INVESTIGATING STILLBIRTHS IN SOUTH AFRICA

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School of Population and Global Health
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THESIS DECLARATION

I, Tina Lavin, certify that:

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Date: 10th December 2018
STATEMENT OF ORIGINAL CONTRIBUTION

I declare that the work contained within this thesis is my own, except where referenced or acknowledged otherwise. This thesis has not been previously submitted for a degree at this or any other university.

The studies within this thesis were conceptualized by myself in consultation with my doctoral supervisors, Prof David Preen, Dr Lee Nedkoff and Prof Robert Pattinson. I undertook all data analysis in this thesis. I undertook the planning, analysis and writing of all manuscripts and am the primary author on each of the paper, and my contribution to each of these studies is greater than 85%.

This thesis is presented as series of papers and therefore contains published work and work submitted for publication, all of which has been co-authored. The bibliographical details of the work and where each one appears in the thesis are outlined below. The signed co-author permission page can be found in Appendix A.


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ABBREVIATIONS

aOR – adjusted odds ratio
AGA – appropriate-for-gestational-age
AIDS – acquired immunodeficiency syndrome
ANC – antenatal care
APA – antepartum haemorrhage
ART – antiretroviral therapy
BANC – basic antenatal care
BANC-plus – basic antenatal care plus
CNS – central nervous system
CI – confidence interval
cDCF – data capturing form
END – early neonatal death (<7 days life)
GDG - Guideline Development Group
GDP – gross domestic product
GIT – gastro-intestinal tract
HELP - haemolysis, elevated liver enzymes, low platelet count syndrome
HIC – high-income country
HIV – human immunodeficiency virus
HRP – Human Reproduction Program (World Health Organization)
ICD-10 - 10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICD-PM - International Classification of Diseases (ICD-10) to perinatal deaths
ICD-MM - WHO application of the ICD-10 to deaths during pregnancy, childbirth and the puerperium, maternal mortality
IUD – intrauterine death
IUGR – intrauterine growth restriction
LGA – large-for-gestational-age
LMIC – low-to-middle-income-country
MDG – millennium development goal
MNCHW - maternal, neonatal, child and women’s health
NHI – national health insurance
NICHD - National Institute of Child Health and Human Development
OR – odds ratio
PAF - population attributable fraction
PCP pneumonia
PHC – primary health clinic
PMTCT - prevention of mother-to-child transmission
PPIP – Perinatal Problem Identification Program
RCT – randomized controlled trial
RR – relative risk
SGA – small-for-gestational-age
SFH – symphysis fundal height
UK – United Kingdom
UWA – University of Western Australia
UNDP – United Nations Development Programme
UNFPA – United National Population Fund
UNICEF – United Nations International Children's Emergency Fund
WHO-ANC – World Health Organization Antenatal Care Trial
WHO – World Health Organization
ABSTRACT

INTRODUCTION

Reducing stillbirths has remained a global public health challenge. Approximately 55% of stillbirths occur in sub-Saharan Africa and South Africa has a high stillbirth rate that has not declined in over 10 years. Small-for-gestational-age (SGA) babies represent a significant proportion of stillbirths in low-to-middle-income-countries (LMICs). A number of public health strategies have been employed to target the reduction of stillbirths in LMICs, including: a) revision of evidence on the optimal number of antenatal care contacts to prevent stillbirths; b) the development of global fetal growth reference curves to be used to detect SGA in LMICs; c) the development of a globally standardised perinatal death classification system.

A lack of maternal and perinatal mortality data is a significant limitation to the understanding of the underlying factors that contribute to these poor outcomes in many LMICs. Uniquely, South Africa has a robust perinatal mortality data collection system that has been in place since 1990. This enabled the following aims of the thesis to be met in relation to the global strategies developed outlined above:

1. To investigate the causes of, and risk associated with, SGA fetuses in relation to maternal and fetal characteristics in South Africa between 2013-2016
2. To compare INTERGROWTH-21st with local standard fetal growth charts (Theron-Thompson) to identify small-for-gestational-age fetuses in stillbirths in South Africa
3. To explore the impact of timing of antenatal care on stillbirth risk across pregnancy in South Africa
4. To assess the utility of a new standardised, global classification system (ICD-PM) for categorising perinatal deaths in South Africa

METHODS

A range of analyses (descriptive statistics, stillbirth incidence, cox regression modelling, fetuses-at-risk modelling) using the perinatal mortality data from June 2013 to December 2016 were conducted. The main dataset used number of stillbirths, number of live births, primary cause of perinatal death, maternal condition at time of death and gestational age at time of death to conduct these analyses. In addition Aim 4 was addressed utilising implementation research techniques.

RESULTS

This thesis is presented as a series of papers. Chapters 4-8 present the accepted or published manuscripts in peer-reviewed journals. This body of work has: 1) established the causes of death, condition of mother and timing of deaths in SGA fetuses in South Africa; 2) established which fetal
growth chart (local charts/global charts) is optimal for detecting SGA fetuses in the antenatal period in South Africa; 3) established the optimal timing of antenatal care to reduce stillbirth risk; 4) implemented ICD-PM codes to the existing perinatal mortality database in South Africa. The key findings are summarized below:

- Maternal risk-profiling is not an adequate method to up-refer women from community antenatal care settings as nearly half of all antenatal stillbirths have no maternal complication and there is no increase in this proportion for SGA pregnancies (CHAPTER 4)
- Current antenatal SGA detection methods are inadequate to detect SGA pregnancies with increased periods of stillbirth risk for SGA pregnancies even when frequent antenatal care is delivered (CHAPTER 5)
- INTERGROWTH-21st and Theron-Thompson growth charts identified the same SGA incidence in stillbirths (~32%). However, there are differences in the proportion of SGA fetuses identified at different gestational ages depending on the growth chart used which have not been considered in previous published papers (CHAPTER 6)
- It is crucial to have antenatal care contacts in the third trimester to reduce stillbirth risk. There was an increase in deaths due to hypertension occurring in the third trimester without antenatal care presenting an opportunity to target this to reduce deaths (CHAPTER 7)
- It is feasible to implement ICD-PM to existing perinatal mortality data collection systems in LMICs. The main advantage of ICD-PM was increased ability to identify time of death, with most deaths (58.2%) occurring in the antenatal period (CHAPTER 8)

CONCLUSION
In summary, there are significant challenges detecting pregnancies at risk of stillbirth particularly SGA pregnancies in South Africa. The public health strategies to reduce stillbirths including increased number of antenatal care contacts in the third trimester and the ICD-PM appear to be promising strategies to reduce stillbirth and increase the ability to document and understand the causes of perinatal death. The ability of global fetal reference curve to increase the detection of SGA pregnancies appears less promising and more research in this area is needed. As South Africa is one of the few LMICs with robust data to conduct such analyses this thesis has contributed findings that are generalizable to surrounding countries in sub-Saharan Africa.
PUBLICATIONS ARISING FROM THIS THESIS

Peer-reviewed journal publications


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CHAPTER 1 INTRODUCTION

1.1 Background

Approximately 99% of the world’s maternal deaths, stillbirths and neonatal deaths occur in low-and-middle-income countries (LMICs)(1). The majority of these deaths are preventable when adequate resources, coverage and quality of care are available (2-4). Maternal and newborn health are closely related and maternal complications are present in 25.3% of stillbirths and 21.2% of early neonatal deaths (5). Globally an estimated 2.6 million stillbirths occur every year (1) and there has been specific focus on accelerating progress to end preventable stillbirths in the global health agenda in recent years (6, 7). South Africa, a country with a high stillbirth rate (8), has been challenged along with most countries in reducing stillbirths. In 2014, the Every Newborn Action Plan developed by the World Health Organization (WHO) set a target of 12 or fewer stillbirths per 1000 births in every country by 2030 (8). South Africa is still above this target at 17.6 per 1000 births (9) compared to Australia at 7.2/1000 (10). A particularly high risk groups is fetuses that are not growing properly, which represent 20% of stillbirths in South Africa (11, 12).

Despite the burden of maternal and perinatal deaths in LMICs, there is a lack of robust empirical data on the underlying causes, characteristics, and health system factors contributing to high mortality. This lack of information impedes the ability to better inform governments and policy makers to enable evidence-based approaches to reduce perinatal deaths. Research in LMICs is further limited by a lack of vital registration systems, poor methodology around data collection processes and inconsistent definitions for maternal and perinatal conditions and classifications of deaths (13-16). In addition, the majority of the current evidence base on stillbirth is conducted in high-resource settings (17). As a result the majority of guidelines and clinical strategies for managing pregnancies to reduce maternal and perinatal mortality/morbidity are based on evidence from high-income countries despite vast differences in health systems, availability of resources and characteristics of the obstetric population. Consequently, the external validity of existing findings to LMICs countries is uncertain.
It is widely accepted that most maternal and perinatal deaths are avoidable through the use of existing, low-cost technologies and interventions (2-4). However, health systems in LMICs continue to struggle to deliver high quality care during pregnancy and birth (14). This is particularly the case in community settings where the majority of care in LMICs is delivered, including antenatal care (18). In South Africa clinical care for obstetric women is largely delivered at the community level by a nurse or midwife (18); access to routine ultrasound or other forms of technology is limited (19, 20).

Current issues experienced by clinicians and public health specialists in South Africa include lack of understanding around: (1) the primary causes of perinatal deaths for SGA pregnancies and the associated health condition of mother at time of death; (2) the optimal growth chart to use to detect SGA pregnancies during routine antenatal care in resource-restricted settings; and (3) the optimal timing of routine antenatal care delivery in resource-restricted settings to prevent perinatal mortality and improve obstetric outcomes. A number of global health strategies have been initiated recently to reduce perinatal deaths, namely the development of standardised global fetal growth charts (INTERGROWTH-21st) to detect SGA pregnancies and the development of a standardised global classification system to classify deaths (The 10th edition of the International Classification of Diseases (ICD-10) to perinatal deaths (ICD Perinatal Mortality, ICD-PM). The adoption of these strategies has been advocated by professional bodies.

1.2 Thesis rationale

The reporting and investigating causes of stillbirths provide crucial information which can be used to target efforts for reducing deaths. Deaths occurring in high-income countries are typically reported and investigated (16), however, in LMICs many stillbirths and early neonatal deaths are not recorded (15) and accurate population data do not exist (21, 22). This doctoral work provides a unique opportunity to examine the challenges with reducing stillbirth in LMICs; South Africa is one of the few LMIC worldwide with a whole-population routine national clinical audit system in place (23). South
Africa’s Perinatal Problem Identification Programme (PPIP) is a quality of care audit system able to capture perinatal deaths in addition to potential modifiable factors for perinatal mortality and maternal condition across all levels of care (12). Such data are rarely available in LMICs despite the success of clinical audit in improving quality of care in high-income countries (24). This doctoral research will provide insight into the challenges experienced in reducing South Africa’s high stillbirth rate.

This project was chosen as the candidate has a personal interest in maternal health in African countries and was fortunate enough to have received a Research Collaboration Award to support the work.

1.3 Aims and objectives

The overall aim of this research was to conduct a series of epidemiological analyses to examine the clinical and health system factors contributing to the high stillbirth rate in South Africa, and the potential impact of the public health strategies outlined above.

The specific aims of this doctorate, informed by the issues outlined above, are:

1. To investigate the causes of, and risk associated with, SGA fetuses in relation to maternal and fetal characteristics in South Africa between 2013-2016
   a. To explore the gestational age at death, medical causes and condition of mother of perinatal deaths
   b. To determine stillbirth risk across gestational age for growth-restricted pregnancies as compared to appropriately-growing pregnancies with regular antenatal care in the Western Cape region of South Africa

2. To compare INTERGROWTH-21st with local standard fetal growth charts (Theron-Thompson) to identify small-for-gestational-age fetuses in stillbirths in South Africa

3. To explore the impact of timing of antenatal care on stillbirth risk across pregnancy in South Africa

4. To assess the utility of a new standardised, global classification system (ICD-PM) for categorising perinatal deaths in South Africa
a. To assess if ICD-PM codes can be applied to existing perinatal mortality datasets in LMICs using South Africa as an example

b. To evaluate if the new features of ICD-PM are advantageous in classifying perinatal deaths (including the consideration of the mother-infant dyad as a single entity and information around the timing of deaths)

1.5 Structure of thesis

This thesis is presented as a series of papers, with contextualising information provided in preceding chapters and a discussion of thesis findings (across all papers). Chapter 2 provides context in relation to the studies within this thesis and a critical review of the literature. Chapter 3 provides a brief overview of the common data sources used for analyses as well as the data collection processes and quality of data. Chapters 4-8 present the original research papers and each include an abstract, introduction, methods, results and discussion section. Chapter 9 presents an integrated discussion including contextualising the findings of the thesis, the clinical and policy implications and future research directions.
CHAPTER 2 BACKGROUND AND CRITICAL REVIEW OF LITERATURE

The following chapter provides context for the South African setting including background sociodemographic information and an outline of the health system. Following this, epidemiology of perinatal mortality is discussed, an overview of perinatal data reporting is presented, causes and risk factors for stillbirth and a critical review of the literature concerning antenatal care and detection of women at risk of stillbirth in LMICs.

2.0 South African Context

2.0.1 Demographics for South Africa

South Africa is a country in Southern Africa with a population of 56 million (25). In the 2016 Census 76.4% of the population identified as African, 9.1% White, 8.9% Coloured, 2.5% Asian and 0.5% unspecified (25). Approximately 22.3% of the population live in informal dwellings (defined as a makeshift structure not erected according to approved architectural plans, for example shacks or shanties). The national poverty level is 56.8% (25). Life expectancy at birth is 57 years (compared to 82 years in Australia) (26). South Africa has one of the highest adolescent fertility rates in the world with 47 births per 1000 women 15-19 years (in 2016), this is compared to 14/1000 in Australia (in 2016) (25, 27). South Africa’s HIV prevalence in 2016 was 18.9% in people aged 15-49 years, also one of highest in the world (25).

2.0.2 Overview healthcare system in South Africa

Healthcare in South Africa is delivered in parallel through the private and public sector. Approximately 20% of South Africans have private health insurance and use the private sector (28). The remaining 80% access public health care. South Africa spends 8.7% GDP on health with ~50% of health care spending on public facilities (28). South Africa has a relatively low physician to population density at 0.818 per 1000 population (2016) compared to 3.5 per 1000 in Australia (29). The nurse/midwife per population is density is 5.3 per 1000 (compared to 12.6 in Australia) (29). In addition to an under-resourced workforce, 79% of doctors work in the private sector despite only 20% of care delivered in
the country’s private system (30). There are also workforce shortages in rural areas with most health professionals concentrated in urban areas (28). This disproportionate distribution is also prevalent between the provinces, with the Western Cape and Gauteng provinces having higher doctor-to-population ratios including in the maternity sector compared with other provinces (30).

Maternal and child (<6 years) healthcare services have been publically subsidised in South Africa since 1994 (31). A 5-year macro plan for the health sector was developed for 2010-2014 (Negotiated Service Delivery Agreement, Outcome 2) by the national government (32). This included maternal, neonatal, child and women’s health (MNCWH) in the four outputs of the macro plan which the health sector is expected to achieve. These outputs are: (a) increasing life expectancy, (b) decreasing maternal and child mortality, (c) combating HIV and AIDS and (d) decreasing the burden of disease from tuberculosis and strengthening health system effectiveness (33). MNCWH is consistently a healthcare priority in South Africa with the Millennium Development Goals and the National Core-standards (31, 34-36).

There are ~57,9000 births per year in South Africa. Antenatal care services and birth services are free in South Africa at public health facilities. Skilled birth attendance is high at 96.7% as is antenatal care coverage of at least 4 contacts at 76% (37). Approximately 20% of births occur in the PHC, 41% in district hospitals, 25% in regional hospitals, 8% in provincial tertiary hospitals and 6% in national central hospitals (9). Across South Africa, ANC is primarily midwife-led and delivered in the community setting with more than 3000 Primary Health Care Clinic (PHC). In addition, there are 188 district hospitals, 42 regional hospitals, 12 provincial tertiary hospitals and 10 national central hospitals.

### 2.1 Epidemiology of perinatal mortality

#### 2.1.1 Definitions for perinatal mortality and stillbirth

Classification of perinatal deaths includes fetuses that are born dead (stillbirths) and babies that die in the first week after birth (early neonatal deaths) (38). The perinatal period age of viability as defined
by the WHO begins at 22 weeks of gestation which differentiates the death between a stillbirth and miscarriage (38). Stillbirths and early neonatal deaths are often grouped into a single category of perinatal deaths on the hypothesis that the deaths have similar causes, in particular obstetric causes (38, 39).

There is some inconsistency in stillbirth definition depending on the country and region. In Australia, the accepted parameters for defining stillbirth are a fetus that is at least 20 weeks gestation or at least 400 grams (40). This is similar to other high income countries (HICs) such as the USA (20 weeks, no weight minimum), UK (24 weeks, no weight minimum) and Norway (22 weeks, no weight minimum). The inclusive recommendation from the WHO calls for a definition of perinatal deaths that includes stillbirths with a mass of 500 grams or at 22 complete weeks of pregnancy. However, for international comparisons, the WHO has a more conservative definition that restricts perinatal deaths to stillbirths weighing 1000 grams or 28 weeks gestation (38). The more inclusive criteria may allow for a reduction of under-reporting of perinatal deaths and tracking of stillbirths as well as the inclusion of meaningful data (e.g., cause of death at younger gestations). A recent systematic review of stillbirths in LMICs (comprising 142 studies) found the definition of stillbirth varied with 10.6% of studies adopting the stillbirth cut-off as ≥22weeks, and 32.4% adopting ≥28weeks with the remaining studies using various other definitions (41).

In South Africa, the Births and Deaths Registration Act (Act No. 51 of 1992) states that ‘A stillborn in relation to a child, means that it has at least 26 weeks of intra-uterine existence but showed no sign of life after complete birth’ (42). In practice this refers to 28 weeks gestation as last menstrual period (which is 2 weeks before conception) is used to date conception. The Regulations on the Registration of Births and Deaths state that ‘after a death occurs due to natural causes, informants shall give, within 72 hours, notice of death’. If there is any doubt whether the death was due to natural causes, such a death has to be reported to a police officer (43).
The variation in stillbirth definition between regions largely occurs due to differences in the perception of parameters for viability. Therefore, vast differences are seen between HICs and LMICs due to the availability of resources that allow survival of a preterm infant. The difference in definitions hinders the comparison of stillbirth rates between countries or at global level.

2.1.2 Temporal classifications for stillbirth
Stillbirths can also be classified according to when they occur in proximity to the onset of labour. Commonly, stillbirths are referred to as occurring antepartum (prior to the onset of labour) or intrapartum (during labour) (44). In resource-restricted settings it can be difficult to ascertain if there is a fetal heartbeat at the onset of labour due to lack of fetal heart monitoring equipment and skilled birth attendants. Therefore, in LMICs, including South Africa stillbirths are often classified as fresh or macerated assigned by physical appearance of the fetus (45). A macerated fetus displays skin and soft-tissue changes such as skin discoloration/darkening, redness, peeling, and necrosis which begin occurring at eight hours after fetal demise suggesting the death occurred during the antepartum period (46). The average time from fetal demise to birth in macerated cases is 2 days (47) but can be a long as six weeks. A fresh stillbirth does not show changes in skin appearance indicating a recent death (less than eight hours) and is therefore assumed to have occurred in the intrapartum period or just prior to labour onset (45, 46). This approach is imprecise and may under-estimate intrapartum deaths (48). Foot length can also be used by pathologists to determine gestational age at time of fetal demise, but is not commonly recorded in perinatal mortality data collection systems (49, 50).

2.1.3 Perinatal mortality rates
There 2.7 million neonatal deaths (deaths in first month of life) worldwide. In South Africa, neonatal deaths account for 30% of mortality in children under 5 years (51). Between 2012 and 2016 South Africa’s mortality in children under five years reduced by 17.1%. This decrease was largely due to a
reduction of deaths after the neonatal period, with deaths in the first month of life remaining stagnant at 12 per 1000 live births (52).

In addition to neonatal deaths, there are 2.6 million stillbirths globally each year (8). The majority of stillbirths occur in LMICs (98%) and 55% occur in sub-Saharan Africa (8). The stillbirth rate in sub-Saharan Africa and South East Asia (30 per 1000 births) (53) is ten-fold that in high-incomes countries (3 per 1000 births)(54). South Africa also has a high stillbirth rate which has not decreased in the last 10 years (9). In 2014, the Every Newborn Action Plan developed by the World Health Organization set a target of 12 or fewer stillbirths per 1000 births in every country by 2030 (8). South Africa has not met this target at 17.6 per 1000 births (9) at least twice as high as Australia (7.2/1000) (10). Stillbirth affects parents, families and communities with psycho-social consequences including anxiety, depression, post-traumatic stress disorder and stigmatization (55).

2.2 Perinatal data collection and reporting

2.2.1 Data collection for maternal and perinatal morbidity/mortality in LMICs

There are a number of challenges with death reporting and audit in LMICs. Deaths occurring in HICs are generally well-reported and investigated (16), however, reliable data are a challenge in LMICs due to multiple factors. In many LMICs there is a lack of government investment in epidemiological databases as well as routine birth or death registries. Globally only 4% of neonatal deaths and 15% of maternal deaths occur in countries with full-coverage vital registration (56, 57). Where civil registration systems are not implemented maternal and neonatal mortality and morbidity are estimated from periodic household surveys, prospective facility-based studies or facility-based medical reviews (58, 59). Complex modelling techniques must be used to estimate the magnitude of conditions which are limited by large uncertainty estimates (57). These factors have limited the understanding of maternal and perinatal mortality burden in many LMICs to date.
South Africa is one of the few LMICs worldwide with a whole-population routine national clinical audit system in place, known as Perinatal Problem Identification Program (PPIP) (23). PPIP requires mandatory reporting of perinatal deaths. Chapter 3 provides detailed information on PPIP.

2.2.2 Clinical audit for maternal and perinatal deaths in LMICs

Death review audits identify the causes of death, both due to pathophysiological reasons and due to health system failures. Due to lack of systematic infrastructure for collection and reporting of cause of death in many LMICs, perinatal death audits present a means to increase recording of the number of deaths as well as cause of death. The audit cycle includes classifying avoidable deaths, changing service delivery and addressing health system problems (23). A systematic review of clinical audit in high-income countries found only a small positive effect of clinical audit on improving professional practice (60). The effectiveness of clinical audit in LMICs may be greater in countries like South Africa compared to higher-income countries with better resourced health systems because there is greater opportunity to reduce deaths that are avoidable. In non-randomized studies quality-of-care audit in LMICs has been shown to reduce perinatal mortality by up to 30% (23, 61, 62).

Despite the success of clinical audits observed in other LMIC settings, a review of clinical audit for reducing perinatal deaths in South Africa found that there was not a clear decrease in perinatal deaths across facilities, with some facilities showing increased perinatal mortality and others showing decreased mortality (63). This may be related to the other aspects of the audit cycle such as changing service delivery and health system problems rather than the collection of data itself.

