the appropriate international, national, local, and individual levels.

Analysis:

First, I calculated univariate statistics, including prevalence of the pregnancy, delivery, and birth characteristics of interest, in order to describe the population sample. I calculated 95% confidence intervals for all rates.

Second, I calculated crude odds ratios and fit an adjusted multivariable logistic regression model of pregnancy outcome (stillbirth vs. live birth) to assess the contribution of all pregnancy, delivery, and birth characteristics found to be associated with stillbirth in bivariate analyses, adjusting for the demographic and socioeconomic risk factors shown to predict stillbirth in Chapter II. In the multivariable logistic regression model, I only included exposures that were independently associated with stillbirth risk in chi-squared tests for heterogeneity ($p < 0.050$, data not shown).

Third, I repeated the above analyses using the covariate sets pregnancy specific medical conditions of interest, and medications used during this pregnancy or interest.

It should be noted the initial analysis refers to infants while the pregnancy specific medical conditions analysis refers to pregnancies. Infants are referred to in the initial analysis because it is possible for pregnancy characteristics to differ amongst infants in a multiple pregnancy (e.g., different foetal presentation).

STATA 11 was used to carry out all statistical analyses (9).

Results

There were 43,781 births occurring between 2009-2012 at the 6 sites included in this analysis, with 295 resulting in stillbirths. Of the 43,781 births, 39 births were excluded because the mother was lost to follow up during pregnancy, and the infant was not delivered at one of the 6 sites. Therefore, 43,742 births are included in this analysis, with a total of 43,078 pregnancies. One additional birth was excluded, as the mother, grieving from the stillbirth of her infant, was too distraught to provide any information about her pregnancy and refused to consent to any further investigations. This pregnancy will be included in all prevalence analyses but excluded from those analyses relying upon data gathered from interviews and maternal medical records. Thus, there are 294 stillbirths to 289 mothers included in the pregnancy characteristics and complications analyses.

Table 1 shows the prevalence of pregnancy, delivery, and birth characteristics among all stillborn and live born infants. Parity ($p=0.039$), previous preterm births ($p=0.013$), previous birth weight below 2.5 kg or above 4.5 kg ($p<0.001$), previous stillbirth or neonatal death ($p=0.006$), plurality ($p<0.001$), mode of delivery ($p<0.001$), foetal presentation ($p<0.001$), gestational age ($p<0.001$), and birth weight ($p<0.001$) all predicted stillbirth risk. No other significant associations were found ($p>0.050$).

Table 2 shows the stillbirth rates per 1,000 births for given pregnancy, delivery, and birth characteristics (as well as antepartum stillbirth and intrapartum stillbirth rates) and chi-squared tests for heterogeneity. The stillbirth rate for infants born to mothers with parity of 2-3 was 9.4 per 1,000 stillbirths (95% CI: 7.0-11.7), and 12.3 per 1,000 births (95% CI: 3.3-21.8) among infants born to mothers with greater than 5 previous births, while the stillbirth rate for infants born to mothers with parity of 4-5 was only 5.5

per 1,000 births (95% CI: 1.4-9.7). Among infants born to mothers with a previous preterm birth, the stillbirth rate was 12.1 per 1,000 births (95% CI: 6.8-17.8), mediated mainly through an elevated antepartum stillbirth rate of 9.5 per 1,000 births (p=0.027). The stillbirth rate among infants born to mothers with a previous birth below 2.5 kg or above 4.5 kg was 13.7 per 1,000 births (95% CI: 8.3-18.4). Among infants born to mothers with a previous stillbirth or neonatal death, the stillbirth rate was 14.2 per 1,000 births (95% CI: 6.9-22.0). The antepartum stillbirth rate for this group was 10.1 (p=0.047) and the intrapartum stillbirth rate was 4.0 per 1,000 births (p=0.053). The stillbirth rate among twins was 16.9 per 1,000 births (95% CI: 13.1-38.4) and 14.2 per 1,000 births among triplets (95% CI: 0.0-251.2). Multiple pregnancies resulted in significantly higher intrapartum stillbirth rates (p<0.001) and elevated antepartum rates that approached significance (p=0.073). The stillbirth rate among breech infants delivered vaginally with the assistance of forceps or vacuums was 75.5 (95% CI: 1.5-149.4), with elevated antepartum (56.6, p<0.001) and intrapartum (18.9, p<0.001) stillbirth rates. Breech birth generally led to a stillbirth rate of 24.9 per 1,000 births (95% CI: 17.4-32.5). The stillbirth rates per 1,000 births among infants delivered vaginally with assistance (1.3, 95% CI: 0.0-2.7) and among infants delivered via Caesarean section (3.4, 95% CI: 2.6-4.3) were lower than the rate among infants delivered vaginally and spontaneously (9.6, 95% CI: 8.4-10.9). Stillbirth rates varied significantly by gestational age (p<0.001), with a rate of 402.5 per 1,000 births (95% CI: 321.6-483.5) among extremely preterm infants, 130.9 per 1,000 births (95% CI: 93.5-168.3) among very preterm infants, 19.2 per 1,000 births (95% CI: 14.6-23.8) among preterm infants, 6.0 per 1,000 births (95% CI: 1.2-10.7) among postterm infants, and only 2.0 per 1,000 births (95% CI: 1.6-2.5) among term infants.

Stillbirth rates also varied significantly among infants of different birth weights (p<0.001). The stillbirth rates per 1,000 births were elevated among extremely low birth

weight (388.6), very low birth weight (124.6), and low birth weight (13.1) infants. Stillbirth rates per 1,000 births were lower for high birth weight infants (0.9) than for normal birth weight infants (1.9). While the higher stillbirth rate of 12.1 per 1,000 births among infants with foetal distress relative to the rate of 6.6 per 1,000 births among those infants without foetal distress was not statistically significant (p=0.190), the higher antepartum stillbirth rate among infants with foetal distress reached statistical significance (p=0.027). There were no other significant associations (p>0.050).

Table 3 shows univariate logistic regression models of the associations between pregnancy, delivery, and birth characteristics and stillbirth, as well as a multivariable logistic regression model adjusting for maternal demographic and socioeconomic characteristics shown to predict stillbirth in Chapter II. In the univariate models, there were significant associations between parity of 2-3 (OR = 1.60, 95% CI: 1.13-2.25), previous preterm births (OR = 1.83, 95% CI: 1.13-2.98), previous birth weight below 2.5 kg or above 4.5 kg (OR = 2.08, 95% CI: 1.36-3.16), previous stillbirth or neonatal death (OR = 2.14, 95% CI: 1.23-3.72), twin pregnancy (OR = 4.11, 95% CI: 2.47-6.86), triplet pregnancy (OR = 18.31, 95% CI: 4.21-79.61), assisted breech or breech extraction delivery (OR = 8.65, 95% CI: 3.09-24.19), breech presentation (OR = 5.00, 95% CI: 3.59-6.98), extremely preterm gestational age (OR = 380.08, 95% CI: 267.53-539.99), very preterm gestational age (OR = 74.75, 95% CI: 50.92-109.72), preterm gestational age (OR = 10.22, 95% CI: 7.36-14.18), post-term gestational age (OR = 2.90, 95% CI: 1.26-6.67), extremely low birth weight (OR = 364.49, 95% CI: 253.56-523.94), very low birth weight (OR = 83.97, 95% CI: 55.67-126.65), and low birth weight (OR = 7.55, 95% CI: 5.32-10.72) and stillbirth. The association between parity of 6 or more and stillbirth approached significance (OR = 2.14, 95% CI: 0.98-4.68). There was a protective association between vaginal assisted delivery (OR = 0.14, 95% CI: 0.04-0.42) and

Caesarean section delivery (OR = 0.35, 95% CI: 0.27-0.47), and stillbirth. No other significant associations were found in the univariate analyses (data not shown).

In the multivariable regression model, the relations between parity of 2-3 (OR = 1.22, 95% CI: 0.81-1.83), previous stillbirth or neonatal death (OR = 1.16, 95% CI: 0.56-2.41), twin pregnancy (OR = 1.11, 95% CI: 0.49-2.49), triplet pregnancy (OR = 9.81, 95% CI: 0.93-103.33), assisted breech delivery (OR = 0.28, 95% CI: 0.03-2.91), breech presentation (OR = 1.48, 95% CI: 0.74-2.96), and postterm gestational age (OR = 2.68, 95% CI: 0.81-8.85), and stillbirth were no longer statistically significant. The relation between parity of 6 or more and stillbirth was attenuated as well (OR = 0.78, 95% CI: 0.28-2.14). The relation between previous preterm births and stillbirth was reversed (OR = 0.42, 95% CI: 0.19-0.89) in the multivariable model. Vaginal assisted delivery no longer reduced the risk for stillbirth in the multivariable model (OR = 0.44, 95% CI: 0.06-3.34), Among the demographic and socioeconomic risk factors shown to increase the risk of stillbirth in Chapter II, only maternal age ≥40 years (OR = 2.45, 95% CI: 1.24-4.85), and professional/technical training level of highest education (OR = 1.85, 95% CI: 1.03-3.31) remained significant predictors of stillbirth.

Table 4 shows the prevalence of pregnancy specific medical conditions and treatments among all mothers and mothers of stillborn infants. There were statistically significant differences between the prevalence of vaginal bleeding at 15-27 weeks gestation ($p<0.001$), vaginal bleeding after 27 weeks gestation ($p=0.002$), preeclampsia, severe preeclampsia/eclampsia/HELLP syndrome ($p<0.001$), premature rupture of membranes ($p<0.001$), any other pregnancy related condition requiring treatment or referral ($p<0.001$), routine use of aspirin ($p<0.001$), prophylactic steroids for preterm labour ($p=0.006$), and any other treatment ($p<0.001$) among mothers of stillborn infants relative to mothers of live born infants. The difference in the prevalence of using antibiotics for PROM among mothers of stillborn infants relative to mothers of live born

infants approached significance (p=0.058). Stillborn mothers were less likely to have PROM than all mothers, however this association was not significant when missing cases were excluded (p=0.110).

Table 5 shows the stillbirth rates per 1,000 births for given pregnancy specific medical conditions and treatments (as well as antepartum stillbirth and intrapartum stillbirth rates) and chi-squared tests for heterogeneity. Among infants born to mothers with vaginal bleeding at 15-27 weeks, the stillbirth rate was 27.3 per 1,000 births (95% CI: 16.7-39.8), due to higher antepartum (17.8) and intrapartum (9.5) rates. Vaginal bleeding after 27 weeks also led to higher antepartum stillbirth rates relative to that among mothers without bleeding (p=0.011), although there was no significant difference in intrapartum stillbirth rates (p=0.267). The stillbirth rate among infants born to mothers with preeclampsia was 21.7 per 1,000 births (95% CI: 13.2-32.1) and 33.2 per 1,000 births (95% CI: 10.6-58.6) among mothers with severe preeclampsia/eclampsia/HELLP syndrome. Among mothers with other pregnancy related conditions requiring treatment or referral, the stillbirth rate was 21.9 per 1,000 births (95% CI: 15.0-29.9). The stillbirth rate among mothers routinely using aspirin was 21.4. Among mothers using any antibiotics or antivirals not used for PROM, the stillbirth rate was 9.7 per 1,000 births (95% CI: 6.6-11.9). The stillbirth rate among mothers requiring prophylactic steroids for preterm labour was 11.8 per 1,000 births (95% CI: 7.5-17.9). The stillbirth rate among mothers receiving any other treatment was 10.4 per 1,000 births (95% CI: 8.3-12.7). Pregnancy-induced hypertension did not significantly affect stillbirth rates (p=0.067), although the antepartum stillbirth rate among infants born to mothers with pregnancy-induced hypertension was 8.7 per 1,000 births (p=0.013). There were no other significant associations (p<0.050).

Table 6 shows univariate logistic regression models of the associations between pregnancy specific medical conditions and treatments, and stillbirth, as well as a

multivariable logistic regression model adjusting for maternal demographic and socioeconomic characteristics shown to predict stillbirth in Chapter II, including calcium supplementation (a common treatment and prophylaxis for pregnancy induced hypertensive disorders). There were significant associations between vaginal bleeding at 15-27 weeks (OR = 4.59, 95% CI: 2.98-7.07), vaginal bleeding after 27 weeks (OR = 2.35, 95% CI: 1.44-3.86), pregnancy-induced hypertension (OR = 1.54, 95% CI: 1.06-2.23), preeclampsia (OR = 3.63, 95% CI: 2.34-5.63), severe preeclampsia/eclampsia/HELLP syndrome (OR = 5.43, 95% CI: 2.66-11.10), any other pregnancy related condition requiring treatment or referral (OR = 3.73, 95% CI: 2.61-5.33), routine use of aspirin (OR = 3.49, 95% CI: 2.03-6.01), any antibiotics or antivirals not used for PROM (OR = 1.46, 95% CI: 1.06-1.99), prophylactic steroids for preterm labour (OR = 1.98, 95% CI: 1.29-3.04), and any other treatment (OR = 1.82, 95% CI: 1.42-2.34), and stillbirth. There were no other significant associations in the univariate analyses (data not shown). In the multivariable regression model, vaginal bleeding at 15-27 weeks (OR = 3.34, 95% CI: 2.11-5.30), preeclampsia (OR = 2.45, 95% CI: 1.48-4.06), severe preeclampsia/eclampsia/HELLP syndrome (OR = 3.23, 95% CI: 1.49-7.03), any other pregnancy related condition requiring treatment or referral (OR = 2.87, 95% CI: 1.96-4.19), and routine aspirin use (OR = 2.36, 95% CI: 1.34-4.16) remained associated with significantly greater risk of stillbirth relative to healthy mothers, while all other associations were attenuated to statistical insignificance. Among the socioeconomic and demographic risk factors included in the multivariable model, only maternal age of ≥ 40 years (OR = 1.91, 95% CI: 1.16-3.14), primary level of highest education (OR = 1.61, 95% CI: 1.06-2.45), professional/technical training level of highest education (OR = 1.52, 95% CI: 1.08-2.15), and maternal use of 5 or more units of alcohol per week during pregnancy (OR = 2.72, 95% CI: 1.01-7.31) remained significantly associated with stillbirth. Routine maternal use of calcium supplements during pregnancy remained

protective against stillbirth risk (OR = 0.63, 95% CI: 0.48-0.82).

Discussion

There were 43,742 births at the 6 collaborating sites between 2009-2012 included in this study of the relation between pregnancy, delivery, and birth characteristics and stillbirth. Parity, previous preterm births, previous births with weight below 2.5 kg or above 4.5 kg, previous stillbirth or neonatal death, multiple pregnancies, mode of delivery, foetal presentation, gestational age, and birth weight all were associated with stillbirth. There was no relation between suspected growth restricted and stillbirth. Several pregnancy complications were associated with increased risk for stillbirth, including vaginal bleeding after 15 weeks gestation, pregnancy-induced hypertension, preeclampsia, severe preeclampsia/eclampsia/HELLP syndrome, and routine use of aspirin, antibiotics or antivirals not for PROM, prophylactics for preterm labour, and any other medical treatment during pregnancy. There was no significant relation between either gestational diabetes or insulin use and stillbirth.

The findings in this study are similar to those of previous analyses of the relation between pregnancy, delivery, and birth characteristics and stillbirth. Mothers with previous poor pregnancy outcomes have been shown to be more likely to have subsequent poor birth outcomes, including stillbirth (10). The same is found here, as the stillbirth rate among infants born to mothers with a prior stillbirth or neonatal death was 14.2 per 1,000 births.

Infant characteristics were the strongest predictors of stillbirth. The stillbirth rates among very preterm and extremely preterm infants were 130.9 and 402.5 per 1,000 births, respectively. Among very low birth weight and extremely low birth weight infants, the respective stillbirth rates were 124.6 and 388.6 per 1,000 births, respectively. These

characteristics were by far the greatest stillbirth risk factors included in the NCSS Pregnancy and Delivery Form. This could be interpreted as a reflection of the fact that, due to the high percentage of antepartum stillbirths in this cohort, these infants are by definition of a low gestational age, and, subsequently, low birth weights. In the multivariable analysis, greater residual stillbirth is due to birth weight than to gestational age. This suggests that birth weight may be the upstream cause of death, and carefully monitoring intrauterine growth during high-risk pregnancies could improve our understanding of the causes of stillbirth, and possibly improve outcomes. Still, more information is needed to know whether the causes of the low birth weight seen here are preventable, and how birth weight and gestational age are associated.