2.2.3 Classification of cause of deaths

In the same way there is no global definition for stillbirth, no global classification system exists for causes of death that is adopted in all settings. The International Classification of Diseases (ICD)-10 Chapter XV pregnancy, childbirth and the puerperium (O00-O99) and ICD-Maternal Mortality (ICD-
MM) are used in some settings, while other settings develop their own jurisdictional classification systems. South Africa uses its own system (as described in Methods 3.1.4).

A recent systematic review identified 81 different systems used to classify perinatal deaths globally, with only 17 systems using ICD-10 (64). Globally, an average of ten new systems are created or modified each year further complicating the situation (64). The systems reviewed had widely varying characteristics in terms of: (i) comprehensiveness (40 systems classified both stillbirths and neonatal deaths); (ii) extent of use (systems were created in 28 countries and used in 40); (iii) underlying cause of death (64 systems required a single cause of death) (64).

A systematic review including only LMICs observed that just 22% of studies (n=142 studies) used a perinatal death classification system, and within this there were seven different classification systems used (41). Table 2.1 outlines the classifications used in the 60 studies. Other studies have recognised that multiple, disparate systems impede the ability to understand and achieve accurate estimates of cause of death, hindering effective prevention strategies (65, 66).

Table 2.1. Classification systems for cause of death in low-and-middle-income countries (67)

<table>
<thead>
<tr>
<th>Classification system used</th>
<th>Africa</th>
<th>Asia</th>
<th>South America</th>
<th>Multiple continents</th>
<th>Total number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh/Macerated</td>
<td>21</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Not documented</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Wigglesworth</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Aberdeen</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ICD-10</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Maternal/placental/fetal</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nordic-Baltic</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PSANZ-CPG/PDC</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>NICE and CHERG</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>26</td>
<td>6</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases, PSANZ-CPG/PDC, Perinatal Society of Australia and New Zealand Clinical Practice Guide/Perinatal Death Classification, NIC, Neonatal and Intrauterine Death Classification according to Etiology, CHERG, Child Health Epidemiology Reference Group
CHAPTER 2 BACKGROUND AND CRITICAL REVIEW OF LITERATURE

It is recognised that there is a need for a rationalised approach to cause of death classification. The Lancet Stillbirth Series (2011) called for the creation of a “universal classification system” for causes of stillbirth (44, 68). The United Nations Every Newborn Action Plan (2014) identified cause of death as a key gap in the available data, and proposed registration of all stillbirths and neonatal deaths as well as identification of cause of death as one of the global indicators (69).

In light of these recommendations the WHO developed the ICD-10 for perinatal deaths (ICD-PM) which was published in December 2016 (70). The ICD-PM is the first tailored perinatal death classification system developed for application globally (71). It is modelled on the WHO application of the ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-Maternal Mortality (72) and follows all coding rules of the ICD-10 (73). Importantly, the ICD-PM system identifies the timing of perinatal death (i.e., antepartum, intrapartum, neonatal), links causes of death to existing ICD-10 codes and connects maternal condition with perinatal death (70). One of the aims of the ICD-PM is to group ICD-10 codes into clinically relevant and easy to use categories (71). Based on current knowledge, the ICD-PM has not been implemented in any existing national routine data collection system to date.

2.3 Causes of stillbirth and risk factors

2.3.1 Main causes of stillbirth

The largest systematic review (n= 20, 762 cases, across 49 countries) of causes of stillbirths in LMICs found the most frequently reported cause of stillbirth was maternal factors (5-50%) including syphilis, malaria and diabetes (41). Figure 2.1 shows countries included in the review. Congenital anomalies accounted for 2.1-33.3% of stillbirth, followed by, placental causes (7.4-42%), asphyxia and birth trauma (3.1-25%), umbilical problems (2.9-33.3%), and amniotic and uterine factors (6.5-10.7%) (41). Figure 2.2 shows the proportion of stillbirths attributed to specific causes. The wide variation in stillbirth for each cause is likely due to differences between settings in diagnostic capabilities,
screening, treatment regimes for associated conditions (i.e. HIV) and access to antenatal/intrapartum care.

Figure 2.1 Geographical distribution of papers included in Aminu et al. 2014 review (size of bubble approximates the number of studies) (74)

Figure 2.2. Studies attributing causes of stillbirth in review by Aminu et al. 2014 (75)
Subsequent to this review a large observational study (n=109,911) used a prospectively designed classification system in communities in India, Pakistan, Guatemala, Democratic Republic of Congo, Zambia and Kenya to investigate probable causes of stillbirth (76). This study found asphyxia was the cause of 46.6% of stillbirths, followed by infection (20.8%), congenital anomalies (8.4%) and prematurity (6.6%). Among those caused by asphyxia, 38% had prolonged or obstructed labour, 19% antepartum haemorrhage and 18% pre‐eclampsia or eclampsia. However, due to the community-based setting there was limited information on maternal risk factors, however sociodemographic, obstetric and birth characteristics were included. The role of comorbid conditions and growth restriction was not explored. Fetal growth restriction is often an underlying factor in many of these deaths.

Due to differences in the classification systems used between the systematic review and the observational study it is difficult to compare and contrast the causes of death. For example, asphyxia was one of the main causes of death in both studies, however in the observational study the underlying causes where further described as prolonged labour, antepartum haemorrhage and pre‐eclampsia/eclampsia some of which are classified under ‘maternal conditions’ in the systematic review.

2.3.2 Risk factors for stillbirth

There have been many studies in both HICs and LMICs that have explored risk factors for stillbirth (8, 77-83). A systematic review of population studies for stillbirth risk factors in high-income countries (n=96 studies, 8000 stillbirths) found increased maternal weight, maternal smoking, increased maternal age, primiparity, SGA, placental abruption, pre‐existing maternal diabetes and hypertension as the most important potentially modifiable risk factors for stillbirth (83).
The 2016 Lancet Stillbirth Series, including both LMICs and HICs, found the modifiable conditions with the highest estimated population attributable fraction (PAF) were maternal age greater than 35 years (PAF 6.7%), maternal infections (malaria 8.2% and syphilis 7.7%), non-communicable diseases, nutrition and lifestyle factors (such as obesity many of which coexist, each contributing to about 10%), and prolonged pregnancy (14.0%) (8).

A systematic review including only LMICs (n=20, 762), found risk factors for stillbirth to be poverty, lack of education, maternal age (>35 or <20 years), parity (1, >5), lack of antenatal care, prematurity, multiple gestation, maternal morbidity, low birth weight and previous stillbirth to be risk factors (41). These factors are consistent with individual analyses in Africa (Tanzania n=47,681, Zimbabwe n=17,174, Mozambique n=450, Uganda n=37,043, six countries in West Africa n=19870) that employed various study designs such as registry-based retrospective cohort studies (79, 82), matched case-control studies (78) and population-based cross-sectional studies (77, 80). Collectively, these studies identified the following risk factors for stillbirth: lack of antenatal care (RR 2.54, 95% CI 2.21–2.92) (79), pre-eclampsia (aOR 3.99, 95% CI 3.31–4.81; aOR 4.0, 95% CI 2.0-8.0) (77, 82), placental abruption (aOR 22.62, 95% CI 15.41–33.19) (82), non-cephalic presentation (aOR 6.05, 95% CI: 4.77–7.66; aOR 8.4, 95%CI 5.0-14.0) (77, 82), low birth weight (AOR 9.66, 95%CI: 8.66–10.77) (82), obstetric complications (OR 6.9, 95%CI 3.6-12.1) (78), low socio-economic status (OR 1.8, 95% CI 1.1-3.1) (78), multiple births (AOR 2.57, CI 1.66-3.99) (80), previous adverse outcome (AOR 6.16, CI 4.26-8.88; aOR 1.2, 95%CI 0.6-2.2) (80), grand multi-parity among 35 to 49 year olds (aOR 1.97, 95%CI 1.32-2.89) (80) and maternal height (<150cm) (aOR 4.8, 95%CI 2.0-11.4). In LMICs, lack of antenatal care is often reported as a risk factor, whereas due to better access to ANC in high-income settings antenatal care is often not a major contributing risk factor for stillbirth. Eclampsia, pre-eclampsia, obstetric complications, non-cephalic presentation were all found to be risk factors in LMICs but not in HICs, once again this reflects differences in settings where better access to care during pregnancy and birth is present in HICs preventing mortality from these causes.
2.3.3 Impact of Fetal growth restriction/SGA

Fetal growth restriction (FGR) is one of the major causes of stillbirth world-wide, responsible for 30-50% of deaths (8, 84) and present in 4.8-19.0% of live births in LMICs (85). Compared to appropriate-for-gestational-age infants, growth restricted infants are at increased risk of perinatal mortality (86), including a 10-fold increased risk of stillbirth (87). In South Africa, the largest category of perinatal deaths is unexplained stillbirth, of which up to one-quarter have FGR (12).

Fetal growth restriction is defined as the failure of the fetus to reach its full growth potential (88). Conceptually this is a relatively straightforward characterisation, but is difficult to detect and measure in practice. Fetal growth restriction and SGA are often used interchangeably in the literature, however, are not entirely synonymous. SGA describes an infant whose weight is lower than population norms or lower than a predetermined threshold weight (usually <10th percentile for or >2 SD below the mean for gestational age) (89). Section 2.7 outlines different methods of measuring and classifying SGA. SGA may constitute a small but healthy fetus or be due to pathological growth failure (i.e. FGR) (47). Typically obstetric care seeks to identify pregnancies that are SGA to initiate further investigations to ascertain if fetal growth restriction is occurring.

Fetal growth is complex, as intrinsic factors as well as environmental factors, can lead to FGR (88). Causes of FGR can be classified into maternal, placental and fetal causes. Maternal causes may be intrinsic such as placental vascular insufficiency (pre-eclampsia, chronic hypertension, chronic renal disease etc.), or environmental such as malnutrition, smoking, or alcohol intake. Placental causes include chronic poor uterine blood flow to the placental site leading to chronic insufficiency with inadequate substrate transfer (placenta praevia, placental infarct, circumvallate placenta, chorioangioma, velamentous cord insertion) (88). Fetal causes are less common and occur when substrate from the maternal blood is not utilised by the fetus (chromosomal anomalies, congenital
malformations - cardiovascular disease, renal disease, congenital infections). There are known differences in causes of FGR between high- and low-income countries (88), with placental pathology indicated as a major cause in high-income countries and maternal factors the major cause of FGR in LMICs (90, 91). This may be due to many maternal conditions not been managed as well clinically in LMICs as compared to HICs.

Often FGR is not identified as the primary cause of death but is an underlying factor which is frequently co-incidental in intrapartum asphyxia (92), hypertension (93) and other conditions. Only a small percentage of deaths will be classified as having a primary cause of death as FGR, with most been classified under the co-incidental condition. Often classification systems will have SGA/FGR recorded along with primary cause of death (i.e. intrapartum asphyxia with SGA).

### 2.3.4 Limitations ascertaining stillbirth causes and risk factors in LMICs

A lack of robust death reporting and review preclude the ability to comprehensively examine causes and risk factors for stillbirth in many LMICs. Where death information is captured a lack of consistent classification system between settings, as well as inconsistent definitions for stillbirth and SGA/FGR, impede the ability to examine causes of stillbirths between countries. McClure and colleagues (2017) were able to overcome some of these limitations by creating an algorithm to identify probable causes of stillbirth from existing data in six LMICs that use different death classification systems (76). In many settings such complex analyses are not feasible.

In addition, many of the existing stillbirth classification systems have been developed and piloted in high-income settings with access to post-mortem and laboratory investigations to ascertain cause of death. In many LMICs, the limited or non-existent access to these resources renders many stillbirth causes of death ‘unknown’ or ‘unclassifiable’ or classified under alternative available classifications with reduced accuracy. A classic example of this is FGR, where lack of pathology and reliable methods
of gestational age and weight prevent the ability to identify cause of death as FGR in LMICs. In many low-resource countries (including South Africa) FGR is rarely diagnosed from placental histology or fetal or neonatal autopsy, but usually from a case review and verbal autopsy (12). This may reduce the number of perinatal death cases classified as FGR.

Several methodological issues have also been identified in analyses of data from LMICs, including substantial selection bias in hospital-based studies, as a result of only well-resourced hospitals being included, as well as the inability to consider the real prevalence of risk factors in the population (potential issue for (78, 79, 82)). Often hospitals in LMICs with effective death review systems and the capacity to conduct analyses are representative of only the best performing hospitals. This raises issues around the generalisability of findings to the whole obstetric population. In addition, many studies have not examined stillbirths and neonatal deaths separately due to various reasons such as lack of statistical power or the premise that perinatal deaths have similar obstetric causes (38, 39). There is a need for large, multi-country studies with consistent definitions and methodology. There is also a need to link information on maternal morbidities that are known to influence stillbirth risk. Such studies are expensive and difficult to conduct.

2.4 Antenatal care to prevent stillbirth and adverse obstetric outcomes

Antenatal care is an 'umbrella' term used to describe health care and procedures during pregnancy (94). The care includes various screening tests, diagnostic procedures, prophylactic treatments, some of which are performed routinely, and others are provided based on identified problems and risk factors (18). Table 2.2 outlines effective interventions during ANC adopted in South Africa.

While there is some debate as to how best to deliver antenatal care, there is general agreement on the importance of antenatal care to improve maternal and perinatal health (95, 96). Multiple studies in LMICs settings have associated a lack of ANC with increased risk of perinatal mortality (14, 97-99).
The majority of preventable deaths during pregnancy and childbirth in South Africa have been attributed to lack of frequent ANC contacts or poor-quality ANC (97). Absence of ANC impacts maternal outcomes, with a four-fold increased risk of maternal deaths for women who do not attend ANC clinics compared to women who attend any ANC (97). To emphasize its importance, antenatal care was one of the four pillars of the Safe Motherhood Initiative (100) and the WHO identifies ANC as one of the most widely used strategies to improve maternal and child health (101). ANC coverage was one of the key indicators for MDG 5 (101).

Table 2.2 Effective interventions during the antenatal period (102)
2.4.1 Evidence for ANC models

Antenatal care was a concept coined in the early 1900s in Europe (103). Around this time a school of thought emerged that delivering care to women during pregnancy could prevent maternal, fetal and infant death. Dr Janet Campbell, a civil servant in the UK stated in 1929 that “the first requirement of a maternity service is effective supervision of the health of women during pregnancy . . .” (103). The UK Ministry of Health developed the first known guidelines for ANC (around 1930s) which recommended obstetric contacts at 16, 24 and 28 weeks, followed by fortnightly contacts to 36 weeks, and weekly contacts thereafter until birth. The guidelines also outlined which examinations (i.e., measuring uterine height, fetal heart rate monitoring, urine testing) should occur at each contact as well as the cadre of health professional to deliver care (32 and 36 weeks contacts with medical officer). These guidelines largely formed the basis for ANC programs worldwide, despite limited research around the optimal number, timing and content of contacts.

During the late 1980s and early 1990s the examination of ANC became a priority worldwide with the first RCTs investigating the timing and content of ANC conducted. These produced the first evidence-based, validated models of ANC that were subjected to scientific rigor. Numerous RCTs (n=126) examined the effectiveness of specific components of ANC such as nutritional (104-111), antimicrobial (112-115) and other prenatal interventions (116-121) to prevent fetal growth restriction, preterm birth and/or stillbirth (122). Reviews of these studies concluded only a few interventions likely to be beneficial targeting smoking cessation, antimalarial chemoprophylaxis in primigravidae, balanced protein/energy supplementation and calcium supplementation. Further research was suggested for zinc, folate, and magnesium supplementation during pregnancy (122-124).

Several RCTs also examined the impact of reducing the number of ANC contacts on perinatal and maternal outcomes (125-129). This was under the premise that having a reduced number of contacts would reduce the burden and economic costs on already-strained health systems. A systematic review
of these studies (5 studies, n=22,231) found no significant differences in the reduced contact compared to standard contact groups when low birthweight, SGA, caesarean section, induction of labour, antepartum haemorrhage and postpartum haemorrhage were considered as outcome measures (130). Neither the individual studies nor the review had the statistical power to evaluate mortality outcomes. Four out of the five trials reviewed were conducted in HICs, with well-resourced settings and a high number of antenatal care contacts conducted (8-14 contacts), so could not be generalised to LMICs where fewer contacts are prescribed in ANC schedules (3-4 contacts) (130).

One of the only RCTs conducted in LMICs was set in Zimbabwe with a similar local context to South Africa. This was the largest trial at the time (n=15,532) and compared reduced contacts group (6 contacts, n=6138) with standard contacts (10-14 contacts, n=9394) where the reduced contact group had a more goal-orientated structure (126). There were no differences in perinatal mortality between the two groups. The strengths of this study compared to other RCTs at the time were low loss to follow-up (3% compared to 16-30% other RCTs (125, 127-129)) and sufficient statistical power to examine mortality outcomes for the first time. However, there was only a mean difference of two contacts between the control and intervention arms indicating treatment contamination. Subsequently, a second RCT was conducted in rural Zimbabwe in 2007 (n=13,517) which also found no significant difference in perinatal mortality between reduced and standard antenatal care groups (131). However, this study was also influenced by treatment contamination with very little difference in the number of actual contacts between the reduced and standard models (both arms had a median for 4 contacts).

Although these RCTs were a landmark in terms of scientific rigor for empirical evidence of ANC they were limited by small sample sizes (109, 110), scope (almost all examined a single component of ANC or had inadequate statistical power to examine mortality outcomes (130)), complexity (observed homogeneity between control and intervention arms (126, 131)) or failure to examine coexisting
factors (122)), and lacked external validity to LMICs with most RCTs conducted in HICs (105, 106, 108, 124, 125, 127-129). In addition, many of the RCTs were affected by methodological issues such as inadequate concealment of allocation (128), failure of randomization (128), poor execution of intervention (125, 126, 128, 129, 132-136), poorly measured primary outcomes (121), post-randomization exclusions of women (121), large loss to follow-up (16-30%)(125, 127-129), treatment contamination and/or co-intervention (125-129, 131) and errors in data analysis (e.g., individual women as unit of randomisation in cluster randomised trials)(111). In fact, a number of the earlier papers investigating specific interventions have since been retracted (132-136).

In response to these limitations, in 1996 the WHO initiated the first multi-country cluster-RCT to test a reduced 4- contact ANC model for low-risk women in LMICs (137). It was hypothesised that despite reducing the number of contacts maternal and neonatal outcomes would not be compromised. Based on evidence from the UK it was also speculated that reducing the number of ANC contacts would not increase the use of ultrasound or other medical services (including emergency care) (138). This study (the WHO Antenatal Care Trial (WHO-ANC)) was the largest RCT ever conducted around ANC (n=24, 526) and was central to establishing new global guidelines for ANC in 2001.

The WHO-ANC was established in 53 clinics (27 intervention; 26 local standard ANC package) across four LMICs (Thailand, Argentina, Saudi Arabia, Cuba) to represent diverse geographic regions (137, 139, 140). Women undertook a risk assessment (based on obstetric history, current pregnancy, general medical conditions) at the first contact and were classified as low-risk if they did not require further assessment or special care. Women considered low-risk received the package of four ANC contacts known as the basic component of new model. Women who were not considered low-risk were not eligible for the basic component of the new model, but remained in the intervention group as randomised and received the local standard care needed to treat the detected condition.
The basic component of the new model included screening for health conditions known to increase risk for adverse outcomes, antenatal interventions known to be beneficial, and education interventions on signs of obstetric emergencies and how to manage them. In the control arm, women received routine ANC as per local guidelines recommended by local health authorities.

The trial found that more women in the standard model were referred to higher levels of care (13.4% vs 7.3%), but rates of hospital admission, diagnosis, and length of stay were similar. The groups had similar rates of low birthweight (new model 7.7% vs standard model 7.1%), postpartum anaemia (7.6% vs 8.7%; 0.32), and urinary-tract infection (5.9% vs 7.4%). For pre-eclampsia/eclampsia the rate was slightly higher in the new model (1.7% vs 1.4%). Adjustment by several confounding variables did not modify this pattern. It was concluded that there were negligible differences between groups for several secondary outcomes. One of these secondary outcomes was perinatal mortality which was 2% (n=233) in the 4- contact group compared to 1.7% (n=190) in the standard group (p>0.05). Fresh (0.9% n=99 vs 0.7% n=80) and macerated (0.5% n=62 vs 0.4% n=39) stillbirth were also higher in the 4- contact group but not statistically significant (i.e. >0.05).

The authors concluded that the goal orientated 4- contact model was not inferior to standard ANC packages in terms of risk of adverse outcomes for mothers and newborns (137). An economic analysis conducted in parallel concluded that the application of the reduced contact model reduced providers’ and women’s out-of-pocket costs as well as women’s time in access to care (137, 141). As a result the 4- contact model became the recommended ANC package by WHO in 2001 (142, 143) as well an official MDG reproductive health indicator (specifically four or more ANC contacts) (144). The schedule for low risk pregnancies was recommended as five focused contacts: at booking, 20, 26, 32, 38 weeks with an appointment at the hospital at 41 weeks (137). After this recommendation many countries including Thailand (145) and South Africa implemented the 4- contact model (146).
2.4.2 Recent developments in ANC models/guidelines

A decade after the WHO-ANC trial, a 2010 Cochrane systematic review examined reduced-contact ANC models compared to standard ANC models for several obstetric outcomes (7 RCTs, n=60000). The review included four RCTs from high-income countries (United Kingdom (129), three United States of America (125, 127, 147)) and three from LMICs (WHO-ANC (137), the two RCTs from Zimbabwe (126, 131)).

This Cochrane review found an increase in perinatal mortality (not statistically significant) in the reduced contact groups compared to standard care (RR 1.14; 95% CI 1.00-1.31, five trials, n=56431). When examining high-income countries separately to LMICs there was no increase in perinatal mortality in the reduced contacts group (RR 0.90; 95% CI 0.45-1.80), however for LMICs perinatal mortality was higher in the reduced contacts group (RR 1.15; 95% CI 1.01-1.32, three trials).

This information lead to a statement released by WHO in November 2010 calling for a re-examination of the WHO-ANC data (148). This statement suggested that the differences in population and baseline risk between HICs and LMICs may be the cause of the increased perinatal mortality observed in the pooled analysis of the RCTs in LMICs as observed in the 2010 Cochrane review. It was also speculated that the time between contacts in the third trimester may to be too long for timely intervention if complications arise.

As a result a secondary analysis of the WHO-ANC trial was conducted (149). This secondary analysis of the original data was stratified by gestational age (22–27, 28–31, 32–36 and >36 weeks) to explore differences in risks according to timing of fetal death. Interestingly there was a more than two-fold increased relative risk of fetal death specifically between 32 and 36 weeks gestation (aRR 2.24; 95% CI 1.42-3.53). There were no other periods where risk of fetal death was increased. This was an important finding that contributed to the revision of ANC guidelines.