Surprisingly, there was no significant increase in stillbirth risk among infants with suspected intrauterine growth restriction. In a 2012 analysis based upon birth data in New South Wales, Australia between 2002-2006, Gordon et al. found that infants born to mothers previously giving birth to growth restricted infants were indeed at increased risk for stillbirth risk (2). Also in 2012, Stacey et al. found that infants identified to be small for gestational age at birth were more than 9 times more likely to be stillborn than infants identified to be small for gestational age during an antenatal care visit (excluding infants with congenital anomalies) after adjusting for a range of exposures (11). These findings, along with the aforementioned findings in this study about the impact of birth weight on stillbirth, do not support the lack of association between suspected intrauterine growth restriction and stillbirth in this analysis, and suggest that much of the foetal death due to growth restriction is preventable. Still, identification of intrauterine growth restriction remains difficult and is often misinterpreted as low birth weight. The INTERGROWTH-21st Project aims to identify intrauterine growth restriction by determining ideal growth curves. Therefore, there is emphasis placed on distinguishing between low birth weight and intrauterine growth restriction. Population height curve derived identification of

growth restriction is not promoted and may have been the reason for the low levels of reported growth restriction. More evidence is required to confirm if this more stringent definition of growth restriction leads to results differing from those studies where growth restriction is based primarily upon birth weight. The universal growth standard to be created by the INTERGROWTH-21st Project could be useful in differentiating between non-clinically low birth weight and intrauterine growth restriction.

Infants with breech presentation were 5 times more likely to be stillborn than infants with cephalic presentation. Assisted breech or breech extraction delivery led to a stillbirth rate of 75.5 per 1,000 births. This is compared to an overall stillbirth rate of 3.4 per 1,000 births for Caesarean deliveries, and a stillbirth rate of 2.6 per 1,000 births for Caesarean deliveries of infants with breech presentation ($p<0.001$, data not shown). Breech birth has been previously shown to be a perinatal mortality risk, with significantly greater deaths when vaginal delivery is attempted rather than Caesarean delivery (12). This could, however, be due to the complexity of vaginal delivery of breech infants, as there was no significant difference in stillbirth risk between vaginal and Caesarean delivery of breech infants when breech delivery best practices are properly adhered to in other studies (13). Future research is needed to determine whether efforts to improve the quality of vaginal breech deliveries, or a shift to delivering singleton, breech infants through Caesarean section would lead to greater reduction in stillbirth and overall perinatal mortality rates.

The findings in this study about the relation between pregnancy complications and stillbirth are similar to previous findings. Preeclampsia, eclampsia, HELLP syndrome, and pregnancy-induced hypertension all led to significant increases in stillbirth risk in this study. Despite the well-documented evidence that adequate management of these hypertensive disorders can significantly decrease stillbirth and perinatal mortality risk, these disorders continue to be major contributors to the excess stillbirth seen in clinical

settings (14).

While vaginal bleeding occurring before 15 weeks gestation was not associated with stillbirth risk, vaginal bleeding between weeks 15-27 and after 27 weeks gestation were associated with increased risk for stillbirth. Vaginal bleeding can be associated with placental praevia or placentae abruptio, but this bleeding is often of unknown origins (15). In the multivariable logistic regression model, vaginal bleeding at 15-27 weeks gestation remained significantly associated with excess risk of stillbirth. Not enough is known about this stillbirth risk and the potential management of pregnancies with vaginal bleeding to make causal conclusions, but it is likely plausible that haemorrhage leads to foetal death at all stages of pregnancy, with bleeding in the first trimester leading to miscarriage and bleeding at later stages of pregnancy resulting in stillbirth. Such cases of miscarriage are not accounted for here.

Gestational diabetes and insulin use were not associated with stillbirth in this analysis, just as maternal diabetes prior to pregnancy was not associated with stillbirth in Chapter III. The increased risk of stillbirth associated with gestational diabetes and poor management of diabetes has been well documented (16). There are several plausible explanations for this. Management is key for the delivery of healthy infants when mothers are afflicted with gestational diabetes. When kept under control, gestational diabetes can have little effect on stillbirth rates (16). There is no information available for this study population to determine the severity of gestational diabetes. I attempted to gather data about the highest and lowest glucose levels before 15 weeks gestation, between 15-27 weeks gestation, and after 27 weeks gestation, along with diabetic ketoacidosis, however this data was rarely available in maternal medical records for the overall population, as well as for mothers of stillborn infants. There is also the possibility that the overall population is relatively healthier than other populations where the potential relation between gestational diabetes and stillbirth has been assessed. As

mentioned in Chapter II, there is relatively little obesity in this population, which could lead to less gestational diabetes, or less severe cases.

The excess stillbirth risk for mothers using any antibiotics or antivirals not used for PROM, prophylactic steroids for preterm labour, and any other treatment was explained in the multivariable logistic regression model. Routine aspirin use remained a significant risk factor for stillbirth in the multivariable logistic regression model that included maternal hypertension disorders. This is likely due to the fact that routine aspirin is used to treat antiphospholipid syndrome as well as for hypertensive disorders. Antiphospholipid syndrome was not assessed in the INTERGROWTH-21st study, and data for this syndrome is only available for stillbirth cases.

There are several limitations that should be considered when interpreting the results of this study. First, while efforts were made to use maternal medical records whenever possible, some of the information included here was based upon maternal interviews conducted around the time of delivery. While surveys after outcomes have already been determined may introduce bias, maternal medical records have largely validated the pregnancy complications assessed here. Second, there is a significant association between missing data and stillbirth risk. Although this is likely a reflection of the overall lack of information about the high stillbirth risk mothers in clinical institutions, the missing data may bias some of the results. Third, with the exception of preeclampsia, there was no information available about the severity of the pregnancy complications analysed here. This information would make analyses about the management of these disorders in relation to stillbirth risk possible.

In the next chapter, I will move beyond risk factors for stillbirth and attempt to categorize the stillbirths in this population by cause of death and stillbirth characteristics.

Tables/ Figures

Table 1. Pregnancy, delivery, and birth characteristics and stillbirth, 2009-2012.

	All mothers % n=43,077	Mothers of stillborn infants % n=289
Parity		
0	52.2	49.1
1	28.8	25.3
2-3	14.9	20.8
4-5	2.9	2.4
≥ 6	1.3	2.4
Missing	0.0	0.0
Previous preterm births?		
No	92.5	87.2
Yes	7.5	12.8
Missing	0.0	0.0
Previous birth weight below 2.5 kg or above 4.5 kg?		
No	90.2	81.8
Yes	9.8	18.2
Missing	0.0	0.0
Any previous miscarriages?		
No	73.1	75.1
Yes	26.9	24.9
Missing	0.0	0.0
Previous miscarriage in last 2 pregnancies?		
No	94.3	92.0
Yes	5.7	8.0
Missing	0.0	0.0
Previous stillbirth or neonatal death?		
No	95.3	90.5
Yes	4.7	9.5
Missing	0.0	0.0
Plurality		
Singleton	98.5	93.8
Twins	1.4	5.5
Triplets	0.0	0.7
Four or more	0.0	0.0
Missing	0.0	0.0
Pregnancy conceived with fertility treatment?		
No	97.6	99.0
Yes	2.3	1.0
Missing	0.0	0.0
Regular menstrual cycle in 3 months prior to pregnancy		
No	86.5	85.1
Yes	13.5	14.9
Missing	0.0	0.0
Use of hormonal contraceptives or breastfeeding in 2 months prior to this pregnancy		
No	89.1	90.3
Yes	10.9	9.7
Missing	0.0	0.0
	All infants % n=43,741	Stillborn infants % n=294
Mode of delivery		
Vaginal spontaneous	53.5	76.1
Vaginal assisted (e.g. forceps, vacuum)	5.3	1.0
Assisted breech or breech extraction	0.1	1.4
Caesarean section	41.0	20.8
Missing	0.0	0.7
Foetal presentation		
Cephalic	93.4	79.2
Breech	3.5	14.5
Other	3.0	3.8

Missing	0.1	2.4
Gestational age		
Extremely preterm	0.5	27.3
Very preterm	0.8	31.8
Preterm	7.5	15.6
Term	88.8	27.3
Postterm	2.3	2.1
Missing	0.1	0.0
Birth weight		
Extremely low birth weight	0.5	29.4
Very low birth weight	0.6	13.5
Low birth weight	9.1	19.7
Normal birth weight	84.3	24.6
High birth weight	5.1	0.7
Missing	0.4	12.1
Foetal distress		
No	98.3	97.6
Yes	1.7	2.4
Missing	0.0	0.0
Suspected or impaired foetal growth or SGA		
No	96.0	94.8
Yes	4.0	5.2
Missing	0.0	0.6

Table 2. Pregnancy, delivery, and birth characteristics and stillbirth rates per 1,000 total births by timing of death and chi-squared tests for heterogeneity, 2009-2012.

	Stillbirth rate per 1,000 births (95% CI)	p-values	Antepartum rate per 1,000 births	p-values	Intrapartum rate per 1,000 births	p-values
Overall	**6.7 (6.0 - 7.5)**		**5.1**		**1.6**	
Parity		0.040		0.049		0.764
0	6.3 (5.3 - 7.4)		4.8		1.6	
1	5.9 (4.5 - 7.2)		4.6		1.3	
2-3	9.4 (7.0 - 11.7)		7.2		2.2	
4-5	5.5 (1.4 - 9.7)		3.2		2.4	
≥ 6	12.3 (3.3 - 21.8)		10.5		1.8	
Missing	--		--		--	
Previous preterm births?		0.017		0.027		0.348
No	6.8 (5.6 - 7.9)		5.2		1.5	
Yes	12.1 (6.8 - 17.8)		9.5		2.5	
Missing	--		--		--	
Previous birth weight below 2.5 kg or above 4.5 kg?		<0.001		0.001		0.293
No	6.4 (5.3 - 7.6)		5.0		1.5	
Yes	13.7 (8.3 - 18.4)		10.8		2.9	
Missing	--		--		--	
Any previous miscarriages?		0.767		0.706		0.991
No	6.9 (6.0 - 7.8)		5.3		1.6	
Yes	6.3 (4.8 - 7.6)		4.7		1.6	
Missing	--		--		--	
Previous miscarriage in last 2 pregnancies?		0.221		0.420		0.286
No	6.6 (5.5 - 7.6)		5.1		1.5	
Yes	9.3 (4.5 - 14.4)		6.6		2.7	
Missing	--		--		--	
Previous stillbirth or neonatal death?		0.008		0.047		0.053
No	6.8 (5.7 - 8.0)		5.3		1.5	
Yes	14.2 (6.9 - 22.0)		10.1		4.0	
Missing	--		--		--	
Plurality		<0.001		0.073		<0.001
Singleton	6.4 (5.6 - 7.1)		5.0		1.4	
Twins	16.9 (13.1 - 38.4)		9.7		7.2	
Triplets	35.1 (0.0 - 251.2)		17.5		17.5	
Four or more	--		--		--	
Missing	--		--		--	
Pregnancy conceived with fertility treatment?		0.204		0.451		0.379
No	6.8 (6.0 - 7.6)		5.2		1.6	
Yes	2.6 (0.0 - 6.3)		2.6		--	
Missing	--		--		--	
Regular menstrual cycle in 3 months prior to pregnancy		0.816		0.632		0.864
No	6.6 (5.8 - 7.4)		5.0		1.6	
Yes	7.3 (5.2 - 9.6)		5.9		1.4	
Missing	--		--		--	
Use of hormonal contraceptives or breastfeeding in 2 months prior to this pregnancy		0.833		0.894		0.211
No	6.8 (6.0 - 7.6)		5.1		1.7	
Yes	6.1 (3.8 - 8.2)		5.5		0.6	
Missing	--		--		--	
Mode of delivery		<0.001		<0.001		<0.001
Vaginal spontaneous	9.6 (8.4 - 10.9)		0.8		2.2	
Vaginal assisted (e.g. forceps, vacuum)	1.3 (0.0 - 2.7)		--		1.3	
Assisted breech or breech extraction	75.5 (1.5 - 149.4)		56.6		18.9	
Caesarean section	3.4 (2.6 - 4.3)		2.5		0.9	
Missing	222.2 (0.0 - 530.2)		222.2		--	
Foetal presentation		<0.001		<0.001		<0.001
Cephalic	5.7 (4.9 - 6.4)		4.3		1.3	
Breech	24.9 (17.4 - 32.5)		17.2		7.7	
Other	10.2 (4.9 - 15.5)		8.0		2.2	

Missing	381 (117.0 - 644.9)		381.0	--	
Gestational age		<0.001		<0.001	<0.001
Extremely preterm	402.5 (321.6 - 483.5)		305.1	97.5	
Very preterm	130.9 (93.5 - 168.3)		108.6	22.3	
Preterm	19.2 (14.6 - 23.8)		14.7	4.5	
Term	2 (1.6 - 2.5)		1.5	0.5	
Postterm	6 (1.2 - 10.7)		3.0	3.0	
Missing	--		--	--	
Birth weight		<0.001		<0.001	<0.001
Extremely low birth weight	388.6 (307.9 - 469.4)		288.2	100.4	
Very low birth weight	124.6 (85.5 - 163.7)		99.0	25.6	
Low birth weight	13.1 (9.7 - 16.6)		9.9	3.3	
Normal birth weight	1.9 (1.4 - 2.3)		1.4	0.5	
High birth weight	0.9 (-0.3 - 2.2)		0.5	0.5	
Missing	203.1 (139.4 - 266.9)		166.7	36.5	
Foetal distress		0.190		0.027	0.539
No	6.6 (5.9 - 7.4)		5.0	1.6	
Yes	12.1 (4.2 - 19.9)		12.1	--	
Missing	--		--	--	
Suspected or impaired foetal growth or SGA		0.670		0.629	0.987
No	6.7 (5.9 - 7.4)		5.1	1.6	
Yes	8.3 (4.1 - 12.5)		6.6	1.7	
Missing	--		--	--	

Table 3. Crude and multivariable logistic regression models of the associations between pregnancy, delivery, and birth characteristics and risk of a stillbirth occurring during this pregnancy, 2009-2012.

	Univariate		Multivariable		p-values
	OR	95% CI	AOR	95% CI	
Parity					
0	1.07	0.81-1.42	1.66	0.11-25.10	0.788
1	ref	ref	ref	ref	ref
2-3	1.60	1.13-2.25	1.22	0.81-1.83	0.701
4-5	0.95	0.43-2.06	0.65	0.27-1.57	0.239
≥ 6	2.14	0.98-4.68	0.78	0.28-2.14	0.994
Previous preterm births?					
No	ref	ref	ref	ref	ref
Yes	1.83	1.13-2.98	0.42	0.19-0.89	0.032
Previous birth weight below 2.5 kg or above 4.5 kg?					
No	ref	ref	ref	ref	ref
Yes	2.08	1.36-3.16	2.17	1.08-4.36	0.03
Previous stillbirth or neonatal death?					
No	ref	ref	ref	ref	ref
Yes	2.14	1.23-3.72	1.16	0.56-2.41	0.315
Plurality					
Singleton	ref	ref	ref	ref	ref
Twins	4.11	2.47-6.86	1.11	0.49-2.49	0.494
Triplets	18.31	4.21-79.61	9.81	0.93-103.33	0.088
Four or more	--	--	--	--	
Mode of delivery					
Vaginal spontaneous	ref	ref	ref	ref	ref
Vaginal assisted (e.g. forceps, vacuum)	0.14	0.04-0.42	0.44	0.06-3.34	0.445
Assisted breech or breech extraction	8.65	3.09-24.19	0.28	0.03-2.91	0.589
Caesarean section	0.35	0.27-0.47	0.28	0.17-0.45	0.012
Foetal presentation					
Cephalic	ref	ref	ref	ref	ref
Breech	5.00	3.59-6.98	1.48	0.74-2.96	0.675
Other	1.49	0.81-2.74	1.01	0.62-4.43	0.311
Gestational age					
Extremely preterm	380.08	267.53-539.99	7.00	2.54-19.25	<0.001
Very preterm	74.75	50.92-109.72	4.94	2.07-11.79	<0.001
Preterm	10.22	7.36-14.18	3.32	1.87-5.92	<0.001
Term	ref	ref	ref	ref	ref
Postterm	2.90	1.26-6.67	2.68	0.81-8.85	0.192
Birth weight					
Extremely low birth weight	364.49	253.56-523.94	58.72	20.83-165.54	<0.001
Very low birth weight	83.97	55.67-126.65	17.64	6.78-45.89	<0.001
Low birth weight	7.55	5.32-10.72	5.90	3.26-10.67	<0.001
Normal birth weight	ref	ref	ref	ref	ref
High birth weight	0.46	0.11-1.88	0.70	0.17-2.95	0.962
Maternal age (years)					
< 15	4.42	0.60-32.38	--	--	--
15-19	1.04	0.56-1.90	0.78	0.10-6.04	0.86
20-34	ref	ref	ref	ref	ref
35-39	1.26	0.90-1.78	1.32	0.81-2.14	0.44
≥ 40	2.52	1.55-4.08	2.45	1.24-4.85	0.04
Maternal weight (kg)					
< 50	0.57	0.36-0.88	0.30	0.12-0.77	0.024
50-79.9	ref	ref	ref	ref	ref
80-99.9	1.42	1.01-1.99	1.49	0.91-2.42	0.061
≥ 100	0.90	0.37-2.20	0.62	0.16-2.46	0.0522
Marital Status					
Single	1.70	1.06-2.71	0.51	0.14-1.89	0.744
Married/Cohabiting	ref	ref	ref	ref	ref
Separated/Divorced	5.13	2.09-12.61	2.52	0.60-10.62	0.51
Widowed	--	--	--	--	
Highest level of education					
Primary	2.10	1.45-3.04	1.71	0.90-3.23	0.085
Secondary	1.32	0.97-1.80	1.18	0.69-2.04	0.713
Professional/Technical training	1.54	1.09-2.18	1.85	1.03-3.31	0.021
University	ref	ref	ref	ref	ref

Maternal use of tobacco during pregnancy					
None	ref	ref	ref	ref	ref
1-5 cigarettes per day	1.83	1.18-2.83	0.90	0.39-2.06	0.444
> 5 cigarettes per day	--	--	--	--	
5 or more units of alcohol per week during pregnancy?					
No	ref	ref	ref	ref	ref
Yes	4.60	1.88-11.29	1.60	0.14-18.69	0.565
Maternal use of recreational drugs during pregnancy					
No	ref	ref	ref	ref	ref
Yes	4.27	1.57-11.63	0.88	0.13-6.13	0.857

Table 4. Pregnancy specific medical conditions and treatments, and stillbirth, 2009-2012.

	All mothers % n=43,077	Mothers of stillborn infants % n=294
Severe vomiting requiring hospitalisation		
No	98.6	98.6
Yes	1.4	1.4
Missing	0.0	0.0
Gestational diabetes		
No	94.7	95.5
Yes	5.2	4.5
Missing	0.0	0.0
Vaginal bleeding before 15 weeks		
No	96.8	96.2
Yes	3.2	3.8
Missing	0.0	0.0
Vaginal bleeding at 15-27 weeks		
No	98.1	92.0
Yes	1.9	8.0
Missing	0.0	0.0
Vaginal bleeding after 27 weeks		
No	97.4	94.1
Yes	2.6	5.9
Missing	0.0	0.0
Pregnancy-induced hypertension		
No	92.7	89.3
Yes	7.3	10.7
Missing	0.0	0.0
Preeclampsia		
No	97.7	92.4
Yes	2.3	7.6
Missing	0.0	0.0
Severe preeclampsia/Eclampsia/HELLP Syndrome		
No	99.4	97.2
Yes	0.5	2.8
Missing	0.0	0.0
Rhesus disease		
No	99.4	99.7
Yes	0.6	0.4
Missing	0.0	0.0
Premature rupture of membranes		
No	84.8	87.5
Yes	15.2	11.8
Missing	0.0	0.7
Any other pregnancy related condition requiring treatment or referral		
No	96.3	87.9
Yes	3.6	12.1
Missing	0.0	0.0
Maternal use of the following medication during this pregnancy		
Routine aspirin		
No	98.5	95.2
Yes	1.5	4.8
Missing	0.0	0.0
Any antibiotics or antivirals not used for PROM		
No	88.2	83.7
Yes	11.8	16.3
Missing	0.0	0.0
Antibiotics used for PROM		
No	95.1	97.6
Yes	4.8	2.4
Missing	0.0	0.0
Non-steroidal anti-inflammatories		
No	98.1	98.3
Yes	1.9	1.7
Missing	0.0	0.0
Insulin		
No	98.8	98.6

Yes	1.2	1.4
Missing	0.0	0.0
Prophylactic steroids for preterm labour		
No	95.8	92.0
Yes	4.2	8.0
Missing	0.0	0.0
Any other treatment		
No	80.5	69.6
Yes	19.4	30.5
Missing	0.0	0.0

Table 5. Pregnancy specific medical conditions and treatments, and stillbirth rates per 1,000 total births by timing of death and chi-squared tests for heterogeneity, 2009-2012.

	Stillbirth rate per 1,000 births (95% CI)	p-values	Antepartum rate per 1,000 births	p-values	Intrapartum rate per 1,000 births	p-values
Overall	**6.7 (6.0-7.5)**		**5.1**		**1.6**	
Severe vomiting requiring hospitalisation		0.952		0.962		0.989
No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	6.5 (0.1 - 13.2)		4.9		1.6	
Missing	--		--		--	
Gestational diabetes		0.792		0.355		0.450
No	6.8 (6.0 - 7.6)		5.2		1.5	
Yes	5.7 (2.6 - 8.9)		3.1		2.6	
Missing	--		--		--	
Vaginal bleeding before 15 weeks		0.840		0.343		0.308
No	6.7 (5.9 - 7.5)		5.0		1.7	
Yes	7.8 (3.3 - 12.7)		7.8		--	
Missing	--		--		--	
Vaginal bleeding at 15-27 weeks		<0.001		<0.001		<0.001
No	6.3 (5.5 - 7.1)		4.9		1.4	
Yes	27.3 (16.7 - 39.8)		17.8		9.5	
Missing	--		--		--	
Vaginal bleeding after 27 weeks		0.003		0.011		0.267
No	6.5 (5.7 - 7.3)		5.0		1.5	
Yes	14.8 (7.9 - 22.3)		11.3		3.5	
Missing	--		--		--	
Pregnancy-induced hypertension		0.067		0.013		0.861
No	6.5 (5.7 - 7.2)		4.8		1.6	
Yes	9.9 (6.4 - 13.4)		8.7		1.2	
Missing	--		--		--	
Preeclampsia		<0.001		<0.001		0.002
No	6.4 (5.6 - 7.1)		4.9		1.5	
Yes	21.7 (13.2 - 32.1)		15.8		5.9	
Missing	--		--		--	
Severe preeclampsia/Eclampsia/HELLP Syndrome		<0.001		0.003		<0.001
No	6.6 (5.8 - 7.3)		5.0		1.5	
Yes	33.2 (10.6 - 58.6)		20.7		12.4	
Missing	--		--		--	
Rhesus disease		0.819		0.932		0.804
No	6.7 (6.0 - 7.5)		5.1		1.6	
Yes	3.8 (0.0 - 11.5)		3.8		--	
Missing	--		--		--	
Premature rupture of membranes		<0.001		<0.001		0.845
No	6.9 (6.1 - 7.8)		5.3		1.6	
Yes	5.2 (3.4 - 6.9)		3.9		1.3	
Missing	153.8 (0.0 - 367.1)		153.8		--	
Any other pregnancy related condition requiring treatment or referral		<0.001		<0.001		0.292
No	6.1 (5.4 - 6.9)		4.6		1.5	
Yes	21.9 (15.0 - 29.9)		18.8		3.1	
Missing	--		--		--	
Maternal use of the following medication during this pregnancy						
Routine aspirin		<0.001		<0.001		0.636
No	6.5 (5.7 - 7.2)		4.9		1.6	
Yes	21.4 (10.6 - 33.9)		18.3		3.1	
Missing	--		--		--	
Any antibiotics or antivirals not used for PROM		0.020		0.005		0.982
No	6.3 (5.6 - 7.2)		4.7		1.6	
Yes	9.7 (6.6 - 11.9)		8.1		1.6	
Missing	--		--		--	
Antibiotics used for PROM		0.124		0.091		0.958
No	6.9 (6.1 - 7.7)		5.3		1.6	
Yes	3.3 (0.9 - 5.9)		1.9		1.4	
Missing	--		--		--	
Non-steroidal anti-inflammatories		0.901		0.942		0.940

No	6.7 (5.9 - 7.5)		5.1		1.6	
Yes	5.9 (0.8 - 11.5)		4.7		1.2	
Missing	--		--		--	
Insulin		0.921		0.566		0.058
No	6.7 (5.9 - 7.5)		5.2		1.6	
Yes	7.7 (0.2 - 15.5)		1.9		5.7	
Missing	--		--		--	
Prophylactic steroids for preterm labour		0.018		0.032		0.545
No	6.5 (5.7 - 7.2)		4.9		1.6	
Yes	11.8 (7.5 - 17.9)		9.2		2.6	
Missing	--		--		--	
Any other treatment		<0.001		<0.001		0.986
No	5.8 (5.0 - 6.6)		4.2		1.6	
Yes	10.4 (8.3 - 12.7)		8.7		1.6	
Missing	--		--		--	

Table 6. Crude logistic regression models of the associations between pregnancy specific medical conditions and treatments, and risk of a stillbirth occurring during this pregnancy, 2009-2012.

	Univariate		Multivariable		p-values
	OR	95% CI	AOR	95% CI	
Vaginal bleeding at 15-27 weeks					
No	ref	ref	ref	ref	ref
Yes	4.59	2.98-7.07	3.34	2.11-5.30	<0.001
Vaginal bleeding after 27 weeks					
No	ref	ref	ref	ref	ref
Yes	2.35	1.44-3.86	1.63	0.97-2.75	0.054
Pregnancy-induced hypertension					
No	ref	ref	ref	ref	ref
Yes	1.54	1.06-2.23	0.92	0.60-1.40	0.581
Preeclampsia					
No	ref	ref	ref	ref	ref
Yes	3.63	2.34-5.63	2.45	1.48-4.06	<0.001
Severe preeclampsia/Eclampsia/HELLP syndrome					
No	ref	ref	ref	ref	ref
Yes	5.43	2.66-11.10	3.23	1.49-7.03	0.021
Any other pregnancy related condition requiring treatment or referral					
No	ref	ref	ref	ref	ref
Yes	3.73	2.61-5.33	2.87	1.96-4.19	<0.001
Maternal use of the following medication during this pregnancy					
Routine aspirin					
No	ref	ref	ref	ref	ref
Yes	3.49	2.03-6.01	2.36	1.34-4.16	0.001
Any antibiotics or antivirals not used for PROM					
No	ref	ref	ref	ref	ref
Yes	1.46	1.06-1.99	0.94	0.67-1.33	0.987
Prophylactic steroids for preterm labour					
No	ref	ref	ref	ref	ref
Yes	1.98	1.29-3.04	1.10	0.69-1.76	0.784
Any other treatment					
No	ref	ref	ref	ref	ref
Yes	1.82	1.42-2.34	1.07	0.80-1.42	0.411
Maternal age (years)					
< 15	4.42	0.60-32.38	2.21	0.29-17.09	0.444
15-19	1.04	0.56-1.90	0.69	0.36-1.31	0.31
20-34	ref	ref	ref	ref	ref
35-39	1.26	0.90-1.78	1.08	0.76-1.53	0.286
≥ 40	2.52	1.55-4.08	1.91	1.16-3.14	0.008
Maternal weight (kg)					
< 50	0.57	0.36-0.88	0.65	0.42-1.01	0.056
50-79.9	ref	ref	ref	ref	ref
80-99.9	1.42	1.01-1.99	1.18	0.84-1.68	0.237
≥ 100	0.90	0.37-2.20	0.68	0.28-1.68	0.405
Marital Status					
Single	1.70	1.06-2.71	1.28	0.77-2.13	0.39
Married/Cohabiting	ref	ref	ref	ref	ref
Separated/Divorced	5.13	2.09-12.61	2.32	0.70-7.63	0.168
Widowed	--	--	--	--	
Highest level of education					
Primary	2.10	1.45-3.04	1.61	1.06-2.45	0.024
Secondary	1.32	0.97-1.80	1.27	0.92-1.74	0.168
Professional/Technical training	1.54	1.09-2.18	1.52	1.08-2.15	0.015
University	ref	ref	ref	ref	ref
Maternal use of tobacco during pregnancy					
None	ref	ref	ref	ref	ref
1-5 cigarettes per day	1.83	1.18-2.83	1.15	0.69-1.90	0.605
> 5 cigarettes per day	--	--	--	--	
5 or more units of alcohol per week during pregnancy?					
No	ref	ref	ref	ref	ref
Yes	4.60	1.88-11.29	2.72	1.01-7.31	0.048
Maternal use of recreational drugs during pregnancy					
No	ref	ref	ref	ref	ref

Yes	4.27	1.57-11.63	2.19	0.71-6.75	0.41
Routine maternal use of calcium supplements during pregnancy					
No	ref	ref	ref	ref	ref
Yes	0.52	0.40-0.67	0.63	0.48-0.82	0.001

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Chapter V – Causes of stillbirth

Introduction

Identifying and reporting the causes of stillbirth is essential to targeting potential areas for stillbirth reduction, managing subsequent pregnancies, and directing future research. However, the cause of death for nearly 25% of all stillbirths is unknown, with no post-mortem examination conducted in the vast majority of these cases (1, 2). Despite the well-demonstrated effectiveness of post-mortem examinations in lowering perinatal mortality rates (3), the rates of post-mortem examinations have actually been declining globally. In an analysis of perinatal mortality in England, Wales, Northern Ireland, Channel Islands, and the Isle of Man, post-mortem examinations were held in 55% of stillbirths in 2000, compared with only 45% in 2007 (4). In 2000, post-mortem examinations were not conducted because of parental/guardian refusal in 33% of stillbirth cases, compared to 47.1% refusing consent in 2007. This trend demonstrates the under-appreciation of the value of post-mortem examinations in both parents and health care providers.

The Perinatal Mortality Audit Committee at the Royal Prince Alfred Hospital in Australia demonstrated that using the *Clinical Practice Guidelines for Perinatal Mortality Audit* published by the Perinatal Society of Australia and New Zealand Perinatal Mortality Special Interest Group, unexplained antepartum stillbirths fell from 34% of all stillbirths to 13% following investigations and review (5). While a significant portion of stillbirths will remain unexplained given current post-mortem limitations, a basic workup including autopsy, placental examination, cytogenetic analysis, and foetal maternal haemorrhage testing following foetal death could significantly improve stillbirth classification (6).

Once a complete post-mortem assessment has been held, several difficulties in classifying foetal death remain. Typically dependent upon the classification system used, causes of death assigned to stillborn infants will often be unfounded. For example, Korteweg et al. (2012) found abnormal placentas in 89% of stillbirth cases in their study of 1,025 stillbirths in the Netherlands from 2002-2008 in a multicentre cohort study (6). Yet many of these abnormalities, such as placental calcification or placental infarcts are found in high percentages in normal, live births as well, making causal inference impossible (7). Still, such abnormalities in the placenta are often listed as the cause of stillbirth without sufficient supporting evidence.

Given the difficulty in attributing an appropriate cause of death to stillborn infants, clinicians and researchers have worked to create systems and protocols for identifying probable causes of stillbirth based on empirical evidence. The Stillbirth Collaborative Research Network created the Initial Causes of Foetal Death to address this issue, categorizing maternal medical conditions, obstetric complications, maternal or foetal haematological conditions, foetal genetic, structural, and karyotypic abnormalities, placental and/or foetal infections, and pathologic placental conditions as either possible or probable causes of foetal death based upon severity, presentation, and co-morbidities (8).

Using the guidelines presented in the Initial Causes of Foetal Death, I attempt to identify causes of death for all cases of stillbirth in the NCSS cohort using maternal medical records and maternal responses from interviews in this chapter. Given the retrospective nature of this analysis, it was not possible to conduct a post-mortem examination on all stillborn infants. Thus, the analyses in this chapter are reflective of the current practices at the institutions collaborating in the INTERGROWTH-21st Project.

Methods

Data:

The data on 43,781 births was obtained from the 6 INTERGROWTH-21st sites that have enrolled at least 5,000 participants into the NCSS between 2009-2012. Data from the Torino, Italy and Seattle, USA sites were not available at the time of this analysis.

The primary outcome was stillbirth, defined as foetal death at a gestation age of 18 weeks or more. Gestational age was calculated using crown to rump length from early ultrasound examinations whenever possible. In cases without early ultrasound pregnancy dating, maternal reported last menstrual periods were used to estimate gestational age.

Along with using the data collected in the NCSS Pregnancy and Delivery Form, I developed and utilized the Foetal Death Supplementary Form (Appendix III) to gather additional data from maternal medical records on the potential causes of death and the severity of complications found in the 295 NCSS stillborn infants. While I completed the Foetal Death Supplementary Form for all stillbirths occurring at the Oxford, United Kingdom site, clinicians and health care providers working on-site at the other 5 collaborative institutions completed the form for stillborn infants (the sites in Italy and the United States will also complete the form in the future). See below for further information on the creation of the form.

The primary causes of stillbirth have been coded as one of the following: foetal genetic, structural, and karyotypic abnormalities; infection; obstetric complications; foetal conditions, diseases, and events; placental/cord insufficiency; maternal medical conditions; termination; unknown. These categories were developed based upon the Stillbirth Collaborative Research Network's Initial Causes of Foetal Death (8). Notable

differences between the Initial Causes of Foetal Death categories and the categories used exist. The category of maternal and foetal haematological conditions has been eliminated. Maternal haematological conditions have been listed under maternal medical conditions and foetal haematological conditions appear either under placental/cord complications, or a new category, foetal conditions, diseases and events. This was done in attempt to highlight the importance of placental/cord complications as a key stillbirth pathway, independent of other haematological complications. Termination of pregnancy and unknown cause of death were also added.