An updated 2015 Cochrane review observed the same findings as the 2010 Cochrane review with increased perinatal mortality in the LMICs trials. The other primary outcomes examined in the
Cochrane review did not find any difference between reduced contact and standard contact groups: maternal death (RR 1.13, 95%CI 0.50 to 2.57); hypertensive disorders of pregnancy (RR 0.95, 95% CI 0.80 to 1.12; preterm birth (RR 1.02, 95% CI 0.94 to 1.11); and small-for-gestational age (RR 0.99, 95% CI 0.91 to 1.09).

2.4.3 2016 WHO revision of guidelines

In December 2016, the WHO reviewed their guidelines in light of recent evidence including the secondary analysis of WHO-ANC trial, the 2015 Cochrane review, as well as evidence for maternal satisfaction (150-152) and health service factors (153, 154). It was concluded that that the four-contact focused ANC model, developed in the 1990’s did not offer women adequate contact with health-care practitioners and a new schedule of 8-contact at <12 weeks, and 20, 26, 30, 34, 36, 38, 40 weeks was recommended (96). South Africa was one of first countries to adopt this new model with training and implementation beginning in April 2017.

2.4.4 Challenges with translation of evidence into practice in resource-restricted settings

Although the WHO-ANC RCT was conducted in several LMICs increasing the external validity of results to other LMICs, there are challenges with the translation from RCT to real-life settings. While RCTs are often not generalisable to the ‘real world’ because the trial populations don’t represent the real clinical population, this is often not an issue in RCTs investigating ANC.

However, RCTs examining ANC in LMICs are often challenged by the experimental clinical environment being vastly different from the natural clinical environment. While an RCT is conducted the provision of additional resources occurs, such as staff, funding and equipment, once the trial concludes much of these resources are also removed. Therefore, the transition from a RCT which is fully funded and resourced to implementation to the clinical setting is a challenge resulting in no improvement in quality of care despite the benefits of intervention realised. This is reflected where despite previous WHO recommendations for a 4- contact ANC model many LMICs were unable to implement it despite the evidence established from RCTs in LMICs (155).
2.5 Delivery of ANC

2.5.1 Delivery of ANC in LMICs

Despite evidence for the implementation of an 8-contact ANC schedule the reality is that in many LMICs, where resources are limited, antenatal care coverage is poor and many women receive little or no antenatal care (96). Many low-income countries are challenged with widespread poverty and hunger, particularly among rural populations (156). Most LMICs implement some variation of the 4-contact model originally recommended by WHO in 2001. Although ANC coverage (4 contacts) has increased from 51% in 2011 to 62% in 2016, many countries are struggling to establish quality antenatal care with the 4-contact model (155, 157, 158). Often the attendance at ANC appointments for women is logistically and financially impossible (159). There is also inequity in ANC coverage across LMICs with poorer coverage for women who have low socio-economic status, low education and reside in rural areas (160). Equitable coverage is also a challenge in South Africa with barriers for rural women accessing ANC, such as unemployment, less than 20 years of age and unplanned pregnancy (161).

ANC in LMICs is predominately midwife-led (162). In midwife-led care models, midwives (case-load midwifery or team midwifery) support the women through antenatal, intrapartum and postnatal period (163). The midwife-led care model exists within a multidisciplinary network which consultation and referral to other care providers occurs when needed. This model is typically aimed at delivering care health women with uncomplicated pregnancies, although evidence is predominately from high-income countries (163). Midwife-led obstetric units called MOU’s are utilised by women with ‘normal pregnancy’ from antenatal care right through until birth and postnatal follow-up care. These units are managed by midwives. Mothers are referred to district hospitals if ultrasound or care from an obstetrician is required. Midwives in South Africa complete a three-year nursing degree then a one-year additional year in midwifery.
2.5.2 ANC in South Africa

In South Africa there are four main priorities for ANC: (1) promotion and maintenance of the physical and social health of the mother and the baby, (2) detection and management of complications during pregnancy, (3) development of birth preparedness and complication readiness plan and (4) preparation of the women for normal puerperium (37). Three national maternal and child national reports/committees (Saving Mothers, PPIP Saving Babies report, and Saving Children report for the Child Health Problem Identification Programme (CHPIP)) in South Africa highlight the importance of ANC in reducing maternal, perinatal and child deaths (164). These committees recognise that the effectiveness of ANC relies on high-impact, evidence-based interventions as well as on the coverage and quality of the service rendered. Improving access to good quality ANC was highlighted as one of the strategies to significantly reduce perinatal and child deaths (9). Basic Antenatal Care (BANC) is the name given to the approach for antenatal care in the public health system of South Africa governed by the National Department of Health.

2.5.3 Structure of ANC in South Africa

The national maternity guidelines classify facilities into clinics (primary health care clinic, PHC), community health centres (CHCs) and three different levels of hospitals (district, regional, tertiary) and specify what management should be provided at each level of care. It defines the levels of care, referral systems as well as staff required to be designated at those levels (31). However, each province is autonomous and able to adapt or develop guidelines. Figure 2.3 shows the organisation of ANC in South Africa.

Across South Africa, ANC is primarily midwife-led and delivered in the community setting with more than 3000 PHCs. In addition, there are 188 district hospitals, 42 regional hospitals, 12 provincial tertiary hospitals and 10 national central hospitals. Pregnancies are up-referred (referred to higher level of care eg. from primary health clinic to district hospital) to these hospitals if and when identified as high-risk (37). Approximately 20% of births occur in the PHC, 41% in district hospitals, 25% in
regional hospitals, 8% in provincial tertiary hospitals and 6% in national central hospitals (9). The stillbirth rate increases as the level of care increases towards tertiary hospitals, this represents hospital settings caring for high-risk women and PHCs caring for low-risk women. In 2012-13, PHCs had a stillbirth rate of 4.2 per 1000 births, this was compared to 9.4 for district hospitals, 15.1 regional hospitals, 19.6 provincial tertiary hospitals and 21.4 for national central hospitals (9).

Figure 2.3. Organisation of antenatal care in South Africa

The cadre of health professional delivering maternity care at the PHCs are professional nurses who have two weeks midwifery training imbedded into their training. Midwives are nurses who have
received one year additional training in midwifery. Nurse-midwives have the ability to make complex decisions and advance clinical competence (165). However, there are very few advanced midwives in South Africa. There is good evidence to support midwife-led care as a model of care in LMICs, when effective referral systems are in place (162, 163).

2.5.4 BANC and BANC Plus

Basic Antenatal Care (BANC) adopts the 4-contact ANC model recommended by WHO in 2001 (166, 167). The implementation of BANC was designed with the aim of improving ANC-related clinical management and decision making at the PHC level (168). South Africa’s National Department of Health introduced the BANC approach in 2007 and advised that all health facilities providing ANC services should have adopted this approach by the end of 2008 (169).

The National Department of Health set a target for BANC to be implemented in 95% PHC clinics by 2013 (169). Western Cape was the only province to maintain the 8-contact ANC model. However, BANC implementation and ANC access has been incomplete across South Africa. An evaluation in 2011 found that in one district only 46% of PHCs had implemented BANC (170). Across South Africa between 2008-10, 16.6% of maternal deaths did not attend any ANC and a further 7% did not attend four ANC contacts (9). In addition, some PHCs that attempted to resume implementation of the BANC approach failed to sustain the programme (170). There have also been additional challenges in delivering ANC at the community level including staff shortages, lack of cooperation from referral hospitals, insufficient in-service training, transport problems of specimens to laboratories, inadequate material resources, lack of management support and the unavailability of BANC guidelines (171).

In April 2017, South Africa initiated implementation of the new 8-contact model as recommended in the WHO Positive Pregnancy Guidelines in December 2016. South Africa is one of the first countries to implement the 8-contact model, called BANC-Plus. Although implementation occurred in South Africa in April 2017 many clinicians called for the increase in number of contacts in 2015 after the
publication of several case studies where additional ANC contacts would have likely averted death (172).

2.5.5 Challenges with ANC delivery in South Africa

South Africa performs relatively well against indicators such as ANC attendance compared to neighbouring countries. In 2014, 75% of women in South Africa attended at least four ANC contacts, this is compared to 62.0% in Namibia and 50.6% in Mozambique (158). It is estimated that since 1998 more than 90% of women in South Africa have had access to ANC (167).

However, there are known challenges with the ANC model in South Africa which is reflected in the perinatal mortality rate which has not decreased significantly over the last 10 years. Midwife-led care is an approach supported in the literature from high-income countries (162, 163), however, there are issues regarding equitable coverage as well as necessary improvements in the quality of midwifery practice present in South Africa and other LMICs. For example, in 2010 in South Africa certain ANC procedures were found to be inadequate and a significant contributor to perinatal deaths such as: screening/management of syphilis, diagnosing and controlling pre-eclampsia, HIV screening/management, as well as growth monitoring to detect and manage FGR (173). In addition, when BANC was first implemented at PHCs, all nurses and midwives were expected to provide ANC services, despite PHC nurses not having extensive midwifery training (174).

As PHC clinics are the entry point for ANC, failure to meet the requirements of the quality chain at this level are amplified and create subsequent problems. For example, failing to identify and up-refer a high-risk pregnancy results in increased burden on the PHCs where care should only be provided for low-risk women as well as placing the pregnancy at increased risk of perinatal and maternal mortality.
2.6 Antenatal detection of pregnancies at risk of adverse obstetric outcome

2.6.1 Up-referral for high-risk pregnancies in South Africa

The WHO advocates that women should be categorised into ‘low-risk’ or ‘high-risk’ categories based on initial health assessment. Once a woman has been identified as high-risk the pregnancy should be referred to higher level of care (175). This means that only low-risk pregnancies can continue with care at the community level. The risk-profiling of pregnancies is done using a classifying form designed for ANC health providers to identify women who require treatment, more frequent monitoring and up-referral (175). This process facilitates the clinical decision making process by ensuring that the parameters are checked to decide if the pregnancy is evolving normally or there is a complication that needs to be managed (176). This classification system has been adapted for BANC (166). High-risk pregnancies that are candidates for up-referral from the community setting in South Africa are outlined in Table 2.3 and 2.4.

There are known problems with referrals for women with high risk factors in South Africa. Poor communication between the PHCs, the Emergency Medical Rescue Services and with patients are present (170). It is also difficult to detect pregnancies at increased risk in resource-restricted settings such as PHCs. In particular, rural areas and those with large transient and refugee/migrant populations are challenged. Although these issues are known through personal communications, there is no empirical evidence of the effectiveness of referral pathways in South Africa.
Table 2.3. Clinic checklist for classifying first contact (177)

<table>
<thead>
<tr>
<th>Clinic Checklist – Classifying (first) visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of patient</strong></td>
</tr>
<tr>
<td><strong>Address</strong></td>
</tr>
<tr>
<td><strong>Clinic record number</strong></td>
</tr>
<tr>
<td><strong>Telephone</strong></td>
</tr>
<tr>
<td><strong>Cell</strong></td>
</tr>
</tbody>
</table>

**INSTRUCTIONS:** Answer all the following questions by placing a cross mark in the corresponding box.

**Obstetric History**
1. Previous stillbirth or neonatal loss?  
2. History of 3 or more consecutive spontaneous abortions  
3. Birth weight of last baby < 2500g?  
4. Birth weight of last baby > 4500g?  
5. Last pregnancy: hospital admission for hypertension or pre-eclampsia/eclampsia?  
6. Previous surgery on reproductive tract (Caesarean section, myomectomy, cone biopsy, cervical cerclage)

**Current pregnancy**
7. Diagnosed or suspected multiple pregnancy  
8. Age < 16 years  
9. Age > 40 years  
10. Isoimmunisation Rh (-) in current or previous pregnancy  
11. Vaginal bleeding  
12. Pelvic mass  
13. Diastolic blood pressure 90 mmHg or more at booking  
14. AIDS

**General medical**
15. Diabetes mellitus on insulin or oral hypoglycaemic treatment  
16. Cardiac disease  
17. Renal disease  
18. Epilepsy  
19. Asthmatic on medication  
20. Tuberculosis  
21. Known 'substance' abuse (including heavy alcohol drinking)  
22. Any other severe medical disease or condition

Please specify ____________________________________________

A yes to any ONE of the above questions (i.e. ONE shaded box marked with a cross means that the woman is not eligible for the basic component of antenatal care.

Is the woman eligible (circle)  
No  
Yes

If NO, she is referred to __________________________________________

Date________________ Name __________________________ Signature ________________

(Staff responsible for antenatal care)
Table 2.4. Clinic checklist follow-up contacts (178)

<table>
<thead>
<tr>
<th>Clinic Checklist: Follow-up visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Back page of first visit checklist)</td>
</tr>
<tr>
<td><strong>VISITS</strong></td>
</tr>
<tr>
<td>DATE :</td>
</tr>
<tr>
<td><strong>Approximate Gest. Age.</strong></td>
</tr>
<tr>
<td>First visit for all women at first contact with clinics, regardless of gestational age. If first visit later than recommended, carry out activities up to that time</td>
</tr>
<tr>
<td><strong>Classifying form which indicates eligibility for BANC</strong></td>
</tr>
<tr>
<td>History taken</td>
</tr>
<tr>
<td>Clinical examination</td>
</tr>
<tr>
<td>Estimated date of delivery calculated</td>
</tr>
<tr>
<td>Blood pressure taken</td>
</tr>
<tr>
<td>Maternal height/weight</td>
</tr>
<tr>
<td>Haemoglobin test</td>
</tr>
<tr>
<td>RPR performed</td>
</tr>
<tr>
<td>Urine tested</td>
</tr>
<tr>
<td>Rapid Rh performed</td>
</tr>
<tr>
<td>Counsedled and voluntary testing for HIV</td>
</tr>
<tr>
<td>Tetanus toxoid given</td>
</tr>
<tr>
<td>Iron and folate supplementation provided</td>
</tr>
<tr>
<td>Calcium supplementation provided</td>
</tr>
<tr>
<td>Information for emergencies given</td>
</tr>
<tr>
<td>Antenatal card completed and given to woman</td>
</tr>
<tr>
<td><strong>AZT and NVP given (if required) – Check each visit if AZT sufficient</strong></td>
</tr>
<tr>
<td><strong>Clinical examination for anaemia</strong></td>
</tr>
<tr>
<td>Urine test for protein</td>
</tr>
<tr>
<td>Uterus measured for excessive growth (twins), poor growth (IUGR)</td>
</tr>
<tr>
<td><strong>Instructions for delivery/transport to institution</strong></td>
</tr>
<tr>
<td><strong>Recommendations for lactation and contraception</strong></td>
</tr>
<tr>
<td><strong>Detection of breech presentation and referral</strong></td>
</tr>
<tr>
<td>Complete antenatal card and remind woman to bring it when in labour</td>
</tr>
<tr>
<td>Give follow-up visit date for 41 weeks at referring institution</td>
</tr>
<tr>
<td><strong>Initials staff member responsible</strong></td>
</tr>
<tr>
<td><strong>Additional Visits</strong></td>
</tr>
<tr>
<td><strong>Date</strong></td>
</tr>
</tbody>
</table>
2.6.2 Evidence for maternal risk factors as predictor of stillbirth

It is well established in the literature that maternal morbidity is associated with perinatal mortality (179, 180). Global estimates show that maternal complications are present in around 25.3% of stillbirths and 21.2% of early neonatal deaths (5). However much of the research around maternal risk factors as predictors for stillbirth has been restricted to HICs. One multi-site population-based case-control study in the US focused on risk factors that would be known at the start of pregnancy to allow for counselling or referral regarding risks of adverse outcomes (179). This study found non-Hispanic black ethnicity, previous stillbirth, nulliparity, diabetes, maternal age >40 years, maternal AB blood type, history of drug addiction, smoking during pregnancy, obesity/overweight and plurality to be maternal risk factors for stillbirth (179). The most important predictor of stillbirth was history of previous stillbirth or early fetal death. This has also been supported by a recent meta-analysis and systematic review (predominately HICs) which found a dose-response relationship between number of previous pregnancy adverse outcomes and stillbirth risk in current pregnancy (181). A UK study also found similar risk factors for stillbirth such as parity (para 0 and para >3), ethnicity (African, Indian, Pakistani), maternal obesity, smoking, diabetes, history of mental health problems, antepartum haemorrhage and fetal growth restriction (180). The strongest predictor was fetal growth restriction (using customized growth curves) which increased risk of stillbirth 8-fold (aRR 7.8, 95% CI 6.6-10.9). Further the largest population attributable risk for stillbirth was fetal growth restriction and was five-fold greater if it was not detected antenatally (32.0% v 6.2%).

A systematic review from LMICs found the most frequently reported cause of stillbirth was maternal factors (5-50%) including syphilis, positive HIV (with low CD4 count), malaria and diabetes (41). Work in LMICs such as Tanzania identified pre-eclampsia and placental abruption as the strongest maternal risk factors for stillbirth, while non-cephalic presentation and low birth weight were the strongest fetal risk factors (82). However these factors are too late to detect at initial antenatal care assessment so
are of low value when considering maternal risk-profiling (82). Previous stillbirth or early fetal death is identified as one criteria for up-referral from the community level in South Africa (see Table 2.3).

The research that has been conducted in LMICs has been limited by small sample sizes (only a few institutions), scope (identified maternal risk factors undetectable at initial ANC assessment), and complexity (lack of quality maternal morbidity data) (21, 22, 182-184). Further to these limitations two epidemiological surveys in LMICs did not provide information on prevalence and associations with maternal condition (185, 186).

The few studies, including one multi-country analysis that have examined maternal risk factors for SGA, identified young maternal age, nulliparous mothers, chronic hypertension, pre-eclampsia/eclampsia, anaemia, short maternal stature, primiparity, and male sex (85, 187). Consistent with other findings, some of these factors cannot be detected at initial ANC contacts or in community settings so are not appropriate for maternal risk profiling. There have been no studies in LMICs that have examined the impact of maternal condition in growth restricted perinatal deaths as compared to normally growing pregnancies. It is imperative to explore the epidemiological patterns of maternal condition on perinatal mortality to ensure that appropriate interventions are prioritised in resource-restricted settings.

2.6.3 Challenges with maternal risk-profiling in LMICs and South Africa

One challenge with maternal risk profiling is that many LMICs (South Africa, Botswana, Swaziland, Kenya, Zimbabwe) adopted strategies from HICs (188). Research from HICs has explored the best methods to diagnose and manage any complications clinically (179, 180), which renders several issues with generalisability to LMICs.

Firstly, patterns of morbidity and mortality differ considerably between HICs and LMICs influencing the characteristics of women who are considered ‘high-risk’, with the greater incidence in LMICs.
Second, the purpose of risk assessments to identify women at increased risk of adverse outcome initiates an intervention cascade where more frequent care, tests, and hospital-level care result. This system relies on the capacity of the health system to manage referrals. There is a vast difference in technological resources available between HICs and LMICs making maternal risk profiling based on the HIC setting not generalisable to LMICs. Third, this system also presents an opportunity-cost where the scarce resources (in LMICs settings) are funneled to high-risk pregnancies (representing small proportion of all pregnancies) at the cost of ANC care to low-risk pregnancies which represent the majority of the obstetric population (188). To help address this concern in South Africa it has been strategised that high-risk pregnancies be referred to the next level of care so that at the PHC level there is sufficient time to attend low-risk pregnancies (166).

There have been a number of issues identified with maternal risk profiling of women at the community level in South Africa. National reports have shown poor maternal history taking by midwives, poor initial assessment at ANC contacts and incorrect clinical examinations/special investigations performed when assessing patients (97). In the 2012 Saving Mother’s report, a host of avoidable causes for maternal deaths were related to identification of complications antenatally and hindrances with the referral pathway including: poor initial assessments, difficulties recognising maternal complications, delays in referring the pregnant women to higher healthcare facilities resulting in case management at inappropriate healthcare levels, incorrect/substandard management as well as failure to take action (up-refer) when complications were identified (97).

2.7 Antenatal methods to detect fetal growth restriction

WHO (96) and BANC guidelines consider fetal growth restriction as a condition to up-refer pregnancies from the community setting to hospital setting (18). However, in high-income settings 75-82% of stillbirths with growth restriction are not detected during routine antenatal care (180, 189). For pregnancies considered low-risk the proportion of fetuses not detected antenatally is around 85% (189). The proportion of SGA pregnancies not detected antenatally in LMICs is unknown but is
expected to be higher than in HICs due to lack of diagnostic tools. This is of concern as not detecting SGA pregnancies antenatally confers a 4-8-fold increase in risk of stillbirth (87, 180).

Most maternity clinics have a program for identifying of SGA fetuses antenatally because of the increased risk of fetal complications that they present (87). There are several tools that can be employed to detect fetal growth restriction including symphysis fundal height, abdominal palpation, ultrasound and plotting on fetal growth charts.

2.7.1 Symphysis fundal height and abdominal palpation

Abdominal palpation and symphysis fundal height (SFH) are non-invasive methods used to assess fetal growth commonly practiced in community settings. Abdominal palpation involves the palpation of fundal height in relation to anatomical landmarks such as umbilicus, xiphisternum and abdominal girth measurement (190).

SFH uses a tape measure to measure from the pubic symphysis to the uterine fundus. From 24 weeks gestation, the SFH measurement in centimetres should correspond to the number of weeks gestation (with an allowance of 2cm either side) (190). This measurement is plotted onto the growth chart with gestational age. Figure 2.5 shows an example of how gestational age and SPH measurement are plotted onto growth charts. Measurements falling below the corresponding gestational age indicate possible growth restriction requiring further investigation and up-referral. SFH has the potential to detect multiple pregnancy, macrosomia, polyhydramnios and oligohydramnios (190). Due to the unavailability of alternative methods, SFH is the only tool to detect fetal growth restriction at the primary care level in South Africa (191).

Despite palpation and SFH being the only methods used to detect fetal growth restriction in many LMIC settings, there is limited evidence to support their predictive value (192). Abdominal palpation is subjective and has wide inter-observer variation (193) and abdominal girth measurement does not
correlate well with fetal outcomes (194). There have been eight studies that have assessed SFH to detect SGA at birth in low-risk pregnancies, all in HICs conducted in the 1980s (195). The largest (n=2941) found the sensitivity of SFH in detecting SGA to be just 27% (196). Other smaller studies (n=381; n=699) estimated sensitivity to be higher at 64-76% (197, 198). While sensitivity is generally low, there is high degree of specificity with SFH (0.79-0.92)(195), suggesting that a normal SFH measurement is a reasonable indicator of a healthily-growing baby. The consequences of low sensitivity but high specificity in practice mean that few healthy pregnancies are up-referred but most true cases of SGA are missed. A recent Cochrane review concluded that SFH can serve as a clinical indicator along with other clinical investigations, information about medical conditions, and previous obstetric history (195).

The WHO supports the use of abdominal palpation and SFH to assess fetal growth in antenatal settings where ultrasound is not available (96). This is based on the premise that there is no evidence of harm with SFH measurement, however WHO does call for further research to determine the role of SFH measurement in detecting abnormal fetal growth (96).
Figure 2.5. Example of symphysis-fundal-height charts used in South Africa (199); The blue line shows where fundal height in centimeters is plotted against gestational age in weeks (red). Where the two lines intersect on the chart in the background indicates the centile the fetus lies for growth.