Foetal genetic, structural, and karyotypic abnormalities were sub-divided into chromosomal and structural. Infections were subdivided into syphilis, HIV/AIDS, malaria, toxoplasmosis, sepsis, acute chorioamnionitis, puerperal infections, and respiratory infections. Obstetric complications were subdivided into premature rupture of membranes (PROM), acute asphyxia, uterine rupture, prolonged labour, and post-term pregnancy with failure to progress. The Foetal conditions, diseases, and events category was subdivided into antiphospholipid syndrome (APS), meconium aspiration, foetal-maternal incompatibility, and hydrops fetalis. Placental/Cord insufficiency was subdivided into abruptio placentae, placental praevia, placental abnormalities and infarcts, twin-to-twin transfusion syndrome, cord knots, strictures, and torsions, cord entrapment with occlusion, cord tight around neck/body, cord malformations, and cord prolapse. The maternal medical conditions category was subdivided into maternal hypertension, severe pre-eclampsia/eclampsia/HELLP syndrome, gestational diabetes, and maternal death. Termination was subdivided into elective termination, termination after diagnosis of a congenital anomaly, and termination due to pregnancy complications. While there are further potential causes for stillbirth, only causes of death present in this population have been listed here. It was not possible to subdivide unknown causes of

death based up post-mortem completion, nor upon whether consent was sought/given from the parents/guardians.

The study complies with the International Ethical Guidelines for Biomedical Research Involving Human Subjects at the appropriate international, national, local, and individual levels.

Supplementary Form creation:

I designed the Foetal Death Supplementary Form over several months to facilitate the collection of the necessary information to assess the cause of stillbirth as outlined in the Initial Causes of Foetal Death guidelines. Any information already captured by the NCSS Pregnancy and Delivery Form was not included in the Foetal Death Supplementary Form. Per INTERGROWTH-21st protocol, feedback was incorporated from all participating sites on the feasibility of collecting the requested data, and the form was adjusted accordingly. Once a final version of the form was completed, with the help of researchers and clinicians on the INTERGROWTH-21st Team, and outside, and piloted in the UK, I then created an operation manual outlining the procedure for completing the form (Appendix IV). The form was then translated to the relevant languages, and distributed to each INTERGROWTH-21st site, to be completed by local clinicians and healthcare workers. I then ensured the completion of the forms for all relevant cases, and scored the data using the guidelines provided in the Initial Causes of Foetal Death form. While there are clear benefits of completing the Foetal Death Supplementary Form for all births in the INTERGROWTH-21st Project, this was not feasible. Thus, no attempt is made to assess the risk associated with individual items on the Foetal Death Supplementary Form.

Analysis:

First, I calculated stillbirth hazard rates with 95% confidence intervals for gestational age ranges 18-19 weeks, 20-21 weeks, 22-23 weeks, 24-25 weeks, 26-27 weeks, 28-29 weeks, 30-31 weeks, 32-33 weeks, 34-35 weeks, 36-37 weeks, 38-39 weeks, 40-41 weeks, ≥42 weeks. The at-risk population was defined as all pregnancies reaching the gestational age range, including ongoing pregnancies.

Second, I calculated the percentage of stillbirths per cause of death category (foetal genetic, structural, and karyotypic abnormalities; infection; obstetric complications; foetal conditions, diseases, and events; placental/cord insufficiency; maternal medical conditions; termination; unknown) overall and by site.

Third, I calculated the percentage of stillbirths per cause of death category by gestational age at birth (extremely preterm – less than 28 weeks gestation, very preterm – 28 to 31 6/7 weeks gestation, preterm – 32 to 36 6/7 weeks gestation, term – 37 to 41 6/7 weeks gestation, postterm – 42 weeks gestation or more), and then by birth weight (extremely low birth weight – less than 1000 grams, very low birth weight – 1000 to 1499 grams, low birth weight – 1500 to 2499 grams, normal birth weight 2500 to 3999 grams, high birth weight 4000 grams or more), for the overall population only. A stratification of stillbirth causes by gestational age/birth weight and site is uninformative due to the relatively low number of stillbirths for each individual site.

Fourth, I calculated the percentage of stillbirths per specific cause of death (this only includes the following causes of death that occurred with at least 1 of the 295 cases of stillbirth: chromosomal abnormalities; structural abnormalities; syphilis; HIV/AIDS; malaria; toxoplasmosis; sepsis; acute chorioamnionitis; puerperal infections; respiratory infections; PROM; uterine rupture; prolonged labour; post-term pregnancy with failure to induce; direct foetal trauma; contraception related death; APS; meconium aspiration;

foetal/maternal incompatibility; hydrops fetalis; abruptio placentae; placental praevia; placental abnormalities/insufficiencies; twin-twin transfusion; cord knots, strictures, and torsions; cord entrapment with occlusion; cord around neck/body; cord malformations; cord prolapse; maternal hypertension; severe preeclampsia/eclampsia/HELLP syndrome; gestational diabetes; maternal death; termination after diagnosis of congenital abnormalities, termination due to pregnancy complication; and unknown causes) overall and by site.

Results

There were 43,781 births occurring between 2009-2012 at the 6 sites included in this analysis, with 295 resulting in stillbirths. Of these 43,781 births, 39 were excluded because the mother was lost to follow up during pregnancy, and the infant was not delivered at an INTERGROWTH-21st site. Therefore, 43,742 births are included in this analysis, with a total of 43,078 pregnancies. There were a total of 295 stillbirths.

Figure 1 shows the stillbirth hazard per 100,000 foetuses at risk. Stillbirth hazard per 100,000 at risk foetuses is the lowest during gestational weeks 18-19 (Hazard: 22.87, CI: 8.7-37.05) and continues to rise until gestational weeks (Hazard: 75.57, CI: 49.78-101.35). Stillbirth hazard then remains relatively level until it rises during gestational weeks 36-37 (Hazard: 92.00, CI: 62.75-121.25). The stillbirth hazard then climbs during gestational weeks 40-41 (Hazard: 195.87, CI: 125.78-265.97) and finally peaks at the ≥42 weeks gestation range (Hazard: 581.96, CI: 116.29-1047.62).

Figure 2 shows the causes of the 295 stillbirths, separated by antepartum and intrapartum stillbirths. The stillbirth percentages were as follows: 11% foetal, genetic, structural, and karyotypic abnormalities, 4% infection, 4% obstetric complications, 2%

foetal conditions, diseases, and events, 19% placental/cord insufficiency, 10% maternal medical conditions, 3% terminations, and 47% unknown.

Of the 295 stillbirth cases, 224 were macerated, with the following cause of death percentages: 11% foetal, genetic, structural, and karyotypic abnormalities, 4% infection, 4% obstetric complications, 2% foetal conditions, diseases, and events, 19% placental/cord insufficiency, 10% maternal medical conditions, 3% terminations, and 47% unknown. The cause of death percentages for the 71 fresh stillbirth were as follows: 11% foetal, genetic, structural, and karyotypic abnormalities, 7% infection, 4% obstetric complications, 4% foetal conditions, diseases, and events, 18% placental/cord insufficiency, 7% maternal medical conditions, 3% terminations, and 45% unknown.

Figure 3 shows the causes of stillbirth by site. The percentage of stillbirth cases with unknown causes of death varied by site, as 75% of stillbirths were attributed to unknown causes in Oman, while only 29% of stillbirths in China remained unexplained. In Brazil, the leading known causes of stillbirth were placental/cord insufficiencies (20%) and maternal medical conditions (13%). In China, placental/cord insufficiency (32%) and foetal genetic, structural, and karyotypic abnormalities (29%) accounted for the majority of stillbirths. In India, foetal genetic, structural, and karyotypic abnormalities accounted for 21% of stillbirths. In Kenya, placental/cord insufficiencies (21%), maternal medical conditions (15%), and infection (9%) accounted for much of the stillbirth burden. Of the cases of stillbirth with known causes of death in Oman, 50% were due to foetal genetic, structural, and karyotypic abnormalities (13% overall). The leading causes of stillbirth in the United Kingdom were foetal genetic, structural, and karyotypic abnormalities (18%), placental/cord insufficiencies (18%), and terminations (13%).

Figure 4 shows the causes of the 295 stillbirths stratified by gestational age at birth. The leading known causes of stillbirth for term infants were placental/cord insufficiency (27%), maternal medical conditions (12%), and foetal genetic, structural,

and karyotypic abnormalities (9%). The cause of death was unknown for 45% of term infants. Extremely preterm stillbirths were due mostly to foetal genetic, structural, and karyotypic abnormalities (13%), terminations (10%), placental/ cord insufficiency (10%), and obstetric complications (7%), with 47% unknown causes. Very preterm stillbirths were caused by placental/ cord insufficiency (17%), foetal genetic, structural, and karyotypic abnormalities (15%), and maternal medical conditions (15%), with 47% of causes unknown. The causes of preterm stillbirth were similar to those of term stillbirth. Postterm stillbirths were rare (n=6), caused by infection (33%), obstetric complications (17%), and placental/ cord insufficiency (17%), with the remaining cases due to unknown causes of death.

Figure 5 shows the causes of the 295 stillbirths stratified by infant birth weight. The leading known causes of stillbirth for normal weight infants were placental/cord insufficiency (30%), maternal medical conditions (10%), and infection (7%). For normal weight infants, 48% of the causes of stillbirth were unknown. Among extremely low birth weight infants, the leading causes of death were foetal genetic, structural, and karyotypic abnormalities (15%), maternal medical conditions (11%), placental/ cord insufficiency (9%), and termination (7%). Placental/ cord insufficiency (30%), foetal genetic, structural, and karyotypic abnormalities (15%), and maternal medical conditions (8%) were the leading causes of stillbirth among very low birth weight infants, as well as among low birth weight infants (25%, 13%, and 13%, respectively). There were only two stillbirths among infants with high birth weights.

Table 1 shows the specific causes of death within the stillbirth cause of death categories listed in Figure 3, along with antepartum and intrapartum sub-divisions. Of all stillbirth cases, 10% were due to structural abnormalities in the foetal genetic, structural, and karyotypic abnormalities. Of the deaths due to infection, acute chorioamnionitis (2%) accounted for the greatest percentage of overall stillbirths, with no more than one case

for any other infection type. PROM was the most common obstetric complication, accounting for 1% of all stillbirths. APS, meconium aspiration, and hydrops fetalis caused most stillbirths attributable to foetal conditions, diseases, and events, with overall contributions to the stillbirth total of approximately 1% each. Placental/Cord insufficiencies such as abruptio placentae (6%), umbilical cord around the neck/body (4%), placental abnormalities/insufficiencies (2%), cord knots, strictures, and torsions (2%) twin-twin transfusion (1%), cord malformations (1%), and placental praevia (1%) accounted for much of the overall stillbirth burden. Maternal medical conditions such as severe PET/HELLP syndrome (6%), maternal hypertension (2%), and gestational diabetes (2%) also contributed significantly to the stillbirth burden in this population. Of those terminations of pregnancy, 2/3 were terminations occurring after diagnosis of a congenital abnormality, with the remaining cases being due to pregnancy complications, contributing 2% and 1% of the overall stillbirth burden, respectively.

The greatest causes of antepartum stillbirth were structural abnormalities (10%), abruptio placentae (6%), severe preeclampsia/eclampsia/HELLP syndrome (6%), cord around neck/body (4%), maternal hypertension (3%), and placental abnormalities/insufficiencies (3%). The leading causes of intrapartum stillbirth were structural abnormalities (11%), acute chorioamnionitis (6%), abruptio placentae (6%), severe PET/HELLP syndrome (6%), cord around neck/body (4%), and twin-twin transfusion (2%).

Table 2 shows specific causes of death among stillbirth cause of death categories listed in Table 2, along with antepartum and intrapartum sub-divisions by site. In Brazil, the top contributors to the stillbirth burden were maternal hypertension (9%), abruptio placentae (8%), structural abnormalities (6%), cord malformations (6%), and severe preeclampsia/eclampsia/HELLP syndrome (5%). In China, the leading causes of stillbirth were structural abnormalities (24%), abruptio placentae (11%), and cord around

neck/body (11%). In India, structural abnormalities were the only single cause of death leading to multiple stillbirths (21%), with 57% of causes of death remaining unknown. This was also the case in Oman, with 13% of stillbirths being caused by structural abnormalities and 75% of all stillbirths due to unknown causes. The leading causes of stillbirth in Kenya were severe preeclampsia/eclampsia/ HELLP syndrome (11%), cord around neck/body (6.%), and acute chorioamnionitis (5%). In the United Kingdom, the leading causes of stillbirth were structural abnormalities (18%), termination after diagnosis of a congenital abnormality (8%), abruptio placentae (8%), and termination due to pregnancy complications (5%).

Discussion

In this analysis of 43,742 births between 2009-2012, 295 infants were stillborn, leading to a stillbirth rate of 6.7 per 1,000 total births, with antepartum stillbirths making up 76% of all stillbirths. Given the few number of ongoing pregnancies after 40 weeks gestation, post-term pregnancies faced the greatest stillbirth hazard risk, however the vast majority of stillbirths occur during early gestation. While this finding could suggest that universal induction of labour after a certain gestational age could be beneficial, the few post-term stillbirths in this cohort do not provide enough statistical evidence to support such claims. It is also unclear from the medical records why labour was not induced in these late pregnancies.

The cause of approximately 47% stillbirths was identified as unknown. The leading causes of stillbirth were placental/cord insufficiencies (19%), foetal genetic, structural, and karyotypic abnormalities (11%), maternal medical conditions (10%), and infection (4%). The prevalence of stillbirth for each cause of death category varied significantly by study site, gestational age, and birth weight. Structural congenital

abnormalities, abruptio placentae, severe PET/HELLP syndrome, umbilical cords tightly wrapped around necks and body, maternal hypertension, and placental abnormalities/insufficiencies were the leading causes of stillbirth.

The results presented here are indicative of the difficulties in identifying and categorizing causes of stillbirth. Although all of these births occurred in hospital settings, 47% of the cases had no identified cause of stillbirth. I attempted to discover through maternal medical records if, in the cases of stillbirths of unknown origins, a complete post-mortem examination was conducted, but this information was rarely documented.

There was little difference between the cause-specific makeup of antepartum stillbirths and intrapartum stillbirths. This could be an indication that high quality obstetric care at the INTERGROWTH-21st sites limits stillbirths due to obstetric complications. When obstetric complications are rare, fresh stillbirths occur primarily due to complications originating in the antepartum period. Still, there could also be underreporting of obstetric complications, as 45% of fresh stillbirths were labelled as unknown. Although it is understandable for the cause of a high proportion of antepartum stillbirths to be of unknown origins, the same is not necessarily true for intrapartum stillbirths. Intrapartum stillbirths typically can be explained by obstetric complications. Such a high rate of intrapartum stillbirths with unknown causes could suggest inaccurate labelling of these stillbirths.

The stratifications of the causes of stillbirth by gestational age and birth weight provide useful insight into the aetiology of these deaths. Foetal genetic, structural, and karyotypic abnormalities are often identified early, and in some cases, terminated. Those foetuses with severe anomalies are typically of low weight for gestational age, but can reach full term before their demise. The 11% of stillbirths due to foetal genetic, structural, and karyotypic abnormalities (with an additional 2% of stillbirths being terminations of pregnancy due to discovery of a congenital abnormality) is similar to percentages found

in previous stillbirth studies (9). As with the cases of stillbirth with unknown causes, in depth information about these cases was scarce. It was not possible to uncover if any karyotyping was attempted. The great majority of foetal genetic, structural, and karyotypic abnormalities were structural abnormalities. Cardiac and neural abnormalities accounted for 37% and 30%, respectively, of the structural abnormalities leading to stillbirth (data not shown). However, there was a wide array of cardiac and neural disorders that led to stillbirth, limiting the potential to target prevention of specific abnormalities.

Infection, which accounted for 5% of all stillbirths, had a consistent effect on foetuses through the gestational period, suggesting that the onset of an infection can occur at any time during pregnancy. It does not appear that infection limits growth, indicating that the harmful effects of these infections progressed rapidly. Acute chorioamnionitis is an example of this sort of infection, accounting for 2% of all stillbirths in this population. Infection was rare in all sites except Kenya. Aside from chorioamnionitis, there was a wide array of infections that led to stillbirth, limiting the possibility to target specific infections in prevention efforts. Stillbirths due to chorioamnionitis can be prevented through the use of antibiotics and induction of labour (10).

Foetal conditions, diseases, and events appear to be the most dangerous early in pregnancy. As the foetus grows, these events are less likely to cause a death. Any incompatibility and/or immune complications are likely to have caused a crisis earlier in pregnancy.

Placental/ cord insufficiency, the leading cause of stillbirth here, becomes a greater concern as the foetus grows. As the infant grows, it will have greater energy demands, and an insufficient placenta or cord will restrict growth. Monitoring growth restriction during antenatal visits could have the greatest effect on preventing stillbirths

due to this cause. In cases where there is no growth restriction, it is important to systematically eliminate all other plausible causes of death. Placental and cord abnormalities often occur in healthy pregnancies, and there may be an overestimate of the effect of these disorders on stillbirth rates.