2.7.2 Ultrasound

Obstetric ultrasound remains an integral component of prenatal care, particularly for high-risk pregnancies in HICs (200). Conventional ultrasound assists in detecting conditions such as placenta praevia, poor fetal growth, congenital anomalies and malpresentation. The clinical value of conventional ultrasound for use in early pregnancy has been explored with multiple studies in LMICs including sub-Saharan Africa (Kenya, Uganda, Malawi, Rwanda) (201-204). These studies have found that ultrasound provides benefit in terms of determining gestational age and enabling early diagnosis of pregnancy problems (201-205). These benefits are also reported by health professionals working in clinical settings (201, 202, 204, 206). In South Africa, secondary benefits of ultrasound have been described with ultrasound examinations increasing antenatal attendance with the in-direct benefit the translation to better obstetric outcomes (206-208). Contrary to this, a recent cluster RCT in LMICs found that ultrasound is not effective at reducing maternal or perinatal deaths in low-resource settings.
or increasing attendance at antenatal clinic, and is therefore a not an effective use of limited resources (209). In addition, ultrasound is difficult to implement due to high costs and specialist training.

WHO guidelines recommend at least one routine ultrasound during early pregnancy to check for any adverse conditions and to ascertain gestational age (18, 96). It is particularly important to have accurate gestational age in order to detect fetal growth restriction particularly at later gestations.

Doppler ultrasound has the added advantage of being able to assess blood flow in fetal umbilical vessels to identify placental insufficiency (leading to growth restriction). The use of Doppler ultrasound for high and low risk pregnancies has been evaluated in Cochrane reviews (210, 211). In high-risk pregnancies, use of Doppler can reduce perinatal mortality and optimise the use of obstetric interventions (210). However, research is limited in low-risk or unselected populations with only five trials (from three high-income countries) (211). As such there is insufficient evidence to establish whether use of Doppler ultrasound has benefits in these populations, and no trials have been conducted in unselected populations of women in LMICs. The WHO does not currently recommend the routine use of Doppler velocimetry for low-risk populations (96). In South Africa, Doppler ultrasound is only used in high-risk pregnancies in the hospital setting after referral from the community (18).

Due to the high costs and challenges with implementation, many women (including high-risk women) in sub-Saharan Africa do not have ultrasound at all during pregnancy (19, 20). In community settings there is inadequate capacity, training and funding to support ultrasound (212). Currently in South Africa ultrasound is not available in routine ANC at the community level. Some clinicians are calling for greater focus and investment in establishing ultrasound in all primary care settings in sub-Saharan Africa (213). This is said to be achievable by increasing equipment quality, access to smaller devices and the use of mobile data/telemetry (213-216).
2.7.3 Fetal growth charts

Fetal growth charts are used to detect fetuses with compromised growth. Fetal growth charts plot estimated fetal weight or SFH against gestational age to determine fetuses falling on the 10th centile (thus classified as SGA). There are a number of different growth charts used including population-derived charts, customized growth charts and recently developed global ‘standardised’ growth charts (INTERGROWTH-21st, WHO) (217-219).

For many LMICs that do not have the capacity to develop their own fetal growth charts, charts from HICs are adopted for local use. There is substantial inter-country variation between growth charts, meaning that a fetus whose growth is tracking as appropriate using one particular chart may be classified as growth-restricted under another (220). Some studies have reported differences in fetal growth dependent on ethnicity (219, 221, 222). The National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies (NCHID study) found significant differences in fetal growth by ethnicity in American women and has since developed race-specific charts (222). The recent WHO growth charts also found differences in fetal growth based on ethnicity (219).

There are also recognised differences in optimal perinatal outcome achieved at different birth weights in different populations (223, 224). Different populations have different birth weight distributions and optimal fetal growth standards as well as perinatal mortality curves (223, 224). To improve the assessment of fetal growth, customised charts which adjust for factors such as maternal weight and height, age, sex of baby have been proposed (225). Customised growth charts in New Zealand have been shown to have better predictive value of SGA in Maori, European and Pacific women compared to other charts (including INTERGROWTH-21st) (221).

The most recently developed charts (published in 2016 and 2017) were developed by INTERGROWTH-21st and WHO, to obtain a global, multi-ethnic standardised chart that would improve comparison between countries and standardise the classification of SGA between countries/settings. The International Fetal and Newborn Growth Consortium for the 21st Century for fetal growth and size
(the INTERGROWTH-21st) were developed from 13,108 healthy pregnancies in eight countries (Brazil, China, India, Italy, Kenya, Oman, UK and US) (217, 218). Separate fetal charts were developed by the WHO based on healthy pregnancies in ten countries (Argentina, Brazil, Democratic Republic of Congo, Denmark, Egypt, France, Germany, India, Norway and Thailand; n=1387). The INTERGROWTH-21st study did not check for any statistical differences in growth trajectories between countries, while the WHO Fetal growth charts did show natural variation in fetal growth between countries which followed ethnic distribution. However the fetal growth charts are presented as one combined chart for clinical use.

There is considerable debate over whether global standardised charts are the best approach given the cited differences in fetal growth based on ethnicity (221, 222) and population dynamics (223, 224). On the other hand it has been advocated that this new standard should be adopted by professional bodies (226). Due to the development of the global standardised charts been so recent there has been limited examination of the application of these charts in LMICs.

Currently a number of growth charts are used in South Africa including locally developed Theron-Thompson (227), Hadlock (United States population)(228), INTERGROWTH-21st (217) and Solomon (French population) (229). These charts have not been evaluated to ascertain the best chart to use in the South Africa population. Due to lack of available data customised growth charts based on the South African population have not yet been developed.

2.7.4 Challenges with detection of SGA in South Africa

Detecting fetal growth restriction in LMICs is challenged by lack of accurate pregnancy dating, as well as restricted access to ultrasound. In South Africa only women who are considered high-risk have access to regular ultrasound to enable serial plotting of estimated fetal weight against gestational age. Current clinical techniques (including history taking and serial physical assessments) to identify fetuses at increased risk of fetal growth restriction in LMICs have poor predictive value, and have not been
CHAPTER 2 BACKGROUND AND CRITICAL REVIEW OF LITERATURE

shown to affect the rate of stillbirths or perinatal mortality (230, 231). Presently the only way to determine the fetal growth rate at the primary care level in South Africa is by measuring the SFH (191). This is despite limited evidence to support SFH use for the detection of fetal growth restriction (195, 230). In community settings SFH is plotted by–hand to identify fetuses that are not growing properly.

A recent audit in low-resource areas of Kwa-Zulu Natal, South Africa found only 5.3% of patients were plotted correctly (232), demonstrating the problems with relying on this method for SGA detection. There was also a large proportion (62%) of patients that were not plotted at all during antenatal care. The contributing factors to missed detection of fetal growth restriction were failure to calculate gestational age correctly and incorrect plotting at first antenatal care contact. The audit also found that 27 out of 100 pregnancies had antenatal conditions (polyhydramnios, FGR, intra-uterine death) that were not detected during routine antenatal care delivered in the community setting (232).

2.8 Summary

Fifty-five percent of the world’s stillbirths occur in sub-Saharan Africa. Efforts to reduce stillbirths are hindered by a lack of reporting of deaths, poor or non-existent data collection systems, lack of globally accepted definitions of stillbirths and standardised systems capturing cause of death. While it is well-established that antenatal care is a necessary intervention to prevent perinatal deaths, there is less knowledge around the optimal timing of care in resource-restricted settings.

Growth restricted pregnancies are at increased risk of stillbirth and represent a significant proportion of stillbirths in LMICs. There are challenges with the identification of fetal growth restriction during routine antenatal care. This is due to the poor predictive value of and implementation of SFH in determining SGA, as well as lack of information around optimal growth charts to use to track growth and identify growth restricted pregnancies.

A number of global public health strategies have recently been employed targeting the better understanding and prevention of stillbirths. There has been a recent review of literature and revision
of guidelines around antenatal care contacts, including the timing of contacts. In addition two globally-standardised growth charts have been developed and advocated for adoption in all settings. A new coding system specifically for deaths during the perinatal period has also been developed (ICD-PM) to standardize the classification of causes of death and allow comparisons between settings. The potential for these strategies to reduce perinatal mortality need to be further explored.
CHAPTER 3 – GENERAL METHODS

CHAPTER 3 – GENERAL METHODS

This section outlines the main data source used for the research undertaken for this thesis: the PPIP database. An overview of the database design will be followed by management, quality and an overview of the data cohorts used for this thesis.

3.1 Perinatal Problem Identification Program (PPIP)

3.1.1 General overview of PPIP

PPIP is a maternal and perinatal mortality audit system which was introduced by the South African Medical Research Council in 1992 to capture perinatal and maternal mortality, data around livebirths, causes of death, maternal condition at time of perinatal death and identify modifiable risk factors for mortality (233). At the time, South Africa’s public health system was fragmented and lacked a centrally-managed and comprehensive database to address the high maternal and perinatal mortality occurring (234).

PPIP is mandatory in all South African health facilities and is central to tracking and measuring progress towards reducing maternal and perinatal deaths through in-depth investigation of the causes and circumstances surrounding deaths occurring at public health facilities.

3.1.2 Development and implementation of PPIP

PPIP was field tested in the Highveld region of Mpumalanga in 1995 and was subsequently introduced to other sites. In 2000, 27 sites had adopted PPIP. In 2005, the national Department of Health actively promoted the use of PPIP as the method for facility-based perinatal audit. By 2011, the programme was adopted in 94% of hospitals (238/252), with 73% of births (1,330,869/1,820,664) within those hospitals being captured across all levels of care (community health centres to tertiary hospitals) (97). This represented 52% of all births occurring in public health facilities across South Africa. In 2012, the PPIP became mandatory for all facilities delivering pregnant mothers and caring for newborns. It is
now estimated that >90% of births and perinatal deaths are captured through PPIP in some provinces (234).

3.1.3 Management of PPIP

Figure 3.1 shows the flow of data in PPIP. Data are collected and entered at each health facility by trained data collectors. Yearly provincial workshops managed by the Medical Research Council and the PPIP co-ordinator are conducted to provide education on how to enter data, complete forms and perform data validity assessments. As part of the vital checks, the PPIP co-ordinator undertakes a year-round visiting cycle of the health services. At these contacts, the medical records for the deaths are reviewed against the data entered to assess quality and provide feedback to the staff. This process is particularly focused on unexplained stillbirths, in order to ensure identification of contributing factors and potential causes of death.

All data are then routinely uploaded into the national database at the Medical Research Council Unit for Maternal and Infant Health Care Strategies in Pretoria (234). Results from PPIP serve as an audit for feedback at on-site perinatal (and maternal) morbidity and mortality meetings, as well as at a regional and national level. Data are updated weekly with collated national data released every three months to registered data analysts.

A ‘functional PPIP’ facility is considered one that spans all areas of the audit cycle: 1) captures all births and perinatal deaths; 2) enters and identifies direct causes of death and avoidable factors at regular mortality and morbidity meetings; 3) implements management change and policies as a result of meeting findings; and 4) has a central level providing feedback to the facility regarding the data received.
Figure 3.1. Flow of data in Perinatal Problem Identification Program (235).
3.1.4 Data capture process

The process of data collection can be divided into three main steps:

1) Data capture of all deliveries, births and perinatal deaths that occur in the birth and postnatal ward: All deliveries, stillbirths and early neonatal deaths are recorded on the standardised data capturing form (DCF), by the facility health worker, midwife or appointed data collector (hospital level). The number of livebirths and birth weight for each birth are also recorded. For all perinatal deaths, basic clinical data (Table 3.1), primary obstetric cause of death and final cause of neonatal death are recorded. These data are captured from the birth register in the labour ward, neonatal nursery death book and the death registers in the paediatric wards (late neonatal deaths) and emergency and trauma units. The condition (e.g., healthy, medical condition) of the mother at time of death is also recorded.

2) Entering and identifying the causes of deaths: Step 2 involves detailed investigation and recording of cause of deaths. All perinatal deaths are reviewed at regular, compulsory, perinatal mortality and morbidity meetings within each hospital. The meeting is chaired by a doctor and the confidential inquiry into each death occurs with hospital managers, clinicians and midwives present.

Deaths are classified into fresh stillbirths, macerated stillbirths, early neonatal death (0-7 days) or late neonatal death (8-28 days). Macerated stillbirths are clinically diagnosed as a baby where the skin was discoloured, blotchy and friable to touch; a fresh stillbirth is clinically diagnosed as a baby with the skin intact and ‘normal’ in appearance. PPIP has its own coding system and does not use ICD-10 coding to classify deaths. The causes of death are classified according to primary obstetric causes and final causes. The primary obstetric cause of death is defined by the PPIP technical team as the main obstetric event or pregnancy occurrence which was integral in the pathway to perinatal death. As South Africa is a low resource setting this decision comes from case review and verbal autopsy and rarely from placental histology or fetal/neonatal autopsy (12). Each perinatal death is classified using lead and sub-categories (Table 3.2) with maternal condition
recorded through lead categories (Table 3.3). In addition to the cause of death other clinical information is also collected as outlined in Table 3.1.

3) Identification of avoidable factors linked to each death: Step 3 involves exploring avoidable causes of death at the perinatal mortality and morbidity meetings (outlined in Step 2). The avoidable contributors to each death are discussed and coded for analytical purposes and recorded onto the DCF. Avoidable factors are then grouped into patient-related, medical personnel-related or administrative-related factors.
### Table 3.1. Clinical information captured in perinatal death cases in Perinatal Problem Identification Program

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Response categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>Continuous (0-6000)</td>
</tr>
<tr>
<td>Place of birth</td>
<td>Delivered at facility</td>
</tr>
<tr>
<td></td>
<td>Delivered at home</td>
</tr>
<tr>
<td></td>
<td>Delivered in transit</td>
</tr>
<tr>
<td></td>
<td>Delivered at other facility</td>
</tr>
<tr>
<td></td>
<td>Delivery place unknown</td>
</tr>
<tr>
<td>Maternal age</td>
<td>Continuous (0-65)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Parity</td>
<td>Continuous (0-8)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Access to antenatal care</td>
<td>Yes/No</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>22-44</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Certain gestational age</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Method of gestational age determination</td>
<td>Dates</td>
</tr>
<tr>
<td></td>
<td>Ultrasound</td>
</tr>
<tr>
<td></td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Single-multiple pregnancy</td>
<td>Single /Multiple</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Serology positive</td>
</tr>
<tr>
<td></td>
<td>Serology negative</td>
</tr>
<tr>
<td></td>
<td>Serology not determined</td>
</tr>
<tr>
<td></td>
<td>Serology tested but no result available</td>
</tr>
<tr>
<td>HIV serology</td>
<td>Serology positive</td>
</tr>
<tr>
<td></td>
<td>Serology negative</td>
</tr>
<tr>
<td></td>
<td>Serology not determined</td>
</tr>
<tr>
<td></td>
<td>Serology tested but no result available</td>
</tr>
<tr>
<td>ART used (only for HIV positive serology)</td>
<td>Prophylactic ART</td>
</tr>
<tr>
<td></td>
<td>Long-term ART</td>
</tr>
<tr>
<td></td>
<td>Intrapartum ART only</td>
</tr>
<tr>
<td></td>
<td>ART used, but type unknown</td>
</tr>
<tr>
<td></td>
<td>No ART used</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
**Table 3.2. Classification of perinatal conditions in Perinatal Problem Identification Program (PPIP) in South Africa**

<table>
<thead>
<tr>
<th>INTRAUTERINE DEATH</th>
<th>FETAL ABNORMALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained intrauterine death - macerated</td>
<td>Fetal chromosomal abnormality</td>
</tr>
<tr>
<td>Unexplained intrauterine death - fresh</td>
<td>Abnormality of multiple systems</td>
</tr>
<tr>
<td>Unexplained IUD due to lack of notes</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Non-specific fetal abnormality - FLK</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular system abnormality</td>
</tr>
<tr>
<td></td>
<td>Non-immune hydrops fetalis</td>
</tr>
<tr>
<td></td>
<td>Renal system abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>SPONTANEOUS PRETERM LABOUR</td>
<td></td>
</tr>
<tr>
<td>Ideopathic preterm labour</td>
<td></td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic preterm delivery for no real reason</td>
<td></td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
<td></td>
</tr>
<tr>
<td>with chorioamnionitis</td>
<td></td>
</tr>
<tr>
<td>Preterm labour with chorioamnionitis with intact membranes</td>
<td></td>
</tr>
<tr>
<td>Cervical incompetence</td>
<td></td>
</tr>
<tr>
<td>HYPERTENSIVE DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Proteinuric hypertension</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td></td>
</tr>
<tr>
<td>Pregnancy-induced hypertension without proteinuria</td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td></td>
</tr>
<tr>
<td>INTRAPARTUM ASPHYXIA</td>
<td></td>
</tr>
<tr>
<td>Labour related intrapartum asphyxia</td>
<td></td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td></td>
</tr>
<tr>
<td>Cord around the neck</td>
<td></td>
</tr>
<tr>
<td>Cord prolapse</td>
<td></td>
</tr>
<tr>
<td>Ruptured uterus</td>
<td></td>
</tr>
<tr>
<td>Traumatic breech delivery</td>
<td></td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td></td>
</tr>
<tr>
<td>Precipitous labour</td>
<td></td>
</tr>
<tr>
<td>Traumatic assisted delivery</td>
<td></td>
</tr>
<tr>
<td>ANTEPARTUM HAEMORRHAGE</td>
<td></td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td></td>
</tr>
<tr>
<td>Abruptio placenta with hypertension</td>
<td></td>
</tr>
<tr>
<td>Antepartum haemorrhage of unknown origin</td>
<td></td>
</tr>
<tr>
<td>Placenta praevia</td>
<td></td>
</tr>
<tr>
<td>INTRAUTERINE GROWTH RETARDATION</td>
<td></td>
</tr>
<tr>
<td>Idiopathic intrauterine growth retardation</td>
<td></td>
</tr>
<tr>
<td>Postmaturity</td>
<td></td>
</tr>
<tr>
<td>IUGR with histological features of ischaemic placental disease</td>
<td></td>
</tr>
<tr>
<td>NO OBSTETRIC CONDITION</td>
<td>NON-PREGNANCY-RELATED INFECTIONS</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Healthy mother</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Other non-pregnancy-related infections</td>
</tr>
<tr>
<td>Proteinuric hypertension</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension without proteinuria</td>
<td>Complications of antiretroviral therapy</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Wasting syndrome</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Other pneumonia</td>
</tr>
<tr>
<td>HELLP</td>
<td>PCP pneumonia</td>
</tr>
<tr>
<td>Liver rupture</td>
<td>Malaria</td>
</tr>
<tr>
<td>Acute fatty liver</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>OBSTETRIC HAEMORRHAGE</td>
<td>Other meningitis</td>
</tr>
<tr>
<td>Abruption with hypertension</td>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td>Abruption without hypertension</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Other APH not specified</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Ruptured uterus with previous c/s</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Ruptured uterus without previous c/s</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>MEDICAL AND SURGICAL DISORDERS</td>
<td>COINCIDENTAL CONDITIONS</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Herbal medicine</td>
</tr>
<tr>
<td>Other medical and surgical disorders</td>
<td>Other coincidental conditions</td>
</tr>
<tr>
<td>Auto-immune disease</td>
<td>Other accidents</td>
</tr>
<tr>
<td>Haematological disease</td>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>Genito-urinary disease</td>
<td>Assault</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Rape</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>ANAESTHETIC COMPLICATIONS</td>
</tr>
<tr>
<td>CNS disease</td>
<td>Complications of general anaesthetic</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>Complications of spinal anaesthetic</td>
</tr>
<tr>
<td>GIT disease</td>
<td>Complications of epidural anaesthetic</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>EXTRA-UTERINE PREGNANCY</td>
</tr>
<tr>
<td>Skeletal disease</td>
<td>Extra-uterine pregnancy</td>
</tr>
<tr>
<td>PREGNANCY-RELATED SEPSIS</td>
<td>EMBOLISM</td>
</tr>
<tr>
<td>Chorioamnionitis with ruptured membranes</td>
<td>Amniotic fluid embolism</td>
</tr>
<tr>
<td>Chorioamnionitis with intact membranes</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>ACUTE COLLAPSE - CAUSE UNKNOWN</td>
<td></td>
</tr>
<tr>
<td>Acute collapse - cause unknown</td>
<td></td>
</tr>
</tbody>
</table>

Bold – lead categories; normal – sub-categories; * Only lead categories can be linked to perinatal deaths
3.1.5 Data quality and data verification

A number of steps are conducted to ensure high data quality. Firstly, there are a number of built-in mechanisms within the database to prevent missing data and data-entry errors. For example, the inability to leave spaces blank, automatic accuracy checks, and the inability to enter duplicates are incorporated into the PPIP system. The risk of missing data are minimised by correlating monthly aggregate data to the detailed individual perinatal death data. This occurs at the facility level before being sent to the provincial level (Figure 3.1). The maternal, child and women’s health co-ordinator analyses the data for trends in mortality rates (and breakdown by primary cause of death) and ensures that a second verification occurs. After this step, the data are sent to the national database housed at the Medical Research Council Unit for Maternal and Infant Healthcare Strategies in Pretoria. Random audits also occur across levels of care to ensure compliance with PPIP data entry guidelines and that the data entered into PPIP is complete.

3.1.6 Changes over time

Collection of additional data for each death commenced in June 2013 (known as PPIP version 3). This included estimated gestational age (in weeks) at time of death, the method used for estimation of gestational age (ultrasound/palpitation/or last menstrual period), and accuracy of the gestational age estimate (certain/uncertain/unknown). However, in approximately 50% of cases the gestational age estimate is unknown or uncertain (see Section 3.2.3). From this information, size-for-gestational-age is classified using the Theron-Thompson fetal growth curves (small-for-gestational-age, SGA - <10th centile; appropriate gestational age (AGA - >10th centile); large-for-gestational-age (>90th centile) (227).
3.2 Data used for this thesis – overview

The data used for this thesis were from the period October 2013 to the most current complete data available when each analysis was conducted. All data from this study were from public health facilities only (not private sector). This period of time was chosen as the database contained information on gestational age and size-for-gestational-age which were both important variables for analyses conducted. This was also one year after PPIP became mandatory, allowing sufficient time for implementation in all facilities thereby maximising coverage of the data. The provinces with the largest proportion of facilities reporting complete data consistently were Western Cape, Mpumalanga and Limpopo, where it is estimated that >90% of all perinatal deaths were captured. Therefore, data from these provinces were used where appropriate (Chapters 4, 5, 8). For analyses that required a national overview, data across all facilities across South Africa were used, coverage across South Africa is approximately ~75% (Chapters 6, 7).

3.2.1 Study cohorts used for this thesis

Each analysis in this thesis used a different cohort and study period dependant on the aims of each study. Table 3.4 outlines the study cohort, time period and justification for the selected sample for each chapter/analysis.
### Table 3.4. Description of study cohort for each analysis/paper.