Maternal medical conditions also become an increasingly important stillbirth risk as the foetus grows. These conditions do not appear to lead to restricted growth, suggesting that these disorders rapidly kill the foetus. This suggests that women at risk for maternal conditions such as PET, HELLP, and maternal hypertension will require intense monitoring once the foetus reaches a viable gestational age and size. Antenatal care, in these cases, will be of the utmost importance, in order to time induction of labour so as to maximize gestational age while minimizing infant exposure to dangerously high levels of toxins. Much of the excess stillbirths occurring in Kenya and Brazil were due to maternal medical conditions. Maternal medical conditions were the cause of 10% of all stillbirths, and 93% of all stillbirths due to maternal medical conditions occurred in Kenya and Brazil. In Kenya, all stillbirths due to maternal medical conditions were caused by severe preeclampsia/eclampsia/HELLP syndrome, gestational diabetes, and maternal death. Maternal hypertension and severe preeclampsia/eclampsia/HELLP syndrome caused the stillbirths due to maternal medical conditions in Brazil. The excess stillbirths in Kenya could be due to high-risk referrals from regional hospitals. The relative absence of these cases in the other sites suggest that these maternal medical conditions are being adequately managed, given the prevalence of maternal medical conditions and pregnancy complications in this population.

The variation by site in the percentage of stillbirths with unknown causes of death is noteworthy. There are differences in how antepartum stillbirths were recorded and handled at the respective institutions. Most of the sites do not conduct post-mortem examinations on stillborn infants. It remains difficult to find conclusive evidence that

placental and umbilical cord conditions were direct causes of stillbirth. While 11% and 6% of all stillbirths in China and Kenya, respectively, were attributed to umbilical cords being wound tightly around the infant body or neck, none of the other sites listed this as a cause of stillbirth. In Oman and India, the two sites with the greatest percentage of unknown stillbirth causes, no stillbirths were attributed to placental/cord insufficiencies.

There are several limitations that should be considered when interpreting these results. First, there are fortunately few stillbirths occurring at each site. This makes comparisons across sites difficult as well as limits the potential statistical analyses that can be performed. As the analyses of the causes of stillbirth by site rely on such small samples, these findings should be interpreted with much caution. Second, the causes of stillbirth were determined using maternal medical records. However, each site did follow the same protocol for attributing stillbirth causes of death from maternal medical records. Third, there was little additional information about the cases with unknown causes of stillbirth. This prohibited any further analyses of the stillbirth cases of unknown origins.

Tables/ Figures

Figure 1. Prospective stillbirth hazard per 100,000 foetuses with 95% confidence intervals, 2009-2012.

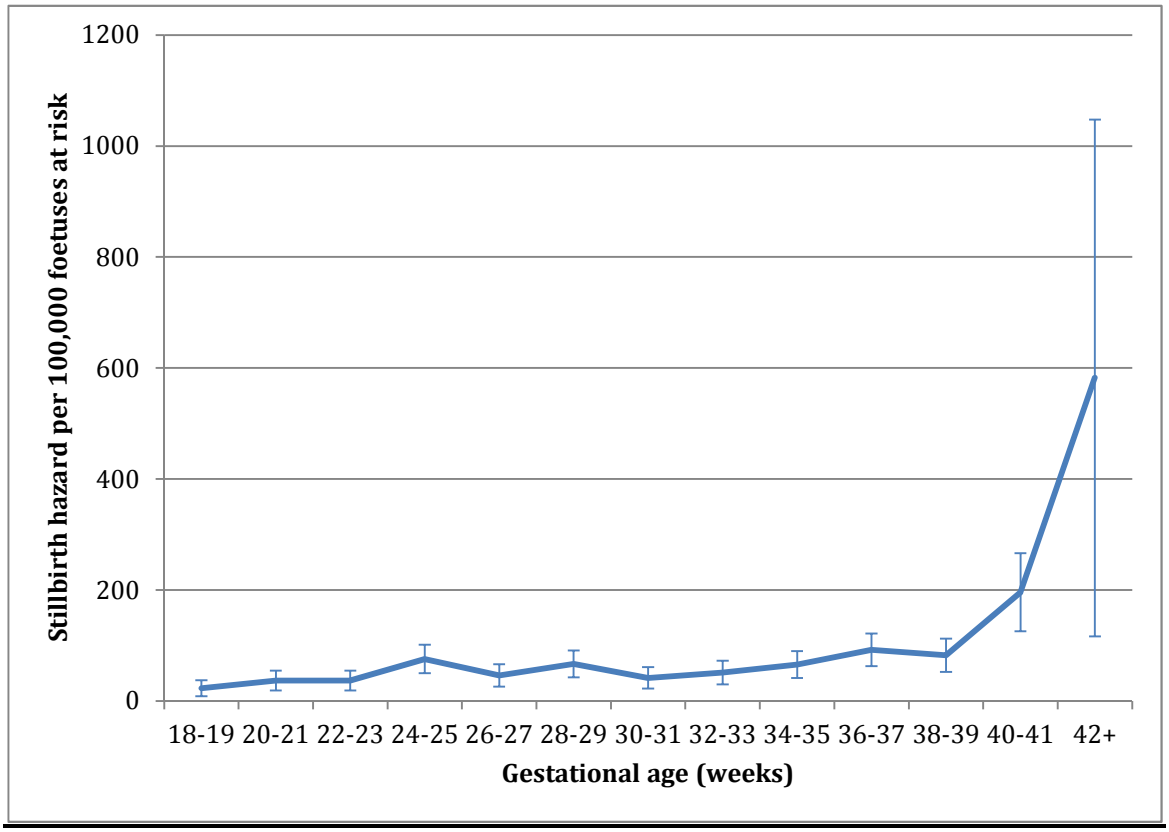

Figure 2. Causes of stillbirth, 2009-2012.

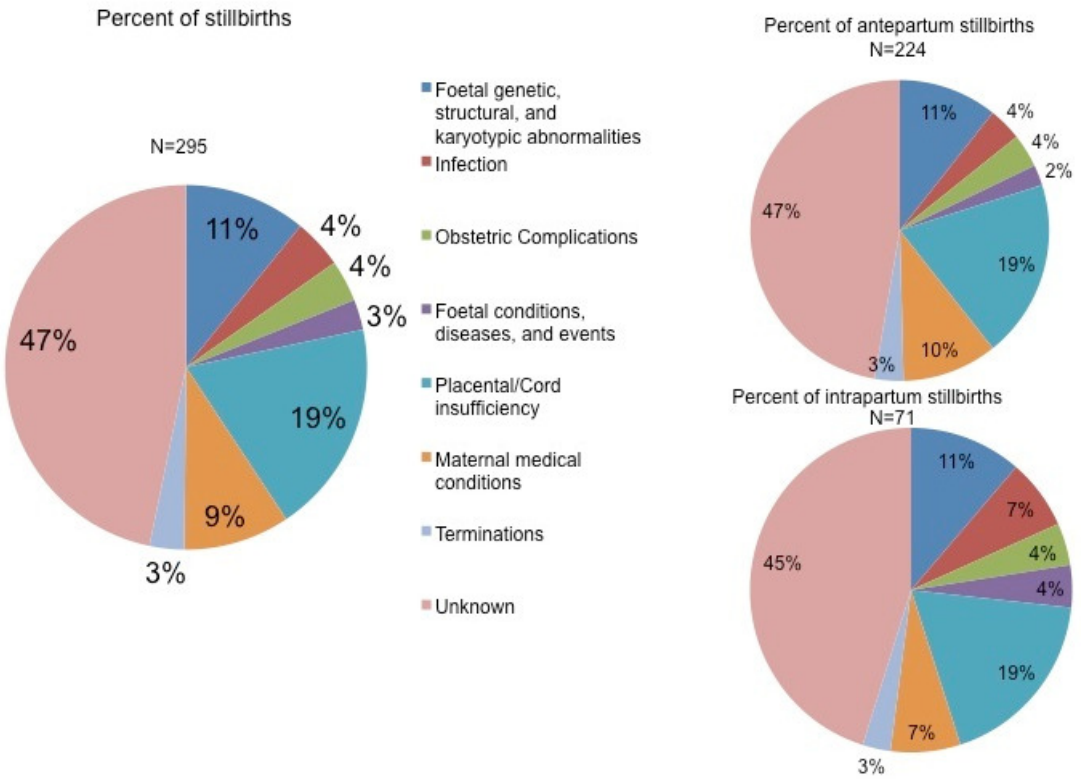

Figure 3. Cause of stillbirth by site, 2009-2012.

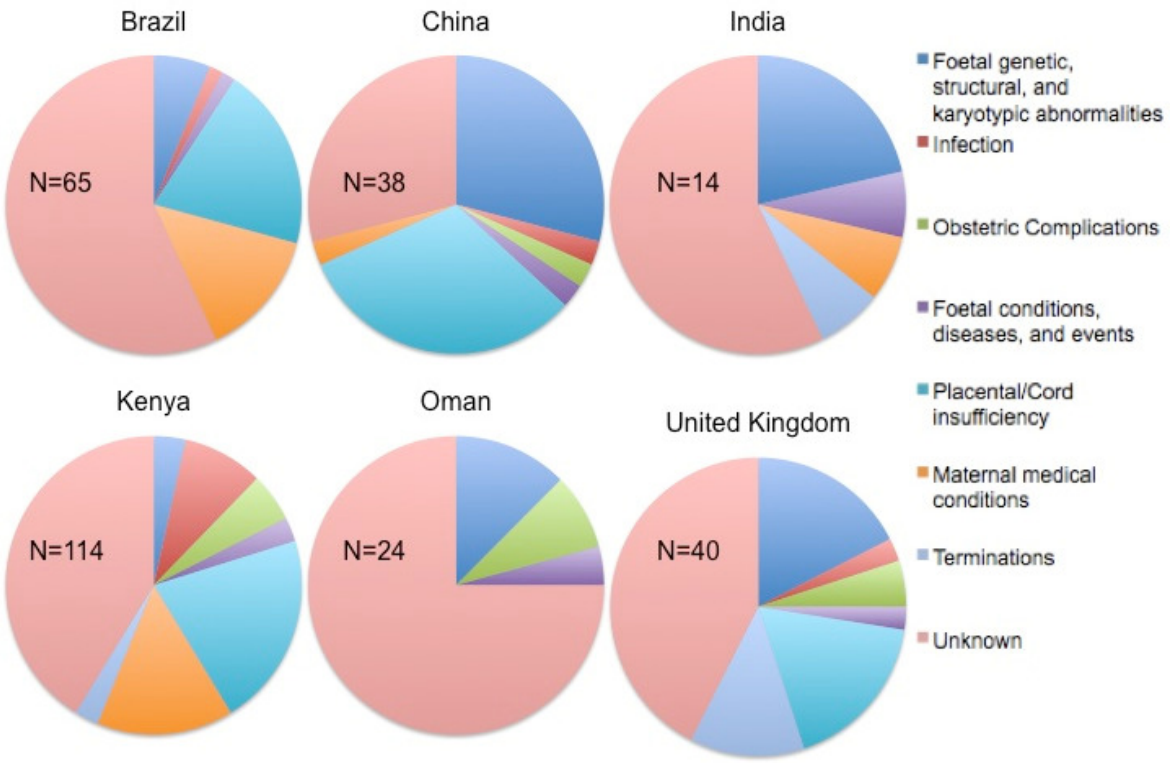

Figure 4. Cause of stillbirth by gestational age, 2009-2012.

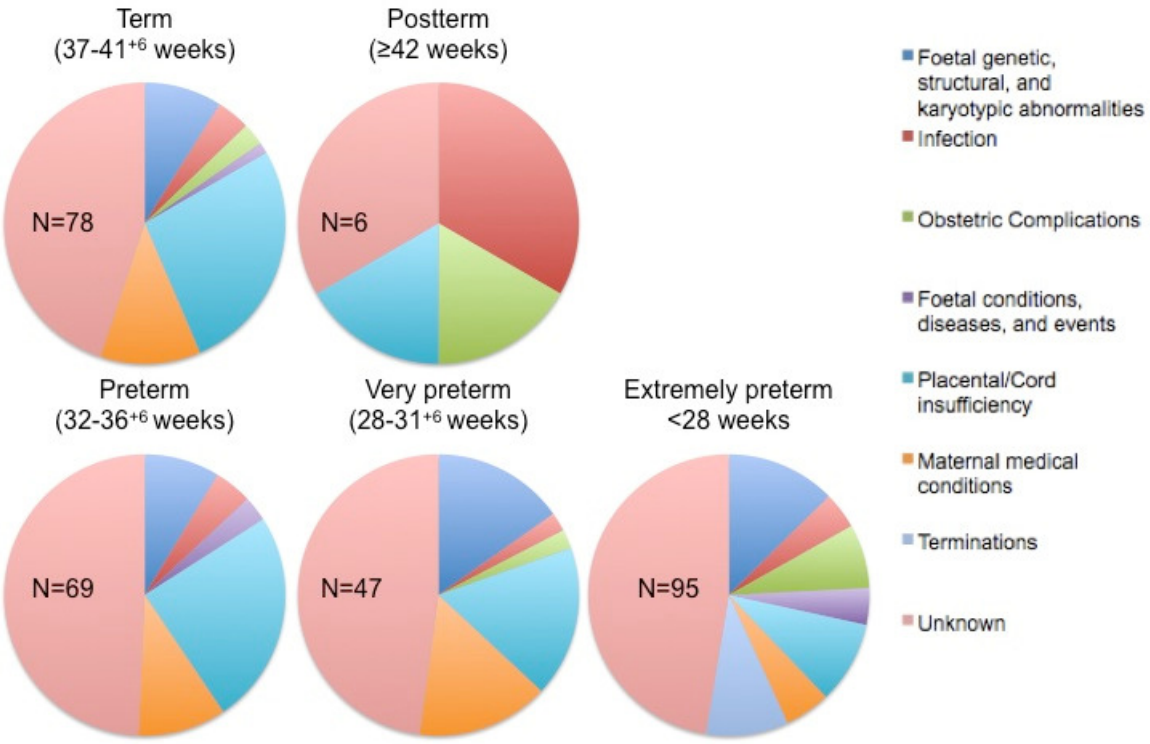

Figure 5. Cause of stillbirth by foetal birth weight, 2009-2012.

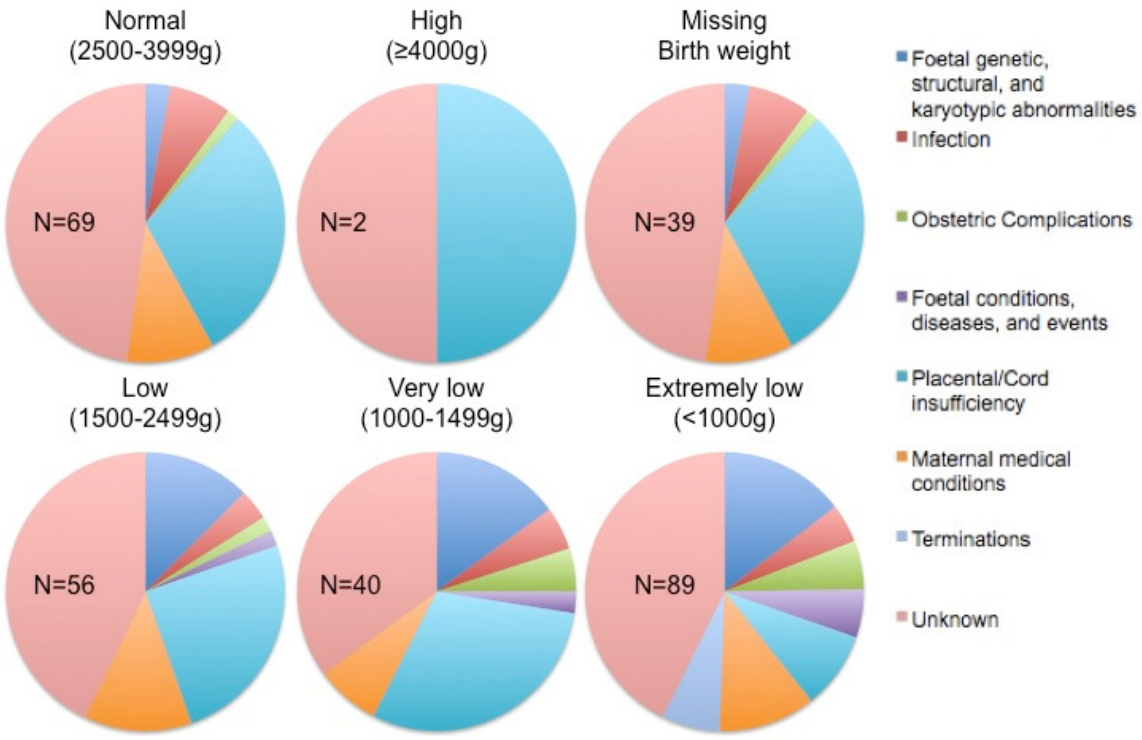

Table 1. Explanation of causes of stillbirth, 2009-2012.

	Overall n (% total stillbirths)	Antepartum n (% antepartum stillbirths)	Intrapartum n (% intrapartum stillbirths)
Foetal genetic, structural, and karyotypic abnormalities			
Chromosomal	2 (0.7)	2 (0.9)	--
Structural	30 (10.2)	22 (9.8)	8 (11.3)
Infection			
Syphilis	1 (0.3)	1 (0.5)	--
HIV/AIDS	1 (0.3)	--	1 (1.4)
Malaria	1 (0.3)	1 (0.5)	--
Toxoplasmosis	1 (0.3)	1 (0.5)	--
Sepsis	1 (0.3)	4 (1.8)	--
Acute chorioamnionitis	6 (2.0)	2 (0.9)	4 (5.6)
Puerperal infections	1 (0.3)	1 (0.5)	--
Respiratory infections	1 (0.3)	1 (0.5)	--
Obstetric Complications			
PROM	5 (1.7)	4 (1.8)	1 (1.4)
Uterine rupture	1 (0.3)	--	1 (1.4)
Prolonged labour	1 (0.3)	--	--
Post-term pregnancy	2 (0.7)	1 (0.5)	1 (1.4)
Direct foetal trauma	1 (0.3)	1 (0.5)	--
Contraception related death	1 (0.3)	1 (0.5)	--
Foetal conditions, diseases, and events			
APS	3 (1.0)	1 (0.5)	1 (1.4)
Meconium aspiration	2 (0.7)	1 (0.5)	--
Incompatibility	1 (0.3)	1 (0.5)	1 (1.4)
Hydrops fetalis	2 (0.7)	2 (0.9)	--
Placental/Cord insufficiency			
Abruptio placentae	17 (5.8)	13 (5.8)	4 (5.6)
Placental praevia	3 (1.0)	2 (0.9)	1 (1.4)
Placental abnormalities, insufficiencies	7 (2.4)	6 (2.7)	1 (1.4)
Twin-twin Transfusion	4 (1.4)	2 (0.9)	2 (2.8)
Cord knots, strictures, and torsions	6 (2.0)	5 (2.2)	1 (1.4)
Cord entrapment w/ occlusion	2 (0.7)	2 (0.9)	--
Cord around neck/body	11 (3.7)	8 (3.6)	3 (4.2)
Cord malformations	4 (1.4)	4 (1.8)	--
Cord prolapse	2 (0.7)	1 (0.5)	1 (1.4)
Maternal medical conditions			
Maternal hypertension	7 (2.4)	7 (3.1)	--
Severe PET/HELLP Syndrome	17 (5.8)	13 (5.8)	4 (5.6)
Gestational diabetes	3 (1.9)	2 (0.9)	1 (1.4)
Maternal death	1 (0.3)	1 (0.5)	--
Terminations			
After diagnosis of congenital abnormality	6 (2.0)	5 (2.2)	1 (1.4)
Due to pregnancy complications	3 (1.0)	2 (0.9)	1 (1.4)
Unknown	138 (46.8)	106 (47.3)	32 (45.1)

Table 2. Explanation of causes of stillbirth by site, 2009-2012.

	Brazil n (% total stillbirths)	China	India	Kenya	Oman	United Kingdom
Foetal genetic, structural, and karyotypic abnormalities						
Chromosomal	--	2 (5.3)	--	--	--	--
Structural	4 (6.2)	9 (23.7)	3 (21.4)	4 (3.5)	3 (12.5)	7 (17.5)
Infection						
Syphilis	1 (1.5)	--	--	--	--	--
HIV/AIDS	--	--	--	1 (0.9)	--	--
Malaria	--	--	--	1 (0.9)	--	--
Toxoplasmosis	--	--	--	1 (0.9)	--	--
Sepsis	--	--	--	1 (0.9)	--	--
Acute chorioamnionitis	--	--	--	6 (5.3)	--	--
Puerperal infections	--	--	--	--	--	1 (2.5)
Respiratory infections	--	1 (2.6)	--	--	--	--
Obstetric Complications						
PROM	--	1 (2.6)	--	3 (2.6)	--	1 (2.5)
Uterine rupture	--	--	--	--	--	1 (2.5)
Prolonged labour	--	--	--	1 (0.9)	--	--
Post-term pregnancy	--	--	--	--	2 (8.3)	--
Direct foetal trauma	--	--	--	1 (0.9)	--	--
Contraception related death	--	--	--	1 (0.9)	--	--
Foetal conditions, diseases, and events						
APS	--	--	--	2 (1.8)	--	1 (2.5)
Meconium aspiration	1 (1.5)	--	--	--	--	--
Incompatibility	--	--	--	1 (0.9)	--	--
Hydrops fetalis	--	--	1 (7.1)	--	1 (4.2)	--
Placental/Cord insufficiency						
Abruptio placentae	5 (7.7)	4 (10.5)	--	5 (4.4)	--	3 (7.5)
Placental praevia	--	1 (2.6)	--	1 (0.9)	--	1 (2.5)
Placental abnormalities, insufficiencies	2 (3.1)	--	--	4 (3.5)	--	1 (2.5)
Twin-twin Transfusion	1 (1.5)	2 (5.3)	--	--	--	1 (2.5)
Cord knots, strictures, and torsions	1 (1.5)	1 (2.6)	--	3 (2.6)	--	1 (2.5)
Cord entrapment w/ occlusion	--	--	--	2 (1.8)	--	--
Cord around neck/body	--	4 (10.5)	--	7 (6.1)	--	--
Cord malformations	4 (6.2)	--	--	--	--	--
Cord prolapse	--	--	--	2 (1.8)	--	--
Maternal medical conditions						
Maternal hypertension	6 (9.2)	--	1 (7.1)	--	--	--
Severe PET/HELLP Syndrome	3 (4.6)	1 (2.6)	--	13 (11.4)	--	--
Gestational diabetes	--	--	--	3 (2.6)	--	--
Maternal death	--	--	--	1 (0.9)	--	--
Terminations						
After diagnosis of congenital abnormality	--	--	1 (7.1)	2 (1.8)	--	3 (7.5)
Due to pregnancy complications	--	--	--	1 (0.9)	--	2 (5.0)
Unknown	37 (56.9)	11 (29.0)	8 (57.1)	47 (41.2)	18 (75.0)	17 (42.5)

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Conclusions

The findings presented here are an attempt to further explain the risk factors and causes of stillbirth. Given the extensive number of variables included in the INTERGROWTH-21st study, it was possible to explore a broad range of demographic, socioeconomic, nutritional, medical, and pregnancy characteristics and their relations to stillbirth. Through the foetal death supplementary form, I was able to gather additional data in order to assign causes of death. Therefore, I have been able to conduct a stillbirth prevalence study across countries with a significantly broader scope of variables than previous stillbirth analyses.

In addition to the contributions to the understanding of stillbirth in general, this study has led to improved efforts to monitor stillbirth within the INTERGROWTH-21st collaborating sites.

The demographic, socioeconomic, and nutritional analyses presented in Chapter I add to the understanding of the risks factors for stillbirth. As found in previous studies, low socioeconomic status, extreme maternal age, and maternal substance abuse (alcohol, tobacco, and recreational drugs) during pregnancy increased the risk of stillbirth. High maternal body mass index has also previously been associated with increased stillbirth risk, however no such relation was found here. Further research is needed to identify regional, cultural, and ethnic variations in the relation between obesity and stillbirth. In addition, the complete aetiological pathways between these demographic, socioeconomic, and nutritional characteristics and stillbirth are still not completely understood. In Chapters II-V, I attempted to explain parts of these pathways by searching for clinical correlates.

In Chapter III, I identified several maternal medical conditions that were each independently associated with increased risk of stillbirth, all of which are preventable to some extent. The data suggested that maternal medical conditions, if well monitored

during pregnancy, have little effect on stillbirth outcome. However, when women are clinically diagnosed or treated for several diseases during pregnancy, stillbirth risk increases significantly. Malaria, syphilis, and HIV/AIDS increased the risk for stillbirth by approximately 9, 7, and 6 times, respectively, when diagnosed or treated during pregnancy.

Future research assessing the possible relation between maternal illnesses of varying severity to stillbirth could allow clinicians to better target at-risk populations. Doing this will likely require case-control studies with the statistical power to examine the effect of rare diseases. As aforementioned, it is plausible that the findings presented in Chapter III are reflective of the importance of disease management. It will be necessary to explore the role of clinical care and disease management of these maternal illnesses on stillbirth outcome in further studies to identify best available practices and target new treatments.

I have identified several associations between pregnancy, delivery, and birth characteristics and stillbirth in Chapter IV. Breech birth, for example, was associated with a 400% increase in stillbirth risk, relative to cephalic presentation, present in 3.5% of the population. Much of this risk was attenuated by Caesarean delivery. Given the knowledge available about safe delivery of breech infants, this suggests that adherence to best practices could lead to significant benefits.

The results from Chapter IV also show the severe effect of hypertensive disorders such as preeclampsia, eclampsia, and HELLP syndrome. Further research into the aetiology of these disorders, and implementation of low cost interventions shown to be effective such as calcium, aspirin, and magnesium sulphate in antenatal and clinical settings could further reduce stillbirth rates.

In Chapter V, I attempted to further understand the independent roles of low birth weight and preterm birth on stillbirth risk. This is a difficult task as these factors could be

causal but also consequences of stillbirth.

The cause of stillbirth was often unknown and when a cause of death was available in maternal medical records, it was typically unclear what, if any, assessment had been completed. Post-mortem workups were not completed for every stillborn infant and the extent of investigation into these deaths varied within and among sites. For those cases where sufficient information was available, placental/ cord insufficiency and congenital abnormalities were the leading causes of death. These disorders lead to early, antepartum stillbirths, whose prevention remains difficult to impossible. The third leading cause of death was maternal medical conditions, which when managed properly, can often be a non-factor in pregnancy outcome.

There were several limitations to this thesis. First, the INTERGROWTH-21st Project was not designed to investigate the epidemiology of stillbirth. Therefore, the INTERGOWTH-21st sites did not conduct post-mortem examinations on each stillborn infant, examine placentas, or consistently report early stillbirth. I attempted to address this shortcoming with the Foetal Death Supplementary Form. However, it became clear that the causes of death attributed to stillborn infants were often based on little evidence. Umbilical cords, for example, are often wrapped around infants and have knots in healthy infants. In the same sense, placentas will often have infarcts and discoloration in normal pregnancies as well as stillbirth cases. In this study, I required that additional information be included in order to consider such disorders a cause of death. Still, more consistent investigation of placentas, infections, etc. in both normal and poor outcome pregnancies would improve the ability to assess cause of stillbirth.

Second, there were, thankfully, few stillbirths within the NCSS. This limited the statistical power of this thesis. Therefore, the analyses conducted using rare exposures often failed to reach statistical significance and/or had wide 95% confidence intervals. Still, the aim of this thesis was identify potential major stillbirth risks to the

INTERGROWTH-21st population and the number of stillbirth events in the NCSS was sufficient for this task.

Third, although the INTERGROWTH-21st Project sites are in 8 different countries, I did not adjust for centres in this thesis. All centres were selected to participate in the Project because of the quality of care provided, along with a range of criteria mentioned in the thesis. There is likely to be some difference in stillbirth risk by site. However, the aim of this thesis was to identify the potential risk factors that explain the general stillbirth in the NCSS, not to identify and explain excess stillbirth in centres. There also was not enough statistical power to adjust for centre given the low number of stillbirths in the NCSS.

Fourth, the NCSS is retrospective and did not begin following mothers at a consistent date. Several women came to the hospital for the first time when they delivered. Therefore, data was collected in some cases after a stillbirth had already occurred. This could have introduced memory bias into the thesis. These women were also less likely to offer medical history and as a result, those with missing data in this thesis were more likely to have a stillborn infant than those with complete medical records.

This study has identified several areas that could benefit from future research. A combination of further studies such as this one that record stillbirth and the causes of death in pregnancy cohorts, as well as larger studies relying upon registry data will be necessary to continue to understand where the remaining stillbirths in clinical studies are occurring, and potential ways to reduce these deaths. Regardless of study design, stillbirth needs to be included as an outcome variable in more perinatal and pregnancy studies in order for antepartum stillbirth rates to decline. The findings presented here and in similar studies should be used to guide future research into further explaining the epidemiology and aetiology of stillbirth toward its prevention.

Appendix I – NCSS Pregnancy & Delivery Form

INTERGROWTH-21ST — UNIVERSITY OF OXFORD

NEWBORN CROSS SECTIONAL STUDY
FETAL GROWTH LONGITUDINAL STUDY
Pregnancy and Delivery

DEV

Study Subject Number 0 1 – _____ **Study Hospital Code** 0 1 – _____

Maternal Hospital Record Number _____

Please answer all yes/no questions by placing an 'x' in the corresponding box

1. Is the woman part of the Fetal Growth Longitudinal Study? yes no
2. **If yes, please obtain the Study Subject Number for the Fetal Growth Longitudinal Study and alert the study coordinator** 0 1 – _____

Section 1: Demographic, socioeconomic and nutritional characteristics

3. Age _____
4. Maternal height (cm) _____ . _____ cm
5. 1st trimester or pre-pregnancy weight (kg) _____ . _____ kg
6. Has she smoked/chewed tobacco during this pregnancy? yes no
7. if she smoked cigarettes, how many per day? _____
8. Has she used any recreational drugs during this pregnancy? yes no
9. Has she had 5 or more units of alcohol per week, on average, during this pregnancy? (1 unit = small glass (125ml) of wine or one bottle/can (330ml) of beer) yes no
10. Has she been involved in any high risk occupation and/or vigorous or contact sport during her pregnancy? (see table) yes no
11. Has she followed any special diets during her pregnancy e.g. vegetarian with no animal products, weight loss programme, malabsorption treatment, gluten-free diet? (see table) yes no
12. *Country specific, see attached sheet* yes no
13. Current marital status (please cross one box only) Single ☐ Widowed ☐ Married/Cohabiting ☐ Separated/Divorced ☐
14. Total number of years of formal education _____
15. Highest level of education she attended? (please cross one box only) Primary ☐ Professional/ technical training ☐ Secondary ☐ University ☐
16. Which of the following best describes her occupational status? (please cross one box only) Housework ☐ Skilled manual work ☐ Manager/professional/technical ☐ Unskilled manual work ☐ Clerical support, service or sales ☐ Other ☐

Section 2: Medical history

Prior to this pregnancy, was she diagnosed with, or treated for any of the following medical conditions? (cross all that apply)

17. Diabetes yes no
18. Thyroid disease yes no
19. Other endocrinological conditions yes no
20. Cardiac disease yes no
21. Hypertension/chronic hypertension yes no
22. Chronic respiratory disease (including chronic asthma) yes no
23. Proteinuria, kidney disease or chronic renal disease yes no
24. Any type of malignancy/cancer yes no
25. Lupus erythematosus yes no
26. Any hematologic condition including sickle-cell anaemia or leukaemia yes no
27. Epilepsy yes no
28. HIV or AIDS yes no
29. Malaria yes no
30. Tuberculosis yes no
31. Crohn's disease, coeliac disease, ulcerative colitis or any severe malabsorption condition yes no
32. Any congenital abnormality yes no
33. Other clinically relevant condition yes no

INTERGROWTH-21ST	NEWBORN CROSS SECTIONAL STUDY FETAL GROWTH LONGITUDINAL STUDY **Pregnancy and Delivery**	DEV Page 2 of 5

Study Subject Number 0 1 – | | | | |

Study Hospital Code 0 1 – | |

Maternal Hospital Record Number | | | | | | | | | |

Section 3: Gynaecological history

34. Did she have regular (24-32 day) menstrual cycles in the 3 months prior to her pregnancy? yes no

35. Has she used hormonal contraceptives or been breastfeeding in the 2 months prior to her current pregnancy? yes no

36. Was this pregnancy conceived with fertility treatment? yes no

37. First day of the last menstrual period (LMP) Date D D – M M – Y Y

38. Was she certain of her date of LMP? yes no

39. Date of the first ultrasound scan during this pregnancy Date D D – M M – Y Y

40. What was the CRL(crown rump length) measurement at the first ultrasound scan? | | | . | | mm

41. What was the BPD(biparietal diameter) measurement at the first ultrasound scan? | | | . | | mm

42. Estimated gestational age at the first ultrasound scan | | Weeks | | Days

Section 4: Obstetric history

43. Number of previous pregnancies, excluding the present pregnancy (if 0, skip to Section 5) | |

44. Have her last two pregnancies before this one ended in miscarriage? yes no

45. How many previous births has she had, excluding this birth (if 0, skip to Section 5)? | |

46. Have ANY of her other babies weighed less than 2.5kg or more than 4.5kg? yes no

47. Have ANY of her other babies been born preterm (<37 weeks gestation)? yes no

48. Has she had ANY previous stillbirths or neonatal deaths? yes no

Section 5: Clinical conditions

During this pregnancy was she diagnosed with, or treated for, any of the following conditions (cross all that apply)