<table>
<thead>
<tr>
<th>Chapter and study title</th>
<th>Aim of study</th>
<th>Provinces used</th>
<th>Time period</th>
<th>Selection criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER 4 Timing and cause of perinatal mortality for small-for-gestational-age babies in South Africa: critical periods and challenges with detection</td>
<td>To explore the timing and cause of stillbirth and early neonatal mortality (END, &lt;7 days) by small-for-gestational age</td>
<td>Limpopo Mpumalanga Western Cape</td>
<td>1 October 2013 to 31 August 2015</td>
<td>Inclusion: Stillbirths and early neonatal deaths (&gt;1000 g and &gt;28 weeks) Exclusion: No antenatal care received</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Greatest PPIP Coverage (&gt;90% of perinatal deaths audited)</td>
<td>Analysis required information on gestational age and size-for-gestational-age collected after June 2013</td>
<td>Only viable pregnancies (as per South African definition) to be included as avoidable stillbirths wanted to be examined. Only women receiving ANC were included as SGA can be detected antenatally.</td>
</tr>
<tr>
<td>CHAPTER 5 Stillbirth risk across pregnancy by size-for-gestational-age in Western Cape, South Africa: application of the fetuses-at-risk approach using perinatal audit data</td>
<td>To compare stillbirth risk across pregnancy by size-for-gestational-age</td>
<td>Western Cape</td>
<td>1 October 2013 to 31 August 2015</td>
<td>Inclusion: ≥1000 g and ≥28 weeks gestation Exclusion: Unknown gestational age; estimated age was considered ‘uncertain’; multiple pregnancies; no ANC received</td>
</tr>
<tr>
<td></td>
<td></td>
<td>It was important that women in this study had regular ANC as ANC influences stillbirth risk. Western Cape is the only province with 8 routine ANC contacts.</td>
<td>Analysis required information on gestational age and size-for-gestational-age collected after June 2013</td>
<td>Only preventable/viable stillbirths were needed for this analysis. As gestational was a crucial element for this analysis only women with certain gestational age were included. There is debate in the literature around if multiple pregnancies have different growth trajectories, risk of SGA and stillbirth risk. Therefore multiple pregnancies were excluded. Only women who had ANC were included as ANC assists the identification of SGA.</td>
</tr>
<tr>
<td>Chapter and study title</td>
<td>Aim of study</td>
<td>Provinces used</td>
<td>Time period</td>
<td>Selection criteria</td>
</tr>
<tr>
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<tr>
<td>CHAPTER 6 INTERGROWTH-21st vs local South African standards (Theron) for identification of small-for-gestational-age in stillbirths: a closer look at variation across pregnancy</td>
<td>To compare INTERGROWTH-21st with local standard (Theron) to identify small-for-gestational-age (SGA) fetuses in stillbirths in the South African setting</td>
<td>All provinces in South Africa</td>
<td>October 2013 to December 2016</td>
<td>Inclusion: Stillbirths (&gt;500g and ≥28 weeks ≤ 40 weeks) Exclusion: Unknown gestational age; estimated gestational age was considered ‘uncertain’</td>
</tr>
<tr>
<td><strong>Justification</strong></td>
<td></td>
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<td></td>
<td>There was no need to select specific provinces as this methodological study sought to explore the concordance between fetal growth charts across a large sample or stillbirths.</td>
<td></td>
<td>Analysis required SGA information (captured after June 2013). December 2016 was chosen as most complete data at time of analysis.</td>
<td>Stillbirths over 500g were chosen (rather than &gt;1000g i.e. viable) as the objective of this study was to compare different growth charts in identifying SGA. As many SGA infants are less than 500g at younger gestations using a cut-off at ≥1000g would exclude the majority of stillbirths at 28/29 weeks. For this analysis the viability of the fetuses was not an issue as we sought to compare charts in fetuses that were already stillborn. The gestational ages below 28 weeks and above 42 weeks could not be used as Theron growth charts are not reliable for gestations &lt;28 weeks and INTERGROWTH-21st estimated fetal weight is only available up to 40 weeks gestation.</td>
</tr>
<tr>
<td>CHAPTER 7 Does antenatal care timing influence stillbirth risk in the third trimester? A secondary analysis of perinatal death audit data in South Africa</td>
<td>To explore stillbirth risk across gestation in three provinces of South Africa with different antenatal care schedules.</td>
<td>Limpopo Mpumalanga Western Cape</td>
<td>1 October 2013 to 31 August 2015</td>
<td>Cases were excluded if the gestational age was unknown or if the estimated age was considered ‘uncertain’. Cases excluded if no ANC received.</td>
</tr>
</tbody>
</table>
| **Justification** | | | | As correct gestational age was crucial for the analysis for timing of stillbirth and calculation of stillbirth risk (Yudkin’s
Western Cape was chosen as this was the only province with 8 routine ANC contacts; Limpopo and Mpumalanga were selected as they have 4 routine ANC contact and greatest PPIP coverage.  

size-for-gestational-age collected after June 2013  

method) only cases where gestational age was certain were included. See Chapter 5. for further information and sensitivity analysis.  
Pregnancies that did not receive ANC were excluded as this study sought to explore the impact of different ANC schedules on stillbirth risk.  

| CHAPTER 8 | Implementation of the ICD-PM codes to existing South African mortality data: strengths, opportunities for improvement and future challenges | To assess if ICD-PM can be applied to existing datasets; To explore if the features of ICD-PM are advantageous in classifying perinatal deaths. | All provinces in South Africa | 1 October 2013 to 31 December 2016 | Inclusion: All perinatal deaths (>1000g and =>28 weeks gestation)  
Exclusion: No exclusion |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Justification</strong></td>
<td>National level data was used to give a complete picture of perinatal mortality in South Africa</td>
<td>December 2016 was chosen as was the most complete data at time of analysis. Start date of October 2013 allowed sufficient time for implementation of mandatory reporting of perinatal deaths to occur.</td>
<td>ICD-PM includes death classifications for both stillbirths and early neonatal deaths so this criteria was adopted. &gt;1000g and &gt;28w was chosen as this is the internationally accepted criteria for viable stillbirths when conducting international comparisons which is important for future comparisons between settings using ICD-PM. Only stillbirths considered viable were included as this study sought to discuss interventions to prevent avoidable stillbirths. As factors such as certain gestational age were not critical for the analysis these cases were not excluded.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.2.2 Stillbirth definition

Stillbirths were considered deaths >1000g and >28 weeks for analyses (except Chapter 6 see Table 3.4). This criteria was adopted for two reasons: 1) it is the definition for stillbirth according to the South African Births and Deaths Registration Act (Act No. 51 of 1992); 2) it is the definition for stillbirth according to the WHO for international comparisons. It was not applied for the analysis in Chapter 6 as many stillbirths at gestations 28 weeks would have been excluded from the analysis if the weight cut-off was >1000g (See Table 3.4 for detailed explanation).

3.2.3 Variable selection and missing data

A decision was required regarding whether to use primary cause of death or end cause of death for analyses in this thesis. Primary cause of death (the main obstetric event or pregnancy occurrence which was integral in the pathway to perinatal death) was chosen because this is the internationally accepted approach (66, 71). The end cause of death is the subsequent cause of death based on secondary complications of the initial complication. Therefore, for intervention purposes the primary cause of death was deemed more relevant and adopted for the current work.

For many of the analyses in this doctorate, cases were excluded if gestational age information was not certain or unknown. In most analyses this resulted in ~50% of cases been excluded. Uncertain gestational age or no information on gestational age are well-documented issues in data collection systems and clinical settings in LMICs including South Africa (64, 232). An analysis was conducted comparing the sociodemographic characteristics between pregnancies with certain gestational age and pregnancies without certain gestational age. There were no significant differences between the two groups for maternal age, parity, HIV status or syphilis infection. Therefore it was concluded that although a large proportion of the cases were excluded the analytic sample was still broadly representative of the full sample.
3.2.4 Previous publication and reporting of PPIP data

The National Department of Health strongly supports three National Committees which review maternal, perinatal and children’s deaths in South Africa and releases a series of triennial reports (164). PPIP forms the basis for one of these reports known as the Saving Babies report, responsible for national reporting around perinatal deaths (97). This report presents the number of births and deaths stratified by weight categories, summary tables on primary causes of deaths, and summary tables on avoidable causes of death. The most recent Savings Babies report was published in 2014 presenting data from 2012-13 (9).

PPIP has been used as an input to the national and regional cause of death estimates compiled by the Child Health Epidemiology Reference Group (236). The data have also being used to assess and triangulate Statistics South Africa’s vital registration data (237). Analyses from the PPIP data have also been published in several peer-reviewed journals. These papers have used the data to assess quality of perinatal audit and challenges reducing perinatal mortality in South Africa (12, 63, 236-238).

3.2.5 Ethical considerations

The PPIP program has ethical approval from the University of Pretoria. The data were collected with permission from the South African Department of Health. All secondary analyses in this thesis were approved by the PPIP technical task team and UWA Human Ethics Committee (RA/4/1/7955) (APPENDIX B).
CHAPTER 4: Timing and cause of perinatal mortality for small-for-gestational-age babies in South Africa: critical periods and challenges with detection

PUBLISHED PAPER

This chapter is published version of the following paper:

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Keywords: small-for-gestational-age, intrauterine growth restriction, perinatal mortality, South Africa, low-and-middle-income countries; Doppler
PREAMBLE

This study was undertaken as an overview of the current causes of perinatal mortality. As information around small-for-gestational-age babies in South Africa was limited, this was a focus of this paper. The results from this study informed the analysis in Chapter 5-7, particularly for analyses involving small-for-gestational-age babies.


4.1 Abstract

Background: Little information exists on timing and cause of death for SGA babies in LMICs, despite evidence from high-income countries suggesting critical periods for SGA babies. This study explored the timing of and cause of stillbirth and early neonatal mortality (END, <7 days) by small-for-gestational age in three provinces in South Africa. In South Africa, the largest category of perinatal deaths is unexplained stillbirth, of which up to one-quarter have intra-uterine growth restriction.

Methods: Secondary analysis of the South African PPI database allowed for the analysis of gestational age at death and clinically confirmed diagnosis of stillbirth and early neonatal death (END) (>1000g and >28 weeks) across gestation. Comparisons by province, size-for-gestational-age, gestational age groups, and maternal condition at death were performed. The provinces investigated were: Western Cape (fortnightly antenatal care contacts from 32-38 weeks), Limpopo and Mpumalanga (no antenatal care contacts between 32-38 weeks).

Results: There were 528727 births in the study period and 8111 stillbirths and 5792 early neonatal deaths. Similar timing of deaths across gestation was seen for the three provinces with the greatest proportion of deaths for SGA babies at 33-37 weeks (stillbirths 52.9%; END 43.3%; p<0.05). SGA babies had a greater proportion of deaths due to hypertension (SGA 22.9%; AGA 18.6%; LGA 18.6%; p<0.05) and intrauterine growth restriction (SGA 6.8%; AGA 1.7%; LGA 1.4%; p<0.05). No increase was seen in poor maternal condition for SGA babies and 54.9% of deaths had a healthy mother. Of mothers that were healthy the greatest proportion of SGA stillbirths were due to unexplained intrauterine death (53.9%).

Conclusion: There was a peak in stillbirths for SGA babies 33-37 weeks in all provinces. Detecting SGA is further complicated as in most cases the mother is healthy. Further research into Umbiflow Doppler velocimetry use in low-risk populations is warranted and may be a viable strategy to increase current detection of SGA babies at risk of mortality in LMICs.
4.2 Background

Approximately 25% of children born in LMICs are SGA (11). Babies who are SGA are at increased risk of mortality and neonatal morbidity (86, 239), making the detection and clinical management of such infants crucial. The condition may constitute a small but healthy fetus or be due to pathological growth failure (intrauterine growth restriction (IUGR)) (47). The purpose of identifying SGA fetuses, defined as a birth weight in the lowest decile on standard growth curves (240), is to recognise those most at risk of poor outcomes (86).

Studies to date have indicated that there may be a critical period for increased mortality for SGA babies (86, 240, 241). A UK study found that stillbirths between 28-36 weeks were increased for SGA babies (240). Other studies have found that SGA babies are at increased risk of stillbirth compared to non-SGA babies at all gestational ages (86), and that the risk of stillbirth for SGA babies increases with advancing gestational age (241).

In South Africa, the largest category of perinatal deaths is unexplained stillbirth, of which up to one-quarter have IUGR (12). Early recognition can prevent some of these deaths. Early antenatal detection of SGA babies remains a challenge in LMICs, but is important as most deaths occur in the late preterm or term period, where survival of live born infants in well-resourced units is high (242). As detection of SGA at the population level is challenging due to resource constraints, identifying critical periods and causes of mortality across gestation may elucidate the best approach.

This study explores the gestational age at death and cause of stillbirth and early neonatal mortality (up to 7 days neonatal life) by size-for-gestational age in three South African provinces.

4.3 Methods

Secondary analysis of the South African PPIP database allowed for the analysis of gestational age at death and clinically confirmed diagnosis of stillbirth and END across gestation. The program also allowed for comparisons between SGA, appropriate-for-gestational-age (AGA) and large-for-
gestational-age (LGA) babies from 1 October and 2013 and 31 August 2015 and between three provinces: Western Cape, Limpopo and Mpumalanga. Western Cape has fortnightly antenatal care contacts between 32 and 38 weeks, while Limpopo and Mpumalanga do not have contacts between 32 and 38 weeks, preventing the opportunity for detection of SGA at these gestations. These provinces were chosen (from nine available) as they have the greatest PPIP coverage, auditing >90% of perinatal deaths. PPIP is a perinatal quality audit system that has been described in detail elsewhere (12, 63).

Briefly, at each clinical site (n=292) across the three provinces the clinical team perform a review shortly after a death has occurred. The primary obstetric cause of death was defined by the PPIP technical team as the main obstetric event or pregnancy occurrence which was integral in the pathway to perinatal death, as described in other published studies (12). IUGR was also identified at the time of death through clinical evaluation. Maternal condition at the time of death was also recorded.

Categories for the primary obstetric cause of stillbirth and early neonatal death were as follows: antepartum haemorrhage, spontaneous preterm labour (intrapartum stillbirth), unexplained intrauterine death, fetal abnormality, hypertensive disorders, infections, intrapartum asphyxia, intrauterine growth restriction, maternal disease, miscellaneous (rhesus isoimmunisation, twin-to-twin transfusion, extra-uterine pregnancy and other cause of death not described), no obstetric cause and trauma. The maternal condition is defined as either healthy (where the clinician examining her could not find any clinical problems) or the occurrence of a recognised medical or obstetric complication (e.g. cardiac, endocrine, respiratory disease or other disease that are an indirect cause of morbidity), categorised as coincidental conditions, medical and surgical disorders, non-pregnancy related infections, extra-uterine pregnancy, pregnancy-related sepsis, obstetric haemorrhage, hypertension, anaesthetic complications, embolism, and acute collapse (cause unknown).

Gestational age was calculated based on date of last menstrual period, ultrasound or clinical examination and cases were excluded if the gestation age was unknown or if the estimated age was considered ‘uncertain’. There was no hierarchy employed based on method of gestational age
estimation. Detailed data were extracted on all stillbirths >1000g and 28-42 weeks gestation and early neonatal deaths less than 7 days of neonatal life. Data were only included up to 42 weeks gestation as Theron weight distribution curves are not considered reliable for growth measurements after 42 weeks gestation (227, 243). Only women who had reported receiving antenatal care were included as SGA can be detected antenatally. Data extracted from the three provinces represent 58.6% of all deaths in South Africa that met the study criteria. Birth weight for gestation was obtained from Theron charts. SGA was defined as neonates with <10\textsuperscript{th} centile for gestational age based on South African specific growth charts (227, 243).

4.3.1 Statistical analysis

Stillbirth and early neonatal death cumulative incidence were calculated for each province using the number of reported births (all births for stillbirth, live births for neonatal death rate) as the denominator. The frequencies of deaths occurring across gestation were compared between SGA, AGA and LGA babies as well as between provinces. Comparisons between the proportion of primary cause of deaths were made by size-for-gestational-age, gestational age at death and in relation to maternal conditions. Gestational age was grouped into three categories for analysis: 28-32 weeks, 33-37 weeks and 38-42 weeks. Frequency distributions were performed and Pearson’s chi-squared test or Fisher’s exact test (where n<5) were used to determine crude differences between proportions for the key comparisons made (i.e. size-for-gestational-age, gestational age at death, maternal condition and between provinces). Independent t-tests were used to compare means between key groups. A p-value <0.05 was accepted as statically significant.

The PPIP program has ethical approval from the Faculty of Heath Sciences Ethics Committee at the University of Pretoria. The data are collected with permission from the South African Department of Health. This secondary analysis was approved by the PPIP technical task team and UWA Human Ethics Committee.
4.4 Results

There were 528,727 births >1000g in the study period (Mpumalanga =145362; Western Cape=173597; Limpopo =209768), of which 8111 (1.5%) were stillbirths (Mpumalanga =2501; Limpopo=3808; Western Cape=1802) and 3792 (0.7%) died in the early neonatal period (<7days) (Mpumalanga =1163; Limpopo=2124; Western Cape=505). The cumulative incidence of stillbirth for the study period was highest in Limpopo (18.2 per 1000 births) and Mpumalanga (17.2/1000) compared to Western Cape (10.4/1000). The cumulative incidence of early neonatal death was highest in Limpopo at 10.3 per 1000 live births, followed by Mpumalanga (8.1 per 1000) and Western Cape (3.0 per 1000). After exclusion of deaths prior to 28 weeks (and after 42 weeks), deaths with unknown or uncertain gestation and women who had not received ANC, the number of deaths used for analysis was 6133 (Mpumalanga n=2198; Limpopo n=3032; Western Cape n=903). The greatest proportion of babies in the study were AGA (61.5%), followed by SGA (22.6%) and LGA (12.3%).

4.4.1 Gestational age at death

There were no differences between provinces in terms of representation and timing of stillbirths between SGA, AGA, LGA, therefore data from the three provinces were combined and presented as means and standard errors. Stillbirths who were AGA or LGA occurred across gestation without any significant increases or decreases. A larger proportion of stillbirths occurred for SGA babies in the 33-37 week period in all provinces (Figure 4.1). When considering macerated and fresh stillbirths a peak at 33-37 weeks was also seen for SGA babies (Figure 4.1). A similar pattern was seen for early neonatal deaths (END) with a peak at 33-37 weeks for SGA babies. The timing of END for AGA and LGA babies increased during the 38-42 week period but remained low at 28-32w and 33-37w.
4.4.2 Primary causes of death

Stillbirths by size-for-gestational-age

The primary cause of stillbirth across the sample was unexplained intrauterine death (33.1%), followed by intrapartum asphyxia (17.2%) and hypertensive disorders (19.7%) (Table 4.1). Some primary causes of death were more frequent in the SGA group, such as fetal abnormality (37.8%) and intrauterine growth restriction (59.8%) which represented up to half of all deaths despite only representing 26.2% of the total sample (p<0.05). Intrapartum asphyxia for SGA babies was indicated in 13.3% of deaths due to intrapartum asphyxia across gestation (p<0.05).

Table 4.1 Primary cause of stillbirth by size-for-gestational age (Western Cape, Limpopo and Mpumalanga combined); n=4059

<table>
<thead>
<tr>
<th>Primary Cause of Stillbirth</th>
<th>SGA n(%)</th>
<th>AGA n(%)</th>
<th>LGA n(%)</th>
<th>All %</th>
</tr>
</thead>
<tbody>
<tr>
<td>APH</td>
<td>145(13.6)</td>
<td>399(16.0)</td>
<td>51(10.2)</td>
<td>14.7</td>
</tr>
<tr>
<td>Unexplained Intrauterine death</td>
<td>367(34.5)</td>
<td>812(32.5)</td>
<td>164(32.8)</td>
<td>33.1</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>54(5.1)*</td>
<td>67(2.7)</td>
<td>22(4.4)</td>
<td>3.5</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>244(22.9)*^</td>
<td>463(18.6)</td>
<td>93(18.6)</td>
<td>19.7</td>
</tr>
<tr>
<td>Infections</td>
<td>26(2.4)</td>
<td>42(1.7)</td>
<td>7(1.4)</td>
<td>1.8</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>93(8.7)**^</td>
<td>512(20.5)</td>
<td>93(18.6)</td>
<td>17.2</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>73(6.8)**^</td>
<td>42(1.7)</td>
<td>7(1.4)</td>
<td>3.0</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>12(1.1)**^</td>
<td>56(2.2)</td>
<td>41(8.2)</td>
<td>2.7</td>
</tr>
<tr>
<td>Misc.</td>
<td>22(2.1)</td>
<td>27(1.1)</td>
<td>6(1.2)</td>
<td>1.4</td>
</tr>
<tr>
<td>No obstetric cause</td>
<td>1(0.1)</td>
<td>2(0.1)</td>
<td>1(0.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Spont. Preterm labour</td>
<td>27(2.5)</td>
<td>65(2.6)</td>
<td>12(2.4)</td>
<td>2.6</td>
</tr>
<tr>
<td>Trauma</td>
<td>1(0.1)</td>
<td>8(0.3)</td>
<td>2(0.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>All</td>
<td>1065</td>
<td>2495</td>
<td>499</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*p<0.05 with AGA; ^p<0.05 with LGA; Pearson chi-sq tests, Fisher’s exact where cell count <5
Figure 4.1 Proportion of deaths (standard error for provinces combined) across gestation by size-for-gestational-age (black line SGA, dark grey AGA, light grey LGA); * p<0.05 with AGA; + p<0.05 with LGA. ^SGA significantly increased at 33-37w compared to 28-32w; # SGA significantly increased at 33-37w compared to 38-42 weeks.
Early neonatal deaths by size-for-gestational-age

The primary cause of early neonatal death was intrapartum asphyxia (42.1%), followed by spontaneous preterm labour (18.7%), fetal abnormality (11.4%) and hypertensive disorders (7.3%)(Table 4.2). Cause of death in SGA babies were intrauterine growth restriction (91.3%), hypertensive disorders (37.0%), fetal abnormality (33.3%), and spontaneous preterm labour (36.0%) which represented a large proportion of all deaths by cause despite representing only 23.7% of the sample.