49. Cardiac disease yes no

50. Chronic respiratory disease (including chronic asthma) yes no

51. Malaria yes no

52. Mental illness e.g. depression yes no

53. Epilepsy yes no

54. Thyroid disease or any other endocrinological condition yes no

55. Lower urinary tract infection requiring antibiotic treatment yes no

56. Pyelonephritis yes no

57. Respiratory tract infection requiring antibiotic/antiviral treatment yes no

58. Any other infection requiring antibiotic/antiviral treatment yes no

59. Positive syphilis test yes no

60. HIV or AIDS yes no

61. Any sexually transmitted infection yes no

62. Any type of malignancy or cancer yes no

63. Any other medical/surgical condition requiring treatment or referral yes no

INTERGROWTH-21ST UNIVERSITY OF OXFORD	NEWBORN CROSS SECTIONAL STUDY FETAL GROWTH LONGITUDINAL STUDY **Pregnancy and Delivery**	**DEV** Page 3 of 5

Study Subject Number 0 1 – _____ **Study Hospital Code** 0 1 – _____

Maternal Hospital Record Number _____

Section 6: Pregnancy related complications

During this pregnancy was she diagnosed with, or treated for, any of the following conditions (cross all that apply)

64.	Severe vomiting requiring hospitalisation	yes / no	71.	Severe preeclampsia/ Eclampsia/HELLP syndrome	yes / no
65.	Gestational diabetes	yes / no	72.	Rhesus disease	yes / no
66.	Vaginal bleeding before 15 weeks	yes / no	73.	Preterm labour	yes / no
67.	Vaginal bleeding at 15-27 weeks	yes / no	74.	Fetal distress	yes / no
68.	Vaginal bleeding after 27 weeks	yes / no	75.	Suspected impaired fetal growth or small for gestational age	yes / no
69.	Pregnancy-induced hypertension	yes / no	76.	Any other pregnancy related condition requiring treatment or referral	yes / no
70.	Preeclampsia	yes / no			

77. Lowest haemoglobin level (if available) — <15 weeks: __ . __ g/dl; 15-27 weeks: __ . __ g/dl; >27 weeks: __ . __ g/dl

Section 7: Nutritional supplements / Medications

During this pregnancy, has she routinely taken any of the following supplements?

78.	Iron	yes / no	81.	Food supplements	yes / no
79.	Folic acid	yes / no	82.	Multi-vitamins/minerals	yes / no
80.	Calcium	yes / no			

During this pregnancy, has she taken any of the following medications?

83.	Routine aspirin	yes / no	87.	Insulin	yes / no
84.	Any antibiotics or antivirals (except those used for PROM)	yes / no	88.	Prophylactic steroids for preterm labour	yes / no
85.	Antibiotics used for PROM	yes / no	89.	Any other treatment	yes / no
86.	Non-steroidal anti-inflammatories	yes / no			

Section 8: Delivery

90. Onset of labour (cross one box only)
Spontaneous ☐ Induced ☐ No Labour ☐

91. Did she have pre-labour rupture of membranes (PROM)? yes / no

92. Mode of delivery (cross one box only)
Vaginal spontaneous ☐ Assisted breech or breech extraction ☐
Vaginal assisted (e.g. forceps, vacuum) ☐ Caesarean section ☐

If labour was induced or a caesarean section was performed please cross all indications that apply

93.	Vaginal bleeding	yes / no	103.	Suspected impaired fetal growth or small for gestational age	yes / no
94.	Fetal death	yes / no	104.	Post term (>42 weeks gestation)	yes / no
95.	Pregnancy-induced hypertension	yes / no	105.	Rhesus disease	yes / no
96.	Preeclampsia	yes / no	106.	HIV or AIDS	yes / no
97.	Severe preeclampsia/ Eclampsia/HELLP Syndrome	yes / no	107.	Any sexually transmitted infections	yes / no
98.	Breech presentation	yes / no	108.	Any infections requiring antibiotic/antiviral treatment	yes / no
99.	Fetal distress	yes / no	109.	Maternal request	yes / no
100.	Failure to progress	yes / no	110.	Any other maternal reason	yes / no
101.	Cephalo-pelvic disproportion	yes / no	111.	Any other fetal reason	yes / no
102.	Prelabour rupture of membranes (PROM)	yes / no	112.	Previous caesarean section	yes / no

INTERGROWTH-21ST UNIVERSITY OF OXFORD	NEWBORN CROSS SECTIONAL STUDY FETAL GROWTH LONGITUDINAL STUDY **Pregnancy and Delivery**	**DEV** Page 4 of 5

Study Subject Number 0 1 – _____ **Study Hospital Code** 0 1 – _____

Maternal Hospital Record Number _____

Section 9: Newborn outcomes and care

113. Date of delivery D D – M M – Y Y

114. Time of delivery (24hr clock) H H : M M

115. Number of babies _____

If more than 1 baby, complete another Pregnancy and Delivery form, (section 9 to 12 only).

116. Gestational age at birth based on the best obstetric estimate _____ wks _____ days

For women in the FGLS study, if the gestational age at birth is <37 weeks please contact study coordinator for the *Preterm Postnatal Follow-up Study*

117. Fetal presentation at delivery (cross one box only)

Cephalic ☐ Breech ☐ Other ☐

118. Apgar score at 5 minutes _____

119. Newborn status at birth (cross one box only)

Alive ☐ Intrapartum death ☐ Antepartum death ☐

120. Newborn sex Male ☐ Female ☐

121 Was the newborn admitted to intensive care or any special care unit? yes no

122. Total amount of days spent in intensive care or special care unit (if less than 24hrs please enter 1 day) _____ days

Was the newborn diagnosed with or treated for any of the following conditions before hospital discharge?

123. Respiratory distress syndrome	yes	no	134. Necrotising enterocolitis, stage 2 or greater	yes	no
124. Transient tachypnea of the newborn	yes	no	135. Seizures	yes	no
125. Apnea of prematurity	yes	no	136. Hypoglycaemia	yes	no
126. No oral feeds for more than 24hrs	yes	no	137. Intraventricular haemorrhage grade 2 or greater/ periventricular haemorrhage/leukomalacia	yes	no
127. Bronchopulmonary dysplasia	yes	no	138. Hypotension requiring ionotropic treatment or steroids	yes	no
128. Retinopathy of prematurity	yes	no	139. Anaemia (requiring transfusion)	yes	no
129. Meconium aspiration with respiratory distress	yes	no	140. Patent ductus arteriosus (requiring pharmacological treatment or surgery)	yes	no
130. Hypoxic-ischaemic encephalopathy	yes	no	141. Polycythaemia	yes	no
131. Hyperbilirubinaemia	yes	no	142. Any other serious condition	yes	no
132. TORCH or any other intrauterine infections	yes	no	143. Congenital abnormality (complete a **neonatal abnormality form**)	yes	no
133. Neonatal sepsis	yes	no			

Section 10: Newborn anthropometry (please carry out as soon as possible, no later than 24 hours after birth)

144. Date of measurement D D – M M – Y Y

145. Time of measurement (24 hr clock) H H : M M

	1st set of anthropometric measurements	Repeat measurements, if required	Repeat measurements, if required
146. Weight	_____ . _____ kgs	_____ . _____ kgs	_____ . _____ kgs
147. Length	_____ . _____ cm	_____ . _____ cm	_____ . _____ cm
148. Head circumference	_____ . _____ cm	_____ . _____ cm	_____ . _____ cm

Study Subject Number 0 1 – | **Study Hospital Code** 0 1 –

Maternal Hospital Record Number

Section 10: Newborn anthropometry (continued)

	2nd set of anthropometric measurements	Repeat measurements, if required	Repeat measurements, if required
149. Weight	. kgs	. kgs	. kgs
150. Length	. cm	. cm	. cm
151. Head circumference	. cm	. cm	. cm

Section 11: Newborn outcomes

152. Newborn status at hospital discharge

Alive ☐ Alive but referred to a higher level of care ☐ Dead ☐

153. Date of hospital neonatal hospital discharge or date of death D D – M M – Y Y

Section 12: Nutritional practices

154. What was the main mode of feeding in the 24hrs prior to hospital discharge? (cross one box only)

Exclusive breast milk ☐ | Predominant breast milk ☐ | Partial breast milk ☐ | Exclusive formula ☐

Section 13: Maternal outcomes

155. Was the mother admitted to intensive care or any special care unit after delivery? yes ☐ no ☐

156. If yes total number of days (if less than 24 hours, please enter as 1 day) ☐☐ days

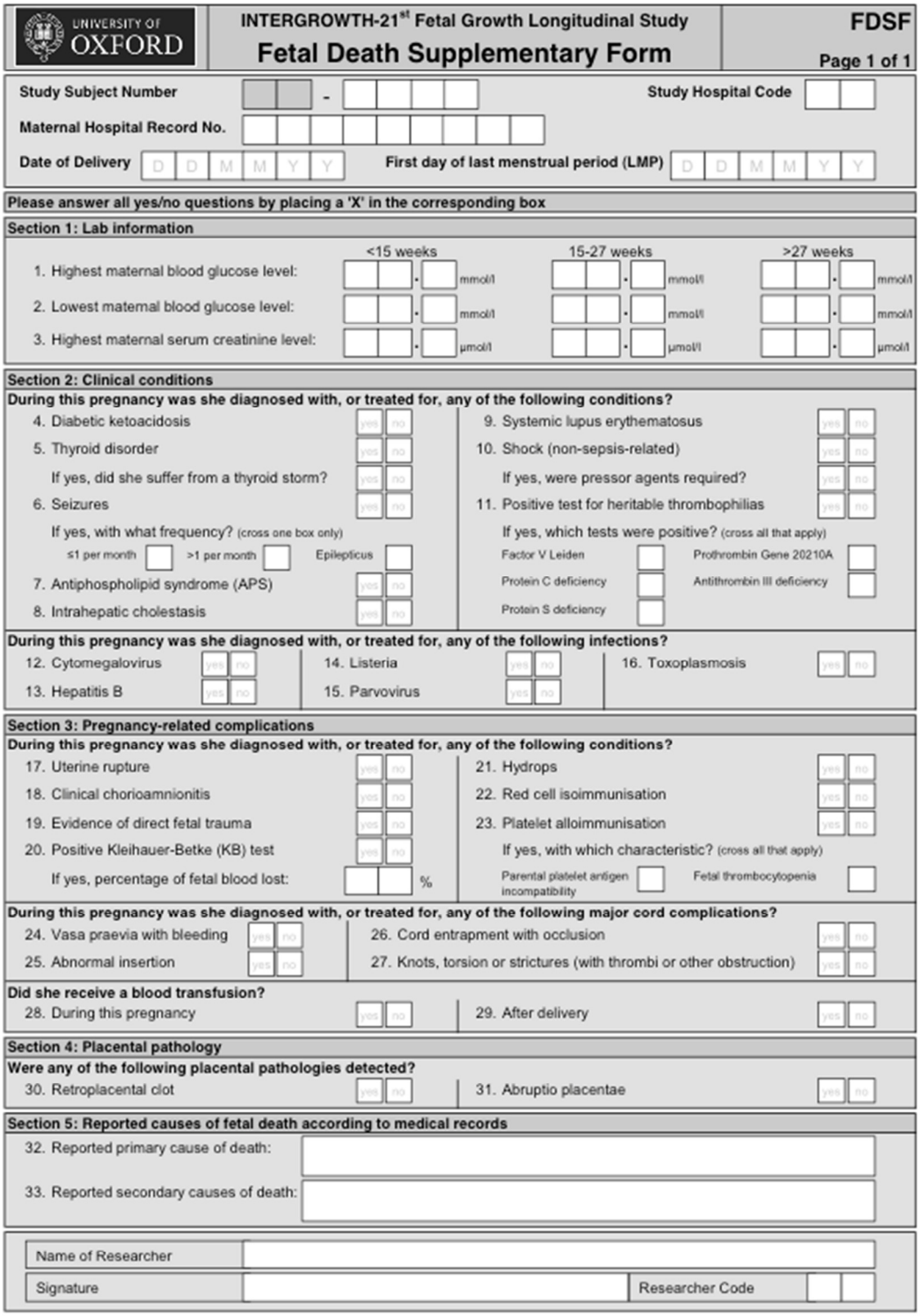
157. Maternal status at hospital discharge Alive ☐ Alive but referred to a higher level of care ☐ Dead ☐

Name of Researcher			
Signature			
Researcher Code	☐☐	Date of interview	D D – M M – Y Y
Code of 1st anthropometrist	☐☐	Code of 2nd anthropometrist	☐☐

Appendix II – High risk occupation and/or vigorous or contact sport

Frequent exposure to the following chemicals or toxic substances:	**Physically demanding work:**	**High-risk sports/vigourous excercise:**
Pesticides Lead or Mercury Solvents Petrochemicals Anaesthetic gases Tetrachloroethylene	More than 7 hours standing per day More than 50 hours work per week Work involving heavy lifting or very awkward postures	Sports that involve a high risk of abdominal trauma, falls or excessive joint stress (e.g. martial arts, rugby, long-distance running or cycling, weight-lifting) Women planning to do 1 hour of vigourous exercise more than 4 times per week into the 2nd half of pregnancy

Appendix III – Foetal Death Supplementary Form



UNIVERSITY OF OXFORD

INTERGROWTH-21st Fetal Growth Longitudinal Study

Fetal Death Supplementary Form

FDSF

Page 1 of 1

Study Subject Number ___ - ____ **Study Hospital Code** ____

Maternal Hospital Record No. _____

Date of Delivery D D M M Y Y **First day of last menstrual period (LMP)** D D M M Y Y

Please answer all yes/no questions by placing a 'X' in the corresponding box

Section 1: Lab information

	<15 weeks	15-27 weeks	>27 weeks
1. Highest maternal blood glucose level:	___.___ mmol/l	___.___ mmol/l	___.___ mmol/l
2. Lowest maternal blood glucose level:	___.___ mmol/l	___.___ mmol/l	___.___ mmol/l
3. Highest maternal serum creatinine level:	___.___ µmol/l	___.___ µmol/l	___.___ µmol/l

Section 2: Clinical conditions

During this pregnancy was she diagnosed with, or treated for, any of the following conditions?

4. Diabetic ketoacidosis yes no
5. Thyroid disorder yes no
   If yes, did she suffer from a thyroid storm? yes no
6. Seizures yes no
   If yes, with what frequency? (cross one box only)
   ≤1 per month ☐ >1 per month ☐ Epilepticus ☐
7. Antiphospholipid syndrome (APS) yes no
8. Intrahepatic cholestasis yes no
9. Systemic lupus erythematosus yes no
10. Shock (non-sepsis-related) yes no
    If yes, were pressor agents required? yes no
11. Positive test for heritable thrombophilias yes no
    If yes, which tests were positive? (cross all that apply)
    Factor V Leiden ☐ Prothrombin Gene 20210A ☐
    Protein C deficiency ☐ Antithrombin III deficiency ☐
    Protein S deficiency ☐

During this pregnancy was she diagnosed with, or treated for, any of the following infections?

12. Cytomegalovirus yes no
13. Hepatitis B yes no
14. Listeria yes no
15. Parvovirus yes no
16. Toxoplasmosis yes no

Section 3: Pregnancy-related complications

During this pregnancy was she diagnosed with, or treated for, any of the following conditions?

17. Uterine rupture yes no
18. Clinical chorioamnionitis yes no
19. Evidence of direct fetal trauma yes no
20. Positive Kleihauer-Betke (KB) test yes no
    If yes, percentage of fetal blood lost: __ %
21. Hydrops yes no
22. Red cell isoimmunisation yes no
23. Platelet alloimmunisation yes no
    If yes, with which characteristic? (cross all that apply)
    Parental platelet antigen incompatibility ☐ Fetal thrombocytopenia ☐

During this pregnancy was she diagnosed with, or treated for, any of the following major cord complications?

24. Vasa praevia with bleeding yes no
25. Abnormal insertion yes no
26. Cord entrapment with occlusion yes no
27. Knots, torsion or strictures (with thrombi or other obstruction) yes no

Did she receive a blood transfusion?

28. During this pregnancy yes no
29. After delivery yes no

Section 4: Placental pathology

Were any of the following placental pathologies detected?