Table 4.2 Primary cause of early neonatal death (<7days) by size-for-gestational age (provinces combined); n=1742

<table>
<thead>
<tr>
<th>Primary Cause Death (END)</th>
<th>SGA n(%)</th>
<th>AGA n(%)</th>
<th>LGA n(%)</th>
<th>All %</th>
</tr>
</thead>
<tbody>
<tr>
<td>APH</td>
<td>18(44)</td>
<td>59(5.1)</td>
<td>3(1.6)</td>
<td>4.6</td>
</tr>
<tr>
<td>Unexplained Intrauterine death</td>
<td>1 (0.2)</td>
<td>2(0.2)</td>
<td>0(0.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>66 (16.0)*</td>
<td>112(9.8)</td>
<td>20(10.9)</td>
<td>11.4</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>47 (11.4)*</td>
<td>68(5.9)</td>
<td>12(6.5)</td>
<td>7.3</td>
</tr>
<tr>
<td>Infections</td>
<td>11 (2.7)</td>
<td>26(2.3)</td>
<td>5(2.7)</td>
<td>2.4</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>103 (25.0)**</td>
<td>619(54.0)</td>
<td>11(62.0)</td>
<td>42.1</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>21(5.1)**</td>
<td>2(0.2)</td>
<td>0(0.0)</td>
<td>1.3</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>1 (0.2)</td>
<td>7(0.6)</td>
<td>2(1.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Misc.</td>
<td>7(1.7)</td>
<td>17(1.5)</td>
<td>5(2.7)</td>
<td>1.7</td>
</tr>
<tr>
<td>No obstetric cause</td>
<td>20(4.9)</td>
<td>44(3.8)</td>
<td>5(2.7)</td>
<td>4.0</td>
</tr>
<tr>
<td>Spont. Preterm labour</td>
<td>117(28.4)**</td>
<td>190(16.6)</td>
<td>18(9.8)</td>
<td>18.7</td>
</tr>
<tr>
<td>Trauma</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>All</td>
<td>412</td>
<td>1146</td>
<td>184</td>
<td>100.0</td>
</tr>
</tbody>
</table>

*p<0.05 with AGA; ^p<0.05 with LGA; Pearson chi-sq tests, Fisher’s exact where cell count <5.

Stillbirths across gestational age groups (28-32, 33-37, and 38-42 weeks)

The main causes of stillbirth at 28-32 weeks and 33-37 weeks for babies of all gestations were unexplained intrauterine death (34.5%; 33.4%, respectively), hypertensive disorders (27.7%; 20.2%) and antepartum haemorrhage (18.2%; 17.9%). For stillbirths during the 38-42 week period the main causes were unexplained intrauterine death (33%), intrapartum asphyxia (31.1%) and hypertensive disorders (13.5%)(Table 4.3). Mortality was highest in the 33-37 week period with death due to
unexplained intrauterine death (31.5%), hypertension (25.5%), antepartum haemorrhage (17.0%).

Most deaths for SGA babies from spontaneous preterm labour (70.4%), antepartum haemorrhage (64.8%) and hypertensive disorders (57.8%) occurred during the 33-37 week period (p<0.05). Most SGA deaths from intrapartum asphyxia occurred during the 38-42 week period (p<0.05).

Table 4.3. Primary cause of stillbirth for SGA babies across GA; n=1042

<table>
<thead>
<tr>
<th>Primary Cause Death</th>
<th>28-32w n(%)</th>
<th>33-37w n(%)</th>
<th>38-42w n(%)</th>
<th>All n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APH</td>
<td>23(13.5)</td>
<td>94(17.0)</td>
<td>28(8.8)</td>
<td>145(13.9)</td>
</tr>
<tr>
<td>Unexplained Intrauterine death</td>
<td>63(37.1)</td>
<td>174(31.5)^</td>
<td>130(40.6)</td>
<td>367(35.2)</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>9(5.3)</td>
<td>30(5.4)</td>
<td>15(4.7)</td>
<td>54(5.2)</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>52(30.6)</td>
<td>141(25.5)^</td>
<td>51(15.9)</td>
<td>244(23.4)</td>
</tr>
<tr>
<td>Infections</td>
<td>3(1.8)</td>
<td>9(1.6)^</td>
<td>14(4.4)</td>
<td>26(2.5)</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>7(4.1)</td>
<td>36(6.5)^</td>
<td>50(15.6)</td>
<td>93(8.9)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>7(4.1)</td>
<td>42(7.6)</td>
<td>24(7.5)</td>
<td>73(7)</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>1(0.6)</td>
<td>6(1.1)</td>
<td>5(1.6)</td>
<td>12(1.2)</td>
</tr>
<tr>
<td>Spont. Preterm labour</td>
<td>5(2.9)</td>
<td>19(3.4)^</td>
<td>3(0.9)</td>
<td>27(2.6)</td>
</tr>
<tr>
<td>Trauma</td>
<td>0(0.0)</td>
<td>1(0.2)</td>
<td>0(0)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>All</td>
<td>170(100.0)</td>
<td>552(100.0)</td>
<td>320(100.0)</td>
<td>1042(100.0)</td>
</tr>
</tbody>
</table>

^ with 38-42 week age group; Pearson chi-sq tests, Fisher’s exact where cell count <5.

**Early neonatal deaths across gestational age groups (28-32, 33-37, and 38-42 weeks)**

The main causes of early neonatal death at 28-32 weeks were spontaneous preterm labour (57.4%), hypertensive disorders (14.8%) and antepartum haemorrhage (10.2%). For deaths between 33-37 weeks the main causes of death were intrapartum asphyxia (47.3%), fetal abnormality (17.7%), spontaneous preterm labour (16%) and hypertensive disorders (9.2%). At 38-42 weeks intrapartum asphyxia was the main cause of death (77.1%), followed by fetal abnormality (11.5%)(Table 4.4). The largest causes of death during the 33-37 week period, when SGA deaths peaked, were for spontaneous preterm labour (36.5%), fetal abnormality (18.6%) and intrapartum asphyxia (18.6%) (Table 4.4). Most deaths from intrapartum asphyxia for SGA babies occurred during the 38-42 week period (68%), while most deaths from hypertensive disorders (48.9%) and fetal abnormality (47%) occurred during the 33-37 week period (p<0.05).
Table 4.4 Primary cause of ENND for SGA babies at each gestation, n=385

<table>
<thead>
<tr>
<th>Primary Cause Death</th>
<th>28-32w n(%)</th>
<th>33-37w n(%)</th>
<th>38-42w n(%)</th>
<th>All n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APH</td>
<td>8(9.2)</td>
<td>5(3.0)</td>
<td>5(3.5)</td>
<td>18(1.1)</td>
</tr>
<tr>
<td>Unexplained Intrauterine death</td>
<td>0(0.0)</td>
<td>1(0.6)</td>
<td>0(0.0)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>7(8.0)</td>
<td>31(18.6)*</td>
<td>28(21.4)</td>
<td>66(4.0)</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>17(19.5)</td>
<td>23(13.8)^</td>
<td>7(5.3)</td>
<td>47(2.9)</td>
</tr>
<tr>
<td>Infections</td>
<td>1(1.1)</td>
<td>5(3.0)</td>
<td>5(3.8)</td>
<td>11(0.7)</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>2(2.3)</td>
<td>31(18.6)*^</td>
<td>70(53.4)</td>
<td>103(6.3)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>2(2.3)</td>
<td>10(6.0)</td>
<td>9(6.9)</td>
<td>21(1.3)</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>1(1.1)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Spont. Preterm labour</td>
<td>49(56.3)</td>
<td>61(36.5)*^</td>
<td>7(5.3)</td>
<td>117(7.1)</td>
</tr>
<tr>
<td>Trauma</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>All</td>
<td>87(100.0)</td>
<td>167(100.0)</td>
<td>131(100.0)</td>
<td>385(100.0)</td>
</tr>
</tbody>
</table>

*p<0.05 with 28-32w age group; ^ with 38-42 week age group; Pearson chi-sq tests, Fisher’s exact where cell count <5.

4.4.3 Maternal condition

There were no significant differences in the proportion of deaths to healthy mothers by size-for-gestational-age (SGA n=605, 54.9%; AGA n=1394, 55.4%; LGA n=279, 53.8%). Of mothers who were healthy, the greatest proportion of stillbirths was seen for unexplained intrauterine death (all sizes-for-gestation 50.6%; SGA 53.9%). More mothers of SGA babies were hypertensive compared to AGA and LGA babies (SGA 26.3%; AGA 21.6%; LGA 21.2%; p<0.05), however fewer mothers of SGA babies had medical and surgical complications compared to LGA babies (SGA 5.1%; LGA 11%; p<0.05).

Causes of stillbirth and condition of mother for SGA babies across gestational groups are presented in Table 4.5. Stillbirths from spontaneous preterm labour were higher in the 33-37 week age group compared to the 38-42 weeks age group (p<0.05). Causes of early neonatal death and condition of mother for small-for-gestational age babies across gestational groups are presented in Table 6.
### Table 4.5. Cause of stillbirth and condition of mother for small-for-gestational age babies, n=1227

<table>
<thead>
<tr>
<th></th>
<th>Healthy Mother</th>
<th>Medical Surgical</th>
<th>Hypertension</th>
<th>Other Maternal Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28-32w 33-37w 38-42w</td>
<td>28-32w 33-37w 38-42w</td>
<td>28-32w 33-37w 38-42w</td>
<td>28-32w 33-37w 38-42w</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>10(4.8) 20(6.9) 8(3.5)</td>
<td>2(25.0) 4(12.5) 0(0.0)</td>
<td>3(5.5) 16(9.4) 4(6.2)</td>
<td>19(76.0) 62(68.1) 16(42.1)</td>
</tr>
<tr>
<td>Unexplained intrauterine death</td>
<td>97(46.2) 151(51.9) 117(51.8)</td>
<td>3(37.5) 8(25.0) 3(18.8)</td>
<td>0(0.0) 1(0.6)^ 6(9.2)</td>
<td>1(4.0) 10(11.0) 9(23.7)</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>21(10.0) 24(8.2) 14(6.2)</td>
<td>0(0.0) 3(9.4) 0(0.0)</td>
<td>2(3.6) 7(4.1) 1(1.5)</td>
<td>0(0.0) 1(1.1) 0(0.0)</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>6(2.9) 11(3.8) 5(2.2)</td>
<td>1(12.5) 5(15.6) 1(6.3)</td>
<td>46(83.6)^* 124(72.9) 47(72.3)</td>
<td>2(8.0) 7(7.7) 4(10.5)</td>
</tr>
<tr>
<td>Infections</td>
<td>6(2.9) 1(0.3)^ 7(3.1)</td>
<td>0(0.0) 2(6.3) 2(12.5)</td>
<td>0(0.0) 1(0.6) 0(0.0)</td>
<td>1(4.0) 5(5.5) 6(15.8)</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>12(5.7) 24(8.2) 42(18.6)</td>
<td>0(0.0) 3(9.4) 4(25.0)</td>
<td>1(1.8) 8(4.7) 2(3.1)</td>
<td>1(4.0) 2(2.2) 2(5.3)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>47(22.4) 36(12.4)^* 21(9.3)</td>
<td>1(12.5) 0(0.0) 0(0.0)</td>
<td>3(5.5) 5(2.9) 3(4.6)</td>
<td>0(0.0) 1(1.1) 0(0.0)</td>
</tr>
<tr>
<td>Spont. Preterm labour</td>
<td>9(4.3) 17(5.8)^ 2(0.9)</td>
<td>0(0.0) 0(0.0) 1(6.3)</td>
<td>0(0.0) 0(0.0) 1(1.5)</td>
<td>0(0.0) 2(2.2) 0(0.0)</td>
</tr>
<tr>
<td>All</td>
<td>210(100) 291(100) 226(100)</td>
<td>8(100) 32(100) 16(100)</td>
<td>55(100) 170(100) 65(100)</td>
<td>25(100) 91(100) 38(100)</td>
</tr>
</tbody>
</table>

*p<0.05 with 28-32 week group; ^p<0.05 with 38-42 weeks group. Pearson’s chi-sq or Fisher’s exact where cell count <5.

### Table 6. Cause of Early neonatal death and condition of mother for small-for-gestational age babies, n=388

<table>
<thead>
<tr>
<th></th>
<th>Healthy Mother</th>
<th>Medical Surgical</th>
<th>Hypertension</th>
<th>Other Maternal Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28-32w 33-37w 38-42w</td>
<td>28-32w 33-37w 38-42w</td>
<td>28-32w 33-37w 38-42w</td>
<td>28-32w 33-37w 38-42w</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>1(1.9) 3(2.5) 3(2.9)</td>
<td>0(0.0) 0(0.0) 0(0.0)</td>
<td>0(0.0) 1(2.9) 0(0.0)</td>
<td>8(50.0) 1(8.3)^ 2(25.0)</td>
</tr>
<tr>
<td>Unexplained intrauterine death</td>
<td>0(0.0) 1(0.8) 0(0.0)</td>
<td>0(0.0) 0(0.0) 0(0.0)</td>
<td>0(0.0) 0(0.0) 0(0.0)</td>
<td>0(0.0) 0(0.0) 0(0.0)</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>6(11.5) 19(16.1) 24(23.1)</td>
<td>0(0.0) 0(0.0) 3(50.0)</td>
<td>1(5.6) 4(11.4) 2(13.3)</td>
<td>0(0.0) 1(8.3) 1(12.5)</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>1(1.9) 9(7.6)^ 1(1.0)</td>
<td>0(0.0) 0(0.0) 1(16.7)</td>
<td>16(88.9) 21(60.0) 5(33.3)</td>
<td>0(0.0) 1(8.3) 0(0.0)</td>
</tr>
<tr>
<td>Infections</td>
<td>0(0.0) 3(2.5) 3(2.9)</td>
<td>0(0.0) 0(0.0) 1(16.7)</td>
<td>0(0.0) 0(0.0) 0(0.0)</td>
<td>1(6.2) 2(16.7) 2(25.0)</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>2(3.8) 24(20.3)^ 58(55.8)</td>
<td>0(0.0) 1(33.3) 1(16.7)</td>
<td>0(0.0) 4(11.4)^ 7(46.7)</td>
<td>0(0.0) 2(16.7) 3(37.5)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>1(1.9) 7(5.9) 8(7.7)</td>
<td>0(0.0) 0(0.0) 0(0.0)</td>
<td>1(5.6) 2(5.7) 1(6.7)</td>
<td>0(0.0) 1(8.3) 0(0.0)</td>
</tr>
<tr>
<td>Spont. Preterm labour</td>
<td>41(78.8) 52(44.1) 7(6.7)</td>
<td>1(100.0) 2(66.7) 0(0.0)</td>
<td>0(0.0) 3(8.6) 0(0.0)</td>
<td>7(43.8) 4(33.3) 0(0.0)</td>
</tr>
<tr>
<td>All</td>
<td>52(100) 118(100) 104(100)</td>
<td>1(100) 3(100) 6(100)</td>
<td>18(100) 35(100) 15(100)</td>
<td>16(100) 12(100) 8(100)</td>
</tr>
</tbody>
</table>

*p<0.05 with 28-32 week group; ^p<0.05 with 38-42 weeks group. Pearson’s chi-sq or Fisher’s exact where cell count <5.
4.5 Discussion

Our findings indicate that there are specific characteristics unique to SGA babies in terms of gestational age at death and causes of perinatal mortality.

Timing of perinatal deaths across gestation

The same pattern of timing of stillbirth across gestation was seen for the three provinces with the greatest proportion of deaths for SGA babies during the 33-37 week period. This was in contrast to AGA and LGA babies where no peaks in the proportion of stillbirths across gestation were seen. This is consistent with observations in high-income countries where peaks have been observed between 34-37 weeks and 32-36 weeks (86, 240). In the current study a greater proportion of ENDs for SGA babies also occurred during the 33-37 week period, suggesting that this is a critical time for both antepartum and postpartum mortality. It is also well-established that there is increased neonatal mortality for SGA preterm babies compared to AGA preterm babies (11), stressing the vulnerability of SGA babies in particular.

Current antenatal care timing differs between the provinces, with Western Cape, the most well-resourced province, continuing fortnightly antenatal care contacts between 32-38 weeks, while Limpopo and Mpumalanga cease antenatal care contacts between 32-38 weeks. Previous work has shown that stillbirth risk is increased during periods without antenatal care (149, 244). The peak in stillbirths for SGA babies seen in all provinces between 33-37 weeks gestation suggests that the current detection and management of SGA is not adequate even in Western Cape where frequent antenatal care contacts occur.

Causes of death/mother’s condition

Growth restriction may not necessarily play a principal role in the cause of death for all SGA babies, as SGA may also be due to slow growth of an otherwise healthy baby (47, 93). In our study a greater proportion of SGA babies had deaths due to hypertension which is known to have placental pathology
(93), indicating that growth restriction played a role in these deaths. It is important to consider that all the babies in the current cohort were considered viable (i.e. >1000g and >28 weeks) and that very severe cases of placental insufficiency and congenital abnormalities could have died as late miscarriages. Therefore the deaths in the current study could have been potentially avoided if at risk fetuses were detected early.

Detecting SGA is complicated as in most cases the mother is healthy. In the current study there was no increase in poor maternal condition for SGA babies and more than half of all deaths had a healthy mother. Of mothers that were healthy the greatest proportion of SGA stillbirths were due to unexplained intrauterine death. Earlier detection of fetuses at risk antenatally may reduce the number of unexplained intrauterine deaths.

Challenges with detection

Better detection of SGA babies is needed in South Africa and LMICs. Palpation and symphysis fundal height are commonly used in LMICs due to limited alternative resources, despite the limited evidence to support this as an effective method to predict growth restriction (192). Clinical trials in high-income countries estimate that up to 76% of SGA cases can be detected antenatally (198). The use of Doppler velocimetry to measure altered umbilical artery blood flow in high risk women has enhanced the ability to detect fetuses with pathological growth restriction (245), reducing perinatal mortality (246). However, challenges with Doppler measurement in South Africa are present as there are a large number of perinatal deaths to low-risk healthy mothers (12) and who would therefore not be referred for screening. Studies in South Africa have explored the use of a continuous wave Doppler analyser using a PC (Umbiflow), a simpler alternative to umbilical artery Doppler, which can be operated by nurses and midwives at the primary health care centre level (247, 248). The Umbiflow is able to detect fetuses at risk of stillbirth based on abnormal umbilical artery blood flow. While meta-analyses in high-income countries found Doppler use in low-risk pregnancies to be ineffective to reduce perinatal mortality and morbidity (211), there may be potential benefit of Doppler or Umbiflow use in
low risk populations in LMICs where stillbirth rates are higher. However, once a fetus at risk of stillbirth is detected, quality clinical care must also be provided to increase the risk of survival.

Challenges with clinical management

Once SGA has been detected there are challenges in the clinical management of such babies. Currently there are no effective approaches for the reversal or improvement of the growth pattern of a fetus (123), therefore prenatal clinical management is focused on identifying the optimal timing of birth. The gestational age of the fetus is a critical component of the decision-making process, as fetal mortality is lower than neonatal mortality prior to 31 weeks (249), and birth after 39 weeks results in increased perinatal mortality (250). While it is known that the neonatal mortality risk is higher for preterm SGA babies compared to term SGA babies (11), it unclear how much size-for-gestational age impacts the risk of neonatal mortality in the preterm compared to late preterm infant (251, 252). It has recently been suggested that the birth of SGA babies around 37 weeks is optimal to avoid increased risk of stillbirth occurring after week 37 (253).

Causes of death for SGA babies in other studies have shown different patterns across gestation with a greater proportion of deaths due to congenital abnormality (32-42 weeks) and intrapartum asphyxia (37-42 weeks) at older gestations (240). We observed similar findings in our data with SGA deaths from intrapartum asphyxia and fetal abnormality occurring more frequently at older gestations. Standard guidelines for managing labour in South African include partogram and monitoring of fetal heart rate with a fetal stethoscope or doptone in Community Health Centres and electronically at district hospitals and above. However it is estimated that in 44% of deaths these guidelines are not adhered to due to limited resources and staff (173). Caesarean birth is not readily accessible in some districts, and long transport times exist between Community Health Centres to facilities that are able to perform caesarean section deliveries. It is likely these factors play a role in the high proportion of deaths due to fetal asphyxia observed in the current study. It is also important to note that spontaneous preterm labour is an underlying cause of early neonatal death where the maternal
condition contributes to increased risk of death from disorders associated with prematurity. Early neonatal deaths for preterm neonates reflect access and quality of care after birth for preterm infants. The final cause of death for a preterm neonate could be due to causes such as hyaline membrane disease, hypoxic ischaemic encephalopathy and meconium aspiration. Doppler measurements in combination with growth charts can be used to inform the management of SGA pregnancies (246). This has been shown to decrease the induction of labour and hospital admissions in high-income countries (246).

Limitations

There are some limitations to the current study. First, there is likely some ambiguity in the assignment of gestational age from the perinatal audit data. Last menstrual period or ultrasound estimates for gestational age may not be accurate and the SGA category may erroneously capture appropriately sized infants who measure small for their mis-assigned gestational age. We sought to reduce this issue by using only data where gestational age estimates were considered ‘certain’. Second, macerated SGA babies are likely to be overestimated as death may have occurred up to two weeks prior (254) thus the fetus may have been appropriate-for-gestational age at the time of death. Third, as we had access to aggregated data at a centre level, and data for the number of live births for SGA, AGA and LGA were unavailable we were unable to calculate stillbirth risk, relative risks between live and stillborn babies or perform individual unit analysis using multivariable regression. Fourth, both multiple and single gestations were included in the current study. These were not separated due to limited statistical power and therefore any differences in patterns of mortality between multiple and single gestations are not be presented in the current study. Deaths directly related to multiple gestation such as twin-to-twin transfusion only represented 0.3% of all deaths in the current study, therefore it is unlikely that the inclusion of multiple gestations introduced significant bias.
Conclusion

Mortality from fetal growth restriction in South Africa accounts for a considerable number of deaths, yet there is little research on the timing, causes and detection of SGA in low-resource settings. The detection and management of SGA is important as most deaths occur in late preterm or term infants, where the chance of survival is high when adequate care can be delivered. If SGA infants can be detected antenatally and managed effectively there is an opportunity to significantly reduce the burden of perinatal mortality in LMICs. Further studies on the relationship between antenatal detection and outcome of SGA are needed, especially in LMICs.
CHAPTER 5: Stillbirth risk across pregnancy by size-for-gestational-age in Western Cape, South Africa: application of the fetuses-at-risk approach using perinatal audit data

ACCEPTED PAPER

This chapter is the submitted manuscript of the manuscript accepted with minor revisions by the South African Medical Journal (Appendix C)

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\textsuperscript{4} Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

Keywords: stillbirth risk, small-for-gestational-age, large-for-gestational-age, pregnancy, South Africa, fetal death
PREAMBLE

This study built on the finding from Chapter 4 that the greatest proportion of SGA stillbirths occur between 33 and 37 weeks. Employing the fetuses-at-risk approach this was further explored by comparing stillbirth risk across pregnancy between SGA and AGA pregnancies in Western Cape. As previous studies had indicated that antenatal care timing influences stillbirth risk Western Cape was chosen as women receive frequent antenatal care contacts in the third trimester.
CHAPTER 5 STILLBIRTH RISK BY SIZE-FOR-GESTATIONAL-AGE

5.1 Abstract

Background: There is little published work on the risk of stillbirth across pregnancy for SGA and LGA pregnancies in low resource settings.

Objective: To compare stillbirth risk across pregnancy between SGA and AGA pregnancies in Western Cape

Methods: A retrospective audit of perinatal mortality data using data from the South African PPIP was conducted. All audited stillbirths with information on size-for-gestational-age (n=677) between October 2013 and August 2015 in Western Cape were included in the study. Western Cape Province has antenatal care appointments at booking, 20, 26, 32, 34, 36, 38 and 41 weeks gestation (if required). A fetuses-at-risk approach was adopted to examine stillbirth risk (28-42 weeks gestation, ≥1000g) across gestation by size-for-gestational-age (SGA <10th centile Theron growth curves; LGA >90th centile). Stillbirth risk was compared between SGA/LGA and appropriate-gestational-age pregnancies.

Results: SGA pregnancies were at increased risk of stillbirth compared to AGA pregnancies between 30-40 weeks gestation with the Relative Risk (RR) ranging from 3.5 (95% CI 1.6-7.6) at 30 weeks gestation to 15.3 (95% CI 8.8-26.4) at 33 weeks gestation (p<0.001). The risk for LGA babies increased by at least 3.5-fold in the later stages of pregnancy (from 37 weeks) (p<0.001). At 38 weeks the greatest increased risk was seen for LGA pregnancies (RR 6.6; 95% CI 3.1-14.2; p<0.001).

Conclusions: There is an increased risk of stillbirth for SGA pregnancies specifically between 33 and 40 weeks gestation, despite fortnightly antenatal care contacts during this time. LGA pregnancies are at increased risk of stillbirth after 37 weeks gestation. This highlights potential issues with the detection of fetuses at risk of stillbirth even when antenatal care is frequent.
5.2 Background

In LMICs, around one-quarter of infants born are SGA (11). The condition may constitute a small but healthy fetus or be due to pathological growth failure (IUGR)(47). Compared to AGA infants, SGA infants are at increased risk of perinatal mortality (86), including a 10-fold increased risk of stillbirth (87). SGA babies are also at increased risk of neonatal morbidity such as respiratory distress syndrome (255) and bronchopulmonary dysplasia (256).

Studies to date have indicated that there may be a critical gestational period for increased mortality for SGA babies (84, 86, 240, 241). A South African study found that around 50% of SGA stillbirths occur between 33-37 weeks gestation (84), while work in the UK demonstrated a critical period for SGA stillbirth between 28-36 weeks (240). Other studies have found an increased risk for SGA pregnancies to be present at all gestational ages (86), with the risk of stillbirth for SGA babies increasing with advancing gestational age (241).

Most maternity clinics have a program for identifying of SGA fetuses antenatally because of the increased risk of fetal complications that they present (87). SGA fetuses that are not detected during the antepartum period are at a 4-fold increased risk of serious fetal complication compared to SGA fetuses detected before birth, making the detection and management of such infants crucial to prevent adverse outcomes (87). However, many challenges with detection are present in both high-risk and low-resource settings. Barriers to detection of SGA may be the limited effectiveness of fundal height assessment (230) as well as the timing of routine ultrasound (257). A recent French study (n=14,100), highlighted difficulties with the detection of fetal growth restriction even in the presence of obstetric and medical risk factors for fetal growth restriction and suggested that better risk assessment could improve antenatal identification (258).

In South Africa, around half of stillbirths occur in a seemingly healthy mother, who does not present with any clinical complications antenatally (12). Maternal complication is also not increased in SGA
stillbirths as compared to AGA and LGA stillbirths (84). Recently a lack of ANC in the third trimester of pregnancy has been associated with increased stillbirth risk during this time (149, 150, 244), however the risk specifically for SGA babies was not examined. In South African provinces where ANC appointments are not routinely scheduled between 32-38 weeks there is an increased risk of stillbirth specifically during this time, however in the Western Cape province where fortnightly contacts commonly occur between 32 and 38 weeks there is no increased risk for overall stillbirth during this time (244). Given the increased risk of stillbirth specifically for SGA infants observed in other studies, we sought to explore the how stillbirth risk differed for SGA, AGA and LGA infants in Western Cape where fortnightly ANC contacts occur during the third trimester to determine if SGA infants were at increased risk of stillbirth.

5.3 Methods

Data from the South African PPIP were used to analyse stillbirths (≥1000g and ≥28 weeks gestation) and total number of live births occurring between October 2013 and August 2015 in the Western Cape Province. A detailed description of PPIP can be found elsewhere (12, 244). In brief, data for the Western Cape are audited for over 90% of perinatal deaths by the PPIP. The Program allowed for comparisons between SGA, AGA and LGA babies as derived from South African (Theron) growth charts (227, 243). SGA was defined as neonates with <10\textsuperscript{th} centile for gestational age and LGA was defined as >90\textsuperscript{th} centile. Data were included for 28 to 42 weeks gestation were previous studies have reported high stillbirth risk periods (86, 240, 241). Gestational age was calculated based on date of last menstrual period, ultrasound or clinical examination and cases were excluded if the gestation age was unknown or if the estimated age was considered ‘uncertain’. No hierarchy was employed in determining gestational age. Only singleton pregnancies to women who had reported receiving antenatal care were included. After exclusion of deaths prior to 28 weeks (and after 42 weeks), deaths with unknown or uncertain gestation, multiple pregnancies and women who had not received ANC, the number of deaths used for analysis was 677. The PPIP has ethical approval from the University of
5.3.1 Statistical Analysis

Stillbirth rate

Stillbirth rate was calculated using the number of audited stillbirths/the total number of births identified in the PPIP data and expressed as stillbirths per 1000 births. Overall incidence of stillbirth for the study period was calculated as well as cumulative stillbirth rate at each gestational age (weekly at 28-42 weeks).

Stillbirth risk

A fetuses-at-risk (FAR) approach was adopted using Yudkin’s (1987) accepted method of stillbirth risk calculation (259, 260) and was appropriate for this analysis (261). This approach considers the number of fetuses still in-utero as the population at risk (260). These methods have been published previously for similar work with our data (244). As there were no data available in Western Cape regarding the number of SGA/AGA/LGA infants born alive at each gestational age, we used data from the Mamelodi subdistrict to estimate the proportion of SGA/AGA/LGA live births occurring at each gestational age in Western Cape. This involved several steps: 1) Data from the Mamelodi subdistrict were used to ascertain the proportion of live births at each gestation that were SGA/AGA/LGA. As few stillbirths occurred in the 28-32 week period (<10%) these data were combined into a single category. This distribution was applied to the Western Cape data for known live births; 2) The number of SGA fetuses still in-utero at each gestational age was calculated by subtracting the number of SGA live births and the number of SGA stillbirths at each gestational age from the total number of SGA births (live and stillbirths) for the entire pregnancy period. This was repeated for AGA and LGA pregnancies; 3) Stillbirth risk was calculated for SGA/AGA/LGA pregnancies separately e.g. stillbirth risk for SGA
pregnancies at 28 weeks = (no. SGA stillbirths at 28 weeks/no. SGA fetuses still in-utero at 28 weeks) multiplied by 1000. Expressed as the number of SGA stillbirths per 1000 SGA fetuses still in-utero; 4) The crude relative risk between SGA and AGA pregnancies, and LGA and AGA pregnancies were calculated at each gestational age; 5) Sensitivity analysis was conducted as outlined below.

**Hazard ratio**

A proportional hazard approach was adopted to compare stillbirth risk across gestation between SGA and LGA pregnancies with AGA pregnancies. The Cox regression model used an interaction term for size-for-gestational-age multiplied by time across gestation (grouped as a factor) across the gestational period. The time periods adopted for the Cox regression model were <33 weeks, 34-36 weeks, 37 weeks, 38 weeks, 39 weeks and 40+ weeks. Hazard Ratios and 95% Confidence Intervals were calculated at each time point for comparisons between size-for-gestational-age groups.

**Sensitivity analysis**

As the proportion of SGA/AGA/LGA live births occurring at each gestational was derived from Mamelodi subdistrict a sensitivity analysis was conducted to ensure that distribution of SGA/AGA/LGA occurring across pregnancy was a reasonable and valid approach for the calculation of stillbirth risk. Here, we applied the same method as described for Mamelodi data using the proportion of SGA/non-SGA live births at each gestation from a United States (US) cohort (86). As the US cohort did not contain information on LGA births we compared SGA live births with non-SGA births (LGA+AGA). SPSS and SAS were used for statistical analyses.
5.4 Results

There were 1802 stillbirths (≥1000g and ≥28 weeks gestation) in the study period and 119,598 live births.

Clinical characteristics

The maternal characteristics for SGA/AGA/LGA pregnancies are shown in Table 5.1. There were no statistically significant differences in the characteristics between SGA/AGA/LGA pregnancies according to maternal age, parity, HIV status or syphilis infection.

Table 5.1 Maternal characteristics by size-for-gestational-age for Western Cape stillbirths October 2013 and August 2015

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>AGA</th>
<th>LGA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>p-value*</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primi</td>
<td>105</td>
<td>40.9</td>
<td>0.078</td>
</tr>
<tr>
<td>Multi</td>
<td>137</td>
<td>53.3</td>
<td>0.078</td>
</tr>
<tr>
<td>Grand</td>
<td>6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>9</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
<td>0.071</td>
</tr>
<tr>
<td>Positive</td>
<td>59</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>198</td>
<td>77.0</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td></td>
<td></td>
<td>0.324</td>
</tr>
<tr>
<td>Positive</td>
<td>13</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>243</td>
<td>94.6</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
<td>0.099</td>
</tr>
<tr>
<td>15-24</td>
<td>95</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>113</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>46</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>45+</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>5.1</td>
<td></td>
</tr>
</tbody>
</table>

* with AGA
Stillbirth rate

The overall cumulative incidence of stillbirth for the study period was 5.7 per 1000 births. SGA pregnancies had the highest cumulative incidence of stillbirth at 21.4 deaths per 1000 births, followed by LGA (11.1 per 1000) and AGA pregnancies (3.7 per 1000).

Overall stillbirth rate and AGA stillbirth rate increased across pregnancy to peak at 31 weeks (73.2 and 54.9 deaths per 1000 births, respectively) at which time the rate decreased steadily to 40 weeks to a level of 3.2 per 1000 and 2 per 1000, respectively (Figure 5.1). For SGA pregnancies stillbirth rate increased to 33 weeks then decreased steadily to 35 weeks. At 35 weeks (~2000g) stillbirth rate decreased until term. For LGA pregnancies stillbirth rate was high at earlier gestations (range 37-90 deaths per 1000 births) then decreased rapidly to 32 weeks where it continued to decrease to 37 weeks and remained very low (<1 per 1000) until term (Figure 5.1).

Figure 5.1. Cumulative stillbirth rate across pregnancy for all stillbirths (SB), AGA, SGA and LGA stillbirths in Western Cape between October 2013 and August 2015.
For AGA pregnancies the stillbirth risk was low (<0.6 per 1000) and stable across pregnancy then increased at 41 weeks as expected (Figure 5.2). SGA babies were between 3.5 to 5.8-fold increased risk of stillbirth compared to AGA babies between 30 to 40 weeks gestation. SGA pregnancies also saw a rapid increase in stillbirth risk at 41 weeks. The risk for LGA babies increased in the later stages of pregnancy (from 37 weeks) then increased rapidly at 41 weeks. Table 5.2 presents the relative risk (RR) and 95% Confidence Intervals (95% CI) of stillbirth for SGA and LGA pregnancies compared to AGA pregnancies at each gestational age. For SGA pregnancies the greatest increased risk was observed at 33 weeks (RR 15.3; 95% CI 8.8-26.4; p<0.001), while for LGA pregnancies the greatest increased risk was observed at 38 weeks (RR 6.6; 95% CI 3.1-14.2; p<0.001). The proportional hazards model comparing stillbirth risk between SGA and AGA pregnancies showed that SGA pregnancies had a hazard ratio greater than 1 from 35-40 weeks (p<0.05) (Figure 5.3). For LGA pregnancies the hazard ratio was greater than 1 from 37-40 weeks (p<0.05).

![Figure 5.2. Stillbirth risk across pregnancy for all stillbirths, AGA, SGA and LGA stillbirths in Western Cape between October 2013 and August 2015.](image-url)
Table 5.2 Relative risks (95%CI) for stillbirth between SGA and LGA pregnancies as compared to AGA pregnancies.

<table>
<thead>
<tr>
<th>Weeks’ Gestation</th>
<th>SGA vs AGA* Relative risk of stillbirth (95%CI)</th>
<th>LGA vs AGA* Relative risk of stillbirth (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30</td>
<td>3.5 (1.6-7.6)</td>
<td>5.6 (2.3-13.7)</td>
</tr>
<tr>
<td>31</td>
<td>3.5 (1.6-7.6)</td>
<td>-</td>
</tr>
<tr>
<td>32</td>
<td>4.1 (2.1-7.9)</td>
<td>-</td>
</tr>
<tr>
<td>33</td>
<td>15.3 (8.8-26.4)</td>
<td>3.4 (1.0-11.3), p=0.049</td>
</tr>
<tr>
<td>34</td>
<td>7.6 (4.2-13.6)</td>
<td>-</td>
</tr>
<tr>
<td>35</td>
<td>9.6 (5.7-16.1)</td>
<td>-</td>
</tr>
<tr>
<td>36</td>
<td>9.4 (5.7-15.3)</td>
<td>-</td>
</tr>
<tr>
<td>37</td>
<td>7.8 (4.8-12.6)</td>
<td>5.3 (2.4-11.9)</td>
</tr>
<tr>
<td>38</td>
<td>7.8 (4.7-12.9)</td>
<td>6.6 (3.1-14.2)</td>
</tr>
<tr>
<td>39</td>
<td>5.1 (2.8-9.4)</td>
<td>5.6 (2.3-13.3)</td>
</tr>
<tr>
<td>40</td>
<td>5.8 (3.3-10.0)</td>
<td>3.4 (1.2-9.5)</td>
</tr>
<tr>
<td>41</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>42</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*only statistically significant results shown: p<0.001 unless other given

Figure 5.3. Estimated hazard ratio for stillbirth (black solid line - SGA; gray solid line - LGA) and 95% confidence intervals (dotted lines) for size-for-gestational-age (relative to AGA) as a function of time (<33 w, 34-36w, 37 w, 38w, 39w, 40w, 41w)


Sensitivity analysis

The distribution of SGA live births across gestation was fairly consistent between the cohorts tested. In the US cohort the proportion of SGA births at each gestation varied from 9.1% to 12.6%. In the Mamelodi population it varied from 8.0-10.8% between 34-40 weeks, with the highest proportion of SGA live births observed at the later gestational ages (22.5%). The overall pattern of stillbirth risk by size-for-gestational age did not differ significantly between the methods used (Figure 5.4). The relative risks of stillbirth between SGA and non-SGA pregnancies only differed by +/- 0.2 for gestations between 28-40 weeks, with the different methods of estimating the proportion of SGA/non-SGA live births at each gestation (Table 5.3). For example the RR for stillbirth at 36 weeks was RR=8.3 (95% CI 5.1-13.3; p<0.0001) when using the US cohort, which was similar to the model using the Mamelodi cohort (RR=8.4, 95% CI 5.2-13.6; p<0.0001). The largest difference in RR was observed at 41 weeks where the RR in the Mamelodi-distribution model was 3.2 (95% CI 0.9-11; p=0.077) compared to RR=2.6 (95% CI 0.7-9.2, p=0.146) when using the US cohort distribution. Therefore it was concluded that using the distribution of SGA/AGA/LGA live births from Mamelodi subdistrict to calculate the denominator for stillbirth risk was an appropriate approach.

Figure 5.4. Stillbirth risk across pregnancy for Western Cape using US cohort distribution of live births (SGA vs non-SGA).
Table 5.3 Sensitivity analysis comparing stillbirth risk across pregnancy using Mamelodi subdistrict to calculate the denominator compared to US data.

<table>
<thead>
<tr>
<th>Weeks’ Gestation</th>
<th>Mamelodi cohort</th>
<th></th>
<th>US cohort *</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR(95%CI)</td>
<td>p-value</td>
<td>RR(95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>28</td>
<td>0.2 (0.0-2.9)</td>
<td>0.221</td>
<td>0.2 (0.0-2.8)</td>
<td>0.218</td>
</tr>
<tr>
<td>29</td>
<td>0.2 (0.0-3.4)</td>
<td>0.267</td>
<td>0.2 (0.0-3.3)</td>
<td>0.263</td>
</tr>
<tr>
<td>30</td>
<td>2.9 (1.4-6.1)</td>
<td>0.005</td>
<td>2.8 (1.4-6.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>31</td>
<td>3.3 (1.6-7.1)</td>
<td>0.002</td>
<td>3.3 (1.5-7.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>32</td>
<td>3.9 (2.1-7.5)</td>
<td>&lt;0.001</td>
<td>3.9 (2.0-7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>33</td>
<td>13.3 (7.9-22.5)</td>
<td>&lt;0.001</td>
<td>13.1 (7.7-22.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>34</td>
<td>6.7 (3.8-11.8)</td>
<td>&lt;0.001</td>
<td>6.6 (3.7-11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35</td>
<td>9.1 (5.4-15.2)</td>
<td>&lt;0.001</td>
<td>8.9 (5.3-14.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>36</td>
<td>8.4 (5.2-13.6)</td>
<td>&lt;0.001</td>
<td>8.2 (5.1-13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37</td>
<td>6.3 (4.0-10.1)</td>
<td>&lt;0.001</td>
<td>6.2 (3.9-9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>38</td>
<td>6.2 (3.8-10.0)</td>
<td>&lt;0.001</td>
<td>6.0 (3.7-9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>39</td>
<td>4.3 (2.4-7.7)</td>
<td>&lt;0.001</td>
<td>4.2 (2.3-7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40</td>
<td>5.2 (3.0-9.0)</td>
<td>&lt;0.001</td>
<td>5.1 (3.0-8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>41</td>
<td>3.2 (0.9-11.2)</td>
<td>0.0756</td>
<td>2.6 (0.7-9.2)</td>
<td>0.146</td>
</tr>
</tbody>
</table>

*Pilliod et al. 2012

5.5 Discussion

This study found that SGA pregnancies had a higher cumulative incidence of stillbirth during the study period compared with AGA pregnancies. SGA pregnancies were at increased risk of stillbirth throughout pregnancy, particularly between 31-40 weeks pregnancy. LGA pregnancies also had a higher cumulative incidence of stillbirths than AGA pregnancies with the greatest risk of stillbirth observed during the later stages of pregnancy from 37 weeks.

We used a FAR approach to calculate stillbirth risk, which revealed important information that would not be uncovered using only stillbirth rate. In the current study, cumulative stillbirth rate across gestation showed an increase in rate to 31 weeks then a decline from 31-41 weeks. The decline in stillbirth rate after 31 weeks gestation was expected and consistent with the literature as it is well known that perinatal mortality is higher in the preterm infant (260). However, when using a FAR approach a different pattern emerged where early gestational ages carried the
lowest risk of stillbirth with later gestational ages carrying the largest risk. The risk at 41 weeks was around 10-times that of the preterm period. The reason for this difference lies in the denominator used, as the FAR approach uses the number of fetuses still in-utero. By term and post-term dates most babies have been delivered meaning that the denominator is very small. Although stillbirth rate is often used as a conventional method to assess the trends and patterns in stillbirth, this study emphasizes the importance of differentiating between stillbirth risk (FAR) and stillbirth rate. In the current study the FAR approach is a more meaningful denominator as it is calculating the likelihood of death as pregnancy progresses rather than the number of deaths per the number of births that have already occurred.

The finding that stillbirth risk increased in SGA pregnancies with advancing gestational age is consistent with numerous other studies that also used the FAR approach (86, 253, 262). Rosenstein and colleagues (2014) found that stillbirth risk for all sizes for gestational age increased steadily after 37 weeks, while another study found that the risk of stillbirth for SGA pregnancies more than doubled after 37 weeks gestation (253). In the current study this same pattern was observed where SGA pregnancies were elevated from 33 weeks onwards. Pilliod and colleagues (2012) demonstrated a dose-response effect where SGA babies <3rd percentile were at greater risk of stillbirth across all gestations compared to AGA pregnancies as well as SGA infants falling in the 3rd-10th centiles (86). Both SGA and AGA pregnancies saw an increase in stillbirth risk at 41 weeks. Our findings are consistent with this pattern where SGA pregnancies had a greater risk than AGA pregnancies with a rapid increase at 41 weeks. Previous studies have not differentiated between AGA and LGA pregnancies (86, 253, 262).

Previous work has shown that stillbirth risk is increased during periods without antenatal care (149, 150) which we have reported on previously (244). Western Cape has fortnightly antenatal care contacts between 32-38 weeks and overall stillbirth risk (as well as AGA stillbirth risk) was not increased in the third trimester. However, when differentiating by size-for-gestational-age, as in the
current study a pattern emerges where SGA babies are at increased risk of stillbirth between 32-38 weeks gestation despite women continuing to have fortnightly antenatal care contacts during this time. This highlights the challenges experienced in detecting and managing SGA fetuses, despite women attending antenatal care. In high-income countries it is estimated that up to 76% of SGA cases can be detected during the antenatal period (198), however other studies have reported on difficulties of detecting IUGR (258). In LMICs limited resources mean that palpation and symphysis height are commonly used methods to predict growth restriction despite little evidence to support these as effective methods (230). The detection of fetuses at risk of stillbirth is further complicated as around half occur in a seemingly healthy mother, with no increase in the proportion of unhealthy mothers in SGA pregnancies (84). Early antenatal detection of SGA babies is important as most deaths occur in the late preterm or term period, where survival of live born infants in well-resourced units is high (242).

A commonly used detection method in high-resource settings is the use of Doppler velocimetry which measures umbilical blood flow in high-risk women (245). This method can increase the ability to detect fetuses with pathological growth restriction and reduce perinatal mortality in high risk women (246). Doppler velocimetry conducted at younger gestations has poor predictive value in detecting late onset placental insufficiency (263). In South Africa significant challenges persist with Doppler measurement, as a large number of perinatal deaths occur in healthy mothers who are clinically considered low-risk (12) and are therefore not referred for Doppler screening. A simpler alternative to umbilical artery Doppler is the continuous wave Doppler analyser using a PC (Umbiflow), which may be more suitable to the South African context (247, 248). The Umbiflow is able to detect fetuses at risk of stillbirth based on abnormal umbilical artery blood flow. South African studies have demonstrated its ability to be used at the primary health care centre level by nurses and midwives (247, 248). Although a recent meta-analysis in high-income countries found that Doppler or Umbiflow use in low-risk pregnancies was not effective in reducing perinatal mortality (211), there
may be potential benefit of Umbiflow use in low risk populations in LMICs to refer women to higher-level care (264).

Another interesting finding in the current study was the increased stillbirth risk seen in LGA pregnancies between 36 to 40 weeks. Few studies have investigated the stillbirth risk across pregnancy for LGA pregnancies with most research focusing on SGA fetuses. The studies to date, have found that LGA infants (>4500g) are at greater risk of stillbirth than infants weighing 2500-4500g, but the risk across gestation has not been examined. In South Africa, the proportion of stillbirths for AGA and LGA babies was spread evenly across gestation with one-third in each 28-32w, 33-37w, 38-42w gestational age categories (84). The increase in LGA stillbirth risk between 36 to 40 weeks may be explained by undiagnosed gestational diabetes which would present as late stillbirths in LGA pregnancies. LGA babies who are healthy would experience more obstructed labour from 40 weeks resulting in higher mortality risk.