30. Retroplacental clot yes no
31. Abruptio placentae yes no

Section 5: Reported causes of fetal death according to medical records

32. Reported primary cause of death:
33. Reported secondary causes of death:

Name of Researcher

Signature Researcher Code

INTERGROWTH-21st

International Fetal and Newborn Growth Standards for the 21st Century

The International Fetal and Newborn Growth Consortium

Fetal Death Supplementary Form

OPERATION MANUAL

December 2011

UNIVERSITY OF OXFORD

Please read this manual carefully and refer to it throughout the study if any clarification is needed

This Operations Manual was produced by the International Fetal and Newborn Growth Consortium, based on the INTERGROWTH-21st protocol.
www.intergrowth21.org.uk
INTERGROWTH-21st is a large project involving health institutions from eight geographically diverse countries. It is therefore essential that the participating institutions follow the same data collection procedures. This manual is designed to familiarize all staff involved in the study and its implementation with the study procedures for patient selection, data collection and general methodological issues.

Introduction

The causes of many fetal deaths remain largely unknown. Relatively few studies have investigated the epidemiological and biological risk factors of stillbirths, when compared to the breadth of neonatal and infant mortality studies.
This form is meant to gather supplemental information that will be used in conjunction with the Newborn Cross Sectional Study (NCSS) data to better understand the risk factors for fetal death. This supplemental form will be used to collect data on causes of fetal death and assess the presence and severity of maternal illnesses and pregnancy complications.

General Instructions for Form Completion

1. The form should be completed for all cases of fetal death. This includes subjects with 'YES' answered for question 94 and/or 'antepartum death' or 'intrapartum death' for question 119 on the NCSS form.

2. A black ballpoint pen should be used to complete the forms and the writing should be legible and in block capitals where appropriate.

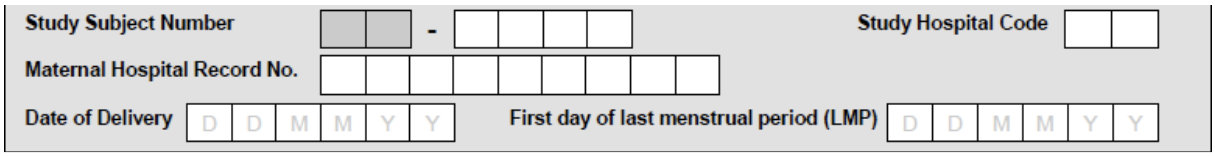
3. Do not write on the forms except in the data boxes. Where there is the option, place a 'X' in boxes that correspond to your answer. Where values need to be written, please write numbers clearly. All dates should be written in the format dd-mm-yy, for example 20th May 2011 should be written 20-05-11.

4. If there is an error made in writing, it must be crossed out, and the correct answer written outside the box and initialed. Correction fluids should not be used.

5. The form header and identification box at the end should only be filled in by the researcher. In the identification box please enter the researcher's name, signature, and their researcher code (provided by the coordinating unit).

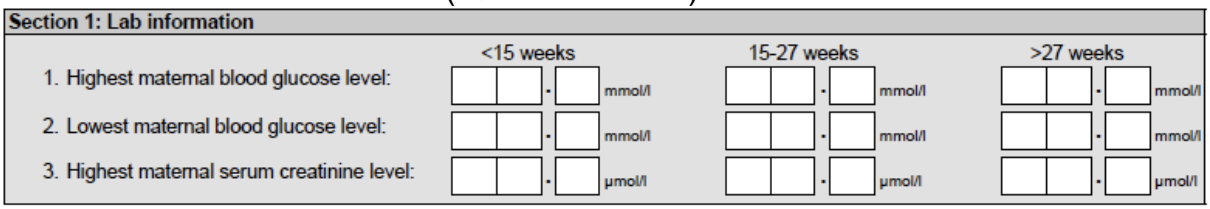
6. It is up to each institution to organize the local arrangements to facilitate this process.

Form Header



Study Subject Number: The first two digits correspond to your country code. For the following four numbers please use the interviewed woman's FGLS number. Please ensure that you enter the correct number as this is vital in enabling us to identify the woman.
Study Hospital Code: Please enter the number of the antenatal clinic (assigned by the coordinating unit) where the woman is interviewed. Please ensure that you enter the correct number from the list as this is vital in enabling us to identify the woman.
Maternal Hospital Record Number: Please enter the woman's unique hospital record number.
Date of Delivery: Please enter the date of the delivery in the format dd-mm-yy, for example, 20th May 2011 should be written 20-05-11. This should be the date of actual delivery and not the date of fetal demise.
LMP: Please enter the first day of the last menstrual period (LMP) for the particular woman. If there is an estimated date of delivery (EDD) and no LMP, then the EDD should be used to estimate the LMP.

Section 1: Lab Information (Questions 1-3)

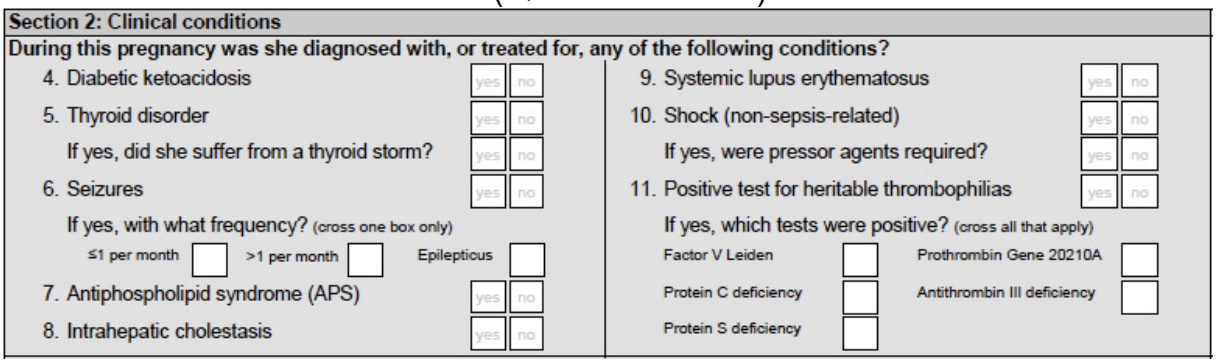


1. **Highest maternal blood glucose**
   In the corresponding boxes, please enter the highest maternal blood glucose level (µmol/L) recorded during the gestational periods of <15 weeks, 15-27 weeks, and >27 weeks.

2. **Lowest maternal blood glucose**
   In the corresponding boxes, please enter the lowest maternal blood glucose level (µmol/L) recorded during the gestational periods of <15 weeks, 15-27 weeks, and >27 weeks.

3. **Highest maternal serum creatinine**
   In the corresponding boxes, please enter the highest maternal serum creatinine level (µmol/L) recorded during the gestational periods of <15 weeks, 15-27 weeks, and >27 weeks.

Section 2: Clinical Conditions (Questions 4-11)



During this pregnancy was she diagnosed with or treated for any of the following conditions?

4. **Diabetic ketoacidosis**
   Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for diabetic ketoacidosis during this pregnancy.
   Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for diabetic ketoacidosis during this pregnancy.

5. **Thyroid disorder**
   Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for thyroid disorder during this pregnancy.
   Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for thyroid disorder during this pregnancy.

   If yes, place an 'X' in the box that says 'YES' if the woman suffered from a thyroid storm. Place an 'X' in the box that says 'NO' if the woman did not suffer from a thyroid storm. Thyroid storm, also referred to as a thyroid crisis, is a potentially life-threatening medical emergency resulting from the release of large amounts of thyroid hormone in a short period of time. This will be documented in any maternal medical records.

6. **Seizures**
   Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for seizures during this pregnancy.
   Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for seizures during this pregnancy.

   If yes, place an 'X' in box next to the ONE option that applies to the woman.
   - ≤1 per month
   - >1 per month
   - Epilepticus

7. **Antiphospholipid syndrome (APS)**
   Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for APS during this pregnancy.

Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for APS during this pregnancy.

8. **Intrahepatic cholestasis**
   Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for intrahepatic cholestasis during this pregnancy.
   Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for intrahepatic cholestasis during this pregnancy.

9. **Systemic lupus erythematosus**
   Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for systemic lupus erythematosus during this pregnancy.
   Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for systemic lupus erythematosus during this pregnancy.

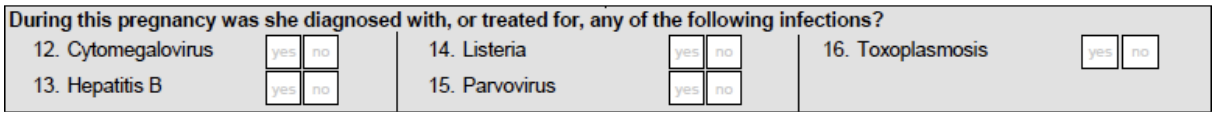
10. **Shock (not sepsis related)**
    Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for shock during this pregnancy.
    Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for shock during this pregnancy.

    If yes, place an 'X' in the box that says 'YES' if the woman was required pressor agents. Place an 'X' in the box that says 'NO' if the woman did not require pressor agents.

11. **Positive test with heritable thrombophilias**
    Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for heritable thrombophilias during this pregnancy.
    Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for heritable thromobophilias during this pregnancy.

    If yes, place an 'X' in ANY box next to a test for which the woman tested positive.
    - Factor V Leiden
    - Prothrombin Gene 20210A
    - Antithrombin III deficiency
    - Protein S deficiency
    - Protein C deficiency

Questions 12-16



During this pregnancy was she diagnosed with or treated for any of the following infections?

12. **Cytomegalovirus**

Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for cytomegalovirus during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for cytomegalovirus during this pregnancy.

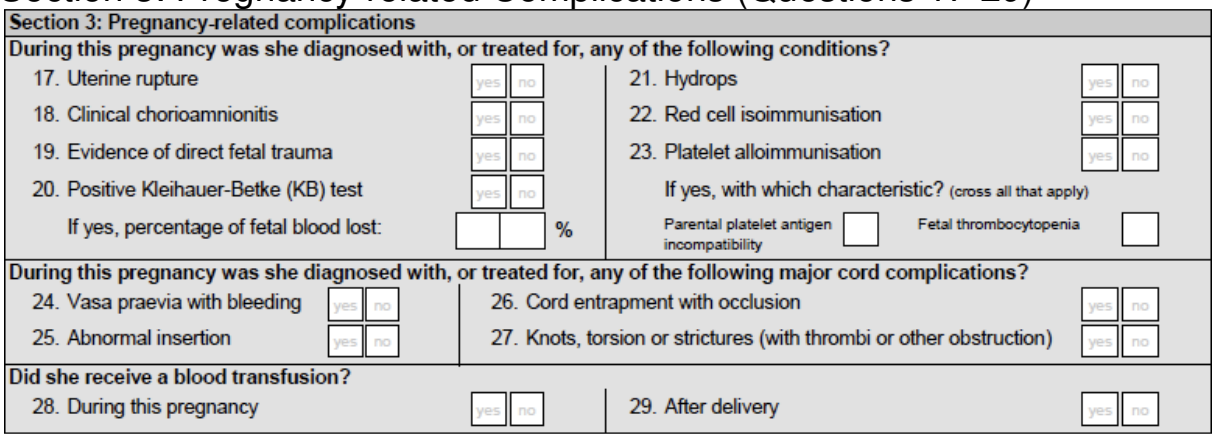
13. **Hepatitis B**
Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for hepatitis B during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for hepatitis during this pregnancy.

14. **Listeria**
Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for listeria during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for listeria during this pregnancy.

15. **Parvovirus**
Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for parvovirus during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for parvovirus during this pregnancy.

16. **Toxoplasmosis**
Place an 'X' in the box that says 'YES' if the woman has been diagnosed with or treated for toxoplasmosis during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman has not been diagnosed with or treated for toxoplasmosis during this pregnancy.

Section 3: Pregnancy-related Complications (Questions 17-29)



During this pregnancy was she diagnosed with, or treated for, any of the following conditions?:

17. **Uterine Rupture**
Place an 'X' in the box that says 'YES' if the woman suffered from uterine rupture during this pregnancy.

Place an 'X' in the box that says 'NO' if the woman did not suffer from uterine rupture during this pregnancy.

18. **Clinical Chorioamnionitis**
    Place an 'X' in the box that says 'YES' if the woman suffered from clinical chorioamnionitis during this pregnancy.
    Place an 'X' in the box that says 'NO' if the woman did not suffer from clinical chorioamnionitis during this pregnancy.

19. **Evidence of direct fetal trauma**
    Place an 'X' in the box that says 'YES' if there was any evidence of direct fetal trauma during this pregnancy.
    Place an 'X' in the box that says 'NO' if there was not any evidence of direct fetal trauma during this pregnancy.

20. **Positive Kleihauer-Betke (KB) test**
    Place an 'X' in the box that says 'YES' if the woman had a positive KB test during this pregnancy.
    Place an 'X' in the box that says 'NO' if the woman had a negative KB test during this pregnancy.

21. **Hydrops**
    Place an 'X' in the box that says 'YES' if there was any evidence of fetal hydrops during this pregnancy.
    Place an 'X' in the box that says 'NO' if there was not any evidence of fetal hydrops during this pregnancy.

22. **Red cell isoimmunization**
    Place an 'X' in the box that says 'YES' if there was any red cell isoimmunization
    Place an 'X' in the box that says 'NO' if there was not any red cell isoimmunization during this pregnancy.

23. **Platelet alloimmunization**
    Place an 'X' in the box that says 'YES' if the woman suffered from platelet alloimmunization during this pregnancy.
    Place an 'X' in the box that says 'NO' if the woman did not suffer from platelet alloimmunization during this pregnancy.

    If yes, place an 'X' in ANY box next to the option that best applies to this pregnancy.
    - ♦ Parental platelet antigen incompatibility
    - ♦ Fetal thrombocytopenia

During this pregnancy was she diagnosed with, or treated for, any of the following major cord complications?:

24. **Vasa praevia with bleeding**
    Place an 'X' in the box that says 'YES' if the woman was diagnosed with, or treated for, vasa praevia with bleeding during this pregnancy.
    Place an 'X' in the box that says 'NO' if the woman was not diagnosed with, or treated for, vasa praevia with bleeding during this pregnancy.

25. **Abnormal insertion**
Place an 'X' in the box that says 'YES' if the woman was diagnosed with, or treated for, abnormal cord insertion during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman was not diagnosed with, or treated for, abnormal cord insertion during this pregnancy.

26. **Cord entrapment with occlusion**
Place an 'X' in the box that says 'YES' if the woman was diagnosed with, or treated for, cord entrapment with occlusion during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman was not diagnosed with, or treated for, cord entrapment with occlusion during this pregnancy.

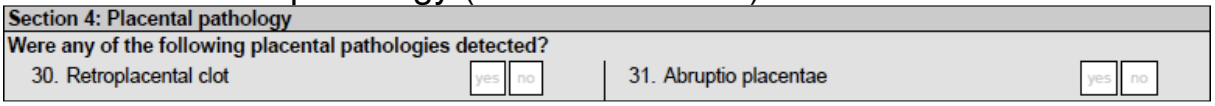
27. **Knots, torsion or strictures (with thrombi or other obstruction)**
Place an 'X' in the box that says 'YES' if the woman was diagnosed with, or treated for, cord knots, torsion or strictures (with thrombi or other obstructions indicating a major complication) during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman was not diagnosed with, or treated for, cord knots, torsion or strictures (with thrombi or other obstructions indicating a major complication) during this pregnancy.

Did she receive a blood transfusion?:

28. **Did she receive a blood transfusion during this pregnancy?**
Place an 'X' in the box that says 'YES' if the woman received a blood transfusion during this pregnancy.
Place an 'X' in the box that says 'NO' if the woman did not receive a blood transfusion during this pregnancy.

29. **After this pregnancy?**
Place an 'X' in the box that says 'YES' if the woman received a blood transfusion after this pregnancy.
Place an 'X' in the box that says 'NO' if the woman did not receive a blood transfusion after this pregnancy.

Section 4: Placental pathology (Questions 30-31)



Were any of the following placental pathologies detected during this pregnancy?

30. **Retroplacental clot**

Place an ‘X’ in the box that says ‘YES’ if there was a retroplacental clot during this pregnancy.
Place an ‘X’ in the box that says ‘NO’ if there was not a retroplacental clot during this pregnancy.

31. **Abruptio Placentae**
Place an ‘X’ in the box that says ‘YES’ if the woman suffered from abruptio placentae during this pregnancy.
Place an ‘X’ in the box that says ‘NO’ if the woman did not suffer from abruptio placentae during this pregnancy.

Section 5: Reported causes of fetal death according to medical records (Question 32-33)

Section 5: Reported causes of fetal death according to medical records	
32. Reported primary cause of death:	
33. Reported secondary causes of death:	

32. **Reported primary cause of death:**
In the corresponding box, please write the primary cause(s) of fetal death given in the medical records.

33. **Reported secondary cause(s) of death:**
In the corresponding box, please write the secondary cause(s) of fetal death given in the medical records.

Completion of the data collection form

Name of Researcher	
Signature	
Researcher Code	

At the end of each form please enter the researcher’s name, signature, and the code assigned to him/her prior to the data collection. This will help the country coordinator to ensure the quality of data and who to go to should a query arise. To avoid confusion, the researcher code will always be ‘99’.