The strengths of this audit are that it uses whole-population data from a real-life setting and that it allowed for the comparison of SGA/AGA/LGA pregnancies of which data are scarce in low-resource settings. One limitation to the current study is that due to the association between growth restriction and preterm birth we expect a greater proportion of preterm births to be SGA due to this association alone. This introduces issues when using the fetuses-at-risk approach as a greater proportion of births will be SGA at earlier gestations. We sought to overcome this by using the denominator of SGA intra-uterine pregnancies. This is not without its own limitations however. The data was cross-sectional with only one data point for each stillbirth case which introduces temporal challenges. First, growth restriction is defined by a longitudinal pattern of faltering growth which was unable to be taken into account in the current analysis. Second, many late stillbirths may not have been SGA before they began to experience growth restriction.

As with all research that explores gestational-age-specific associations between exposures and perinatal outcome, collider bias may be present (265). There is debate in the literature between the
desire to obtain gestational-age-specific associations and awareness that conditioning on such variables can give rise to bias (265-267). In the current analysis associations at lower gestations may appear weaker than at later gestational ages due to collider bias. Therefore the results must be interpreted with caution and in light of the other available evidence.

5.6 Conclusion

The results from this study indicate that stillbirth risk was increased for SGA pregnancies from 33 weeks gestation compared to AGA pregnancies, despite women having fortnightly antenatal care appointments during this time. This suggests that there is an issue with the detection of fetuses at risk of stillbirth rather than an issue of access to antenatal care itself. The further investigation of possible methods to detect fetuses at risk of stillbirth in low risk women suitable to the low resource setting is warranted and necessary.
CHAPTER 6: INTERGROWTH-21st vs local South African standards (Theron-Thompson) for identification of small-for-gestational-age in stillbirths: a closer look at variation across pregnancy

ACCEPTED PAPER

This chapter is the accepted version of the following paper (APPENDIX D):


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2 Cardiovascular Research Group, School of Population and Global Health, The University of Western Australia;

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Keywords: stillbirth, INTERGROWTH-21st, Theron, fetal growth, small-for-gestational-age
PREMABLE

During the PhD candidature INTERGROWTH-21st fetal growth charts were published. These new charts had not been applied in the South African setting to determine SGA in stillbirths previously. The Chapter 6 study was undertaken to compare the new charts to previous South African population fetal growth charts and to determine if the different charts influenced the proportion of stillbirths identified as SGA.
6.1 Abstract

Background: Recently global growth standards for fetuses were developed (INTERGROWTH-21st). It has been advocated that professional bodies should adopt these global standards. The ability of INTERGROWTH-21st to identify small-for-gestational-age (SGA) fetuses in stillbirths compared to local standards (Theron-Thompson) in the South African setting was assessed.

Objectives: To compare INTERGROWTH-21st with local standard (Theron-Thompson) to identify SGA fetuses in stillbirths in the South African setting

Methods: Stillbirths across South Africa were investigated (>500g, 28-40 weeks) between October 2013 and December 2016 (n=14,776). The study applied the INTERGROWTH-21st standards to classify stillbirths as <10th centile (SGA) compared to Theron-Thompson growth charts. This was assessed across pregnancy overall and at specific gestational ages.

Results: The prevalence of SGA was estimated at 32.2% and 31.1% by INTERGROWTH-21st and Theron-Thompson growth charts, respectively. INTERGROWTH-21st captured 13.8% more stillbirths as SGA in the earlier gestations (28-30 weeks, p<0.001) but 4.0% (n=315) fewer between gestations 33-38 weeks (p<0.001). Observed agreement and Kappa was lower at earlier gestations and at 34-36 weeks.

Conclusion: Our findings demonstrated differences in the proportion of stillbirths considered SGA at each gestational age between the INTERGROWTH-21st and the local South African standard which has not been previously considered by other studies.

Keywords: stillbirth, INTERGROWTH-21st, Theron, fetal growth, small-for-gestational-age
6.2 Background

Fetuses that are SGA are at increased risk of stillbirth. SGA fetuses that are not detected during the antepartum period are at a 4-fold increased risk of serious fetal complication compared to SGA fetuses detected before birth (87). It is therefore important to identify SGA pregnancies antenatally so that complications and stillbirth risk can be reduced through appropriate monitoring and clinical care.

Traditionally, country-specific population fetal growth charts have been used to identify SGA infants. However, there is substantial inter-country variation between growth charts, meaning that a fetus whose growth is tracking as appropriate using one particular chart may be classified as growth-restricted under another (220). Recently a global, multi-ethnic standardised chart was developed by International Fetal and Newborn Growth Consortium for the 21st Century for fetal growth and size (the INTERGROWTH-21st) (217, 218). The INTERGROWTH-21st is intended for global use and improves comparison between countries (226). It has been advocated that this new standard should be adopted by professional bodies (226), however uptake to date has been variable. The ability of INTERGROWTH-21st to identify SGA in stillbirth cases compared to local South African standards (Theron-Thompson Growth standards) has not been assessed.

Studies comparing local growth standards with INTERGROWTH-21st have been predominately conducted in high-resource countries such as New Zealand (NZ) and the UK (221, 268). These studies have shown that INTERGROWTH-21st underestimated SGA in at-risk infants in NZ (221) and stillbirths in the UK (268) compared to local standards. The NZ study showed that INTERGROWTH-21st standard was in particular less able to detect at-risk SGA infants compared to local standards among some ethnic groups including Maori, European and Pacific women (221). In a middle-income-setting, a Chinese study found that INTERGROWTH-21st overestimated the proportion of SGA live-born infants compared to local standards resulting in an increase in the number of pregnancies requiring further investigations to ascertain fetal wellbeing (269).
The variation observed in classifying at-risk SGA infants using INTERGROWTH-21st standards in particular for different ethnicities (221) suggests investigation is warranted comparing INTERGROWTH-21st to local Theron-Thompson Growth standards in the South African population of stillbirths. Further, there is limited published literature on the impact of gestational age on the agreement of INTERGROWTH-21st and local fetal growth charts in identifying SGA infants.

The primary aim of this study was to determine the proportion stillbirths classified as SGA using INTERGROWTH-21st as compared to local Theron-Thompson growth charts. This allowed for comparison of the proportion of stillbirths classified as SGA in the South Africa population as compared with global estimates for the first time. The secondary aim was to determine if there were differences in proportion of stillbirths identified as SGA by gestational age.

6.3 Methods

A secondary analysis of all stillbirths across South Africa (>500g and ≥28 weeks ≤ 40 weeks) between October 2013 to December 2016 was conducted. The South African PPIP database was used for this study capturing >90% deaths across all health facility levels in South Africa. PPIP is a perinatal quality audit system that has been described in detail elsewhere (84). Briefly, after each perinatal death the clinical team performed a death review and recorded clinical information around the cause of death as well as weight/gestational age. Gestational age was determined based on date of last menstrual period (LMP), ultrasound or clinical examination. Stillbirths were classified as macerated which are clinically diagnosed as a fetus where the skin was discoloured, blotchy and friable to touch; or as fresh were the skin was intact and ‘normal’ in appearance. Data were extracted in aggregate form at a health facility level. Stillbirth cases were excluded if the gestational age was unknown (n=20786, 46.9%) or if the estimated age was considered ‘uncertain’ (n=8750, 19.7%).
Theron-Thompson growth charts

Theron-Thompson growth charts were developed in 1995 using an urban population in Western Cape, South Africa (n=3643) (227). It included women who presented antenatally at Tygerberg Hospital obstetric service (including attached community clinics) representing half of all women who delivered in the circumscribed urban area. The mean age of the group was 25.1 years (range 14-46 years), 40.6% were primigravidas, and 92.1% were of coloured ethnicity with 4.3% White, 3.4% Black and 0.2% Asian. Gestational age was confirmed by early ultrasound. Centile charts for birth weight by gestational age were constructed for this population.

Classification as SGA

PPPI automatically classifies cases below the 10th centile using Theron-Thompson growth charts as SGA. The classification of stillbirths as SGA using INTERGROWTH-21st was performed by applying the <10th centile birthweight cut-off at each gestational age.

Statistical analysis

The prevalence of SGA was calculated for the study sample as the number of SGA stillbirths divided by the total number of stillbirths and presented as a proportion. This was calculated for Theron-Thompson and INTERGROWTH-21st separately.

Observed agreement for identifying SGA infants using INTERGROWTH-21st and Theron-Thompson growth charts was calculated. Kappa and 95% confidence intervals were calculated for concordance between identification of SGA between INTERGROWTH-21st and Theron-Thompson growth. Observed agreement and Kappa were calculated overall across pregnancy (28-40 weeks) and individually at each gestational age (weeks). This was done separately for all stillbirths, macerated stillbirths, fresh stillbirths and intra-uterine growth restricted stillbirths (IUGR).

Pearson’s chi-squared test or Fisher’s exact test (where n<5) were used to compare the crude proportions of SGA stillbirths between Theron-Thompson and INTERGROWTH-21st charts at each
gestational age (in weeks). Comparisons were made at each gestational age for all stillbirths, and separately for macerated and fresh stillbirths. In addition stillbirths with IUGR as a primary cause of death were examined separately as well as separate analyses by method of gestational age determination. The proportion of SGA stillbirths at each gestational age compared between Theron-Thompson and INTERGROWTH-21st was tested using Pearson’s chi-squared test.

6.4 Results

There were 14,776 eligible stillbirths (after exclusion for unknown gestational age) in the study period (9761 macerated; 5015 fresh). There were no statistically significant differences between the included and excluded cases in terms of maternal age, parity, HIV status or syphilis status. There were 9389 (63.5%) stillbirths not classified as SGA using any criteria. A total of 30.1% (n=4452) of stillbirths were classified as SGA using both criteria, 3.2% (n=465) identified by INTERGROWTH-21st only and 2.1% (n=315) by Theron-Thompson only and 1.1% (n=155) classified as AGA by Theron-Thompson only.

6.4.1 Sociodemographic characteristics

Clinical characteristics of the study cohort are presented in Table 6.1.

Compared to stillbirths that were classified as SGA (both criteria) those that were classified as AGA (using both criteria) were healthier and more frequently primiparous but had fewer HIV positive cases and fewer preterm births. The SGA INTERGROWTH-21st only group had more healthy, primiparous mothers, fewer mothers who had received antenatal care, more HIV-positive infants and a higher proportion of preterm births (Table 6.1).

6.4.2 Prevalence of SGA

The prevalence of SGA was estimated at 32.2% (n=4753) and 31.1% (n=4598) by INTERGROWTH-21st and local criteria, respectively (p=0.052). In IUGR fetuses (n=384) the incidence of SGA was 78.1% (n=300) for INTERGROWTH-21st and 77.6% (n=298) for Theron-Thompson standards (p=0.058).
6.4.3 Observed agreement and Kappa

Overall across pregnancy observed agreement between the methods of SGA determination was high (98.9%), Kappa was also high at 0.976. This was similar for fresh (99.3%, Kappa 0.982) and macerated (98.8%, Kappa 0.968) stillbirths (Table 6.2). When considering each gestational age separately the lowest observed agreement was at lower gestations 28-29 weeks (76.4%, 86.3%, respectively) and 34-36 weeks (94.6%, 92.5%, 94.7%). For stillbirths with a primary cause of death as IUGR observed agreement was lower at 28-29 weeks (67.7%, 93.3%) and 37-39 weeks (95.5%, 94.1%, 86.7%) compared to other gestations. Overall agreement across pregnancy was high at 99.5% (Kappa 0.985) for IUGR deaths.

6.4.4 Proportion of SGA stratified by gestational age

A comparison of INTERGROWTH-21st and Theron-Thompson growth charts across gestation can be seen in Figure 6.1. When considering each gestational age (weeks) separately there were differences in the proportion of SGA fetuses classified as SGA between INTERGROWTH-21st and Theron-Thompson. The INTERGROWTH-21st standards captured 13.8% (n=437) more stillbirths as SGA in the earlier gestations (28-30 weeks, p<0.001) but 4.0% (n=315) fewer between gestations 33-38 weeks (p<0.001) compared to Theron-Thompson growth curves (Figure 6.2 A). This trend was observed for both macerated and fresh stillbirths (Figure 6.2 B, C).

In pregnancies with a primary cause of death of IUGR, INTERGROWTH-21st classified 16.0% more stillbirths as SGA at younger gestations (28-30 weeks) and 9.4% fewer at 38-39 weeks compared to Theron-Thompson growth curves (Figure 6.3). However, the only statistically significant difference was at 28 weeks (p=0.011).
### Table 6.1. Clinical characteristics of SGA stillbirth cases (n, %) by method of classification in South Africa October 2013-December 2016 (n=14,776).

<table>
<thead>
<tr>
<th></th>
<th>All stillbirths</th>
<th>SGA-INTERGROWTH-21st only</th>
<th>SGA-Theron-Thompson only</th>
<th>Both SGA^</th>
<th>AGA#</th>
<th>AGA Theron-Thompson only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=14,776</td>
<td>n=465</td>
<td>n=315</td>
<td>n=4452</td>
<td>n=9389</td>
<td>n=155</td>
</tr>
<tr>
<td>&quot;Healthy&quot; mother %</td>
<td>8182 (55.4)</td>
<td>253 (52.2)</td>
<td>131 (41.5)</td>
<td>2355 (52.9)</td>
<td>5239 (55.8)</td>
<td>88 (56.8)</td>
</tr>
<tr>
<td>Primipara</td>
<td>6076 (41.1)</td>
<td>199 (42.8)</td>
<td>125 (38.3)</td>
<td>1812 (40.7)</td>
<td>3877 (41.3)</td>
<td>81 (52.3)</td>
</tr>
<tr>
<td>Received antenatal care</td>
<td>14096 (95.4)</td>
<td>436 (93.7)*</td>
<td>304 (96.5)</td>
<td>4234 (95.1)</td>
<td>8508 (95.1)</td>
<td>136 (87.7)</td>
</tr>
<tr>
<td>HIV (positive)</td>
<td>4104 (27.7)</td>
<td>193 (41.5)^</td>
<td>86 (27.3)</td>
<td>1296 (29.1)</td>
<td>2525 (56.5)</td>
<td>90 (59.1)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>9530 (64.5)</td>
<td>428 (92.0)^</td>
<td>230 (73.0)</td>
<td>3103 (69.7)</td>
<td>5689 (60.5)</td>
<td>95 (61.3)</td>
</tr>
</tbody>
</table>

*"Healthy mother’ defined as: where the clinician examining could not find any clinical problems or maternal conditions. #neither criteria identified stillbirth as SGA; ^both criteria identified stillbirth as SGA; *p<0.05 comparing INTERGROWTH-21st with Theron-Thompson-only from Pearson’s chi-squared test. Overall across pregnancy there were no stillbirths classified as AGA by INTERGROWTH-21st criteria only (i.e. all fetuses classified as AGA using INTERGROWTH-21st were also classified as AGA using Theron-Thompson).
### Table 6.2. Observed agreement and Kappa between SGA in stillbirths and intra-uterine growth restricted stillbirths (IUGR) for South Africa October 2013-December 2016

<table>
<thead>
<tr>
<th>Gestation</th>
<th>All stillbirths</th>
<th>Fresh stillbirths</th>
<th>Macerated stillbirths</th>
<th>IUGR stillbirths only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed agreement (%)</td>
<td>kappa (95% CI)</td>
<td>Observed agreement (%)</td>
<td>kappa (95% CI)</td>
</tr>
<tr>
<td>Overall (28-40w)</td>
<td>98.9</td>
<td>0.976 (0.972, 0.980)</td>
<td>99.3</td>
<td>0.982 (0.976, 0.988)</td>
</tr>
<tr>
<td>28w</td>
<td>76.4</td>
<td>0.426 (0.379, 0.474)</td>
<td>74.3</td>
<td>0.385 (0.297, 0.473)</td>
</tr>
<tr>
<td>29w</td>
<td>86.3</td>
<td>0.708 (0.658, 0.758)</td>
<td>84.4</td>
<td>0.686 (0.592, 0.779)</td>
</tr>
<tr>
<td>30w</td>
<td>95.9</td>
<td>0.899 (0.871, 0.927)</td>
<td>94.9</td>
<td>0.859 (0.793, 0.926)</td>
</tr>
<tr>
<td>31w</td>
<td>99.2</td>
<td>0.982 (0.967, 0.996)</td>
<td>99.1</td>
<td>0.977 (0.945, 1.00)</td>
</tr>
<tr>
<td>32w</td>
<td>99.2</td>
<td>0.983 (0.973, 0.993)</td>
<td>98.4</td>
<td>0.961 (0.929, 0.992)</td>
</tr>
<tr>
<td>33w</td>
<td>96.9</td>
<td>0.934 (0.910, 0.959)</td>
<td>96.7</td>
<td>0.922 (0.870, 0.975)</td>
</tr>
<tr>
<td>34w</td>
<td>94.6</td>
<td>0.889 (0.892, 0.915)</td>
<td>93.5</td>
<td>0.863 (0.807, 0.919)</td>
</tr>
<tr>
<td>35w</td>
<td>92.5</td>
<td>0.841 (0.805, 0.878)</td>
<td>92.3</td>
<td>0.825 (0.756, 0.894)</td>
</tr>
<tr>
<td>36w</td>
<td>94.7</td>
<td>0.884 (0.859, 0.909)</td>
<td>94.0</td>
<td>0.842 (0.788, 0.897)</td>
</tr>
<tr>
<td>37w</td>
<td>98.1</td>
<td>0.953 (0.936, 0.971)</td>
<td>97.9</td>
<td>0.930 (0.890, 0.971)</td>
</tr>
<tr>
<td>38w</td>
<td>96.8</td>
<td>0.913 (0.891, 0.934)</td>
<td>96.9</td>
<td>0.886 (0.842, 0.930)</td>
</tr>
<tr>
<td>39w</td>
<td>99.6</td>
<td>0.991 (0.981, 1.00)</td>
<td>99.4</td>
<td>0.982 (0.962, 1.00)</td>
</tr>
<tr>
<td>40w</td>
<td>96.0</td>
<td>0.897 (0.863, 0.931)</td>
<td>96.2</td>
<td>0.884 (0.826, 0.941)</td>
</tr>
</tbody>
</table>
6.4.5 Comparison between methods of gestational age determination

Ultrasound determined gestational age in 37% of stillbirths while 63% had gestational age determined by either clinical examination or last menstrual period (or both). When using Theron-Thompson standards to identify SGA infants, ultrasound classified a larger proportion of stillbirths as SGA (34.0%) compared to using clinical examination or LMP (29.2%)(p<0.001). The level of agreement for identifying SGA differed by gestational age between INTERGROWTH-21st and Theron-Thompson depending on the method used (ultrasound vs. clinical examination/LMP) (Table 6.3). The LMP/clinical examination group had slightly higher levels of agreement between the charts than ultrasound 99.2% vs 98.3%. The lowest levels of agreement between the charts were at 28 weeks (ultrasound 74.8%, clinical examination/LMP 77.2%).
Figure 6.2. Proportion of stillbirths that are small-for-gestational-age A) all stillbirths (n=14776); B) macerated stillbirths (n=9761); C) fresh stillbirths (n=5051); Black – INTERGROWTH-21st; Grey – Theron-Thompson; *p<0.05 between INTERGROWTH-21st and Theron-Thompson.
6.5 Discussion

This large national study found the proportion of stillbirths classified as SGA to be similar between INTERGROWTH-21st and local Theron-Thompson growth charts. Overall across pregnancy observed agreement and concordance was high. However, when considering gestational age, INTERGROWTH-21st classified more SGA stillbirths at younger gestations and fewer at later gestations compared with Theron-Thompson estimates. A similar trend was observed for IUGR-specific stillbirths. Observed agreement and kappa varied at each gestational age with lower agreement at lower gestations and at 34-36 weeks.

6.5.1 Proportion of SGA compared to other populations

One of the aims of the INTERGROWTH-21st was that it would enable comparisons in fetal growth and SGA between different settings using a standardised chart. This is the first empirical comparison between the proportion of stillbirths that are SGA in our population with other settings using a standardised classification system. The overall proportion of stillbirths that were SGA in our study was similar to that of a UK study (32.6%) (268). In the UK and NZ it has been reported that INTERGROWTH-21st underestimated SGA in at-risk infants (221) and stillbirths (268) compared to local standards. When considering the proportion of SGA stillbirths at a population level we did not observe any significant under or over-estimation of SGA by INTERGROWTH-21st in the current study. In the current study there were no significant differences in the overall proportion of stillbirths classified as SGA between the INTERGROWTH-21st and local methods and overall observed agreement and Kappa were high. In studies where gestational age is not an important factor and overall SGA prevalence across pregnancy is the outcome of interest INTERGROWTH-21st may offer a standardised method of comparison between populations such as in multi-country studies.
Figure 6.3. Proportion of intra-uterine growth restricted stillbirths that are small-for-gestational-age (n=384); Black – INTERGROWTH-21st; Grey – Theron-Thompson; *p<0.05 INTERGROWTH-21st and Theron-Thompson.
### Table 6.3. Observed agreement and Kappa for method of gestational age determination (ultrasound and clinical examination/last menstrual period)

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Ultrasound Observed agreement (%)</th>
<th>Ultrasound kappa (95% CI)</th>
<th>Clinical examination/last menstrual period Observed agreement (%)</th>
<th>Clinical examination/last menstrual period kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (28-40w)</td>
<td>98.3</td>
<td>0.961 (0.954, 0.969)</td>
<td>99.2</td>
<td>0.982 (0.978, 0.986)</td>
</tr>
<tr>
<td>28w</td>
<td>74.8</td>
<td>0.433 (0.366, 0.499)</td>
<td>77.2</td>
<td>0.418 (0.357, 0.479)</td>
</tr>
<tr>
<td>29w</td>
<td>85.6</td>
<td>0.696 (0.627, 0.764)</td>
<td>87.1</td>
<td>0.033 (0.659, 0.788)</td>
</tr>
<tr>
<td>30w</td>
<td>94.4</td>
<td>0.874 (0.829, 0.919)</td>
<td>96.7</td>
<td>0.916 (0.884, 0.948)</td>
</tr>
<tr>
<td>31w</td>
<td>98.9</td>
<td>0.975 (0.95, 0.999)</td>
<td>99.3</td>
<td>0.986 (0.969, 1.000)</td>
</tr>
<tr>
<td>32w</td>
<td>99.0</td>
<td>0.978 (0.96, 0.995)</td>
<td>99.0</td>
<td>0.987 (0.976, 0.997)</td>
</tr>
<tr>
<td>33w</td>
<td>95.5</td>
<td>0.908 (0.867, 0.950)</td>
<td>98.1</td>
<td>0.958 (0.932, 0.984)</td>
</tr>
<tr>
<td>34w</td>
<td>93.7</td>
<td>0.872 (0.827, 0.917)</td>
<td>95.3</td>
<td>0.903 (0.873, 0.933)</td>
</tr>
<tr>
<td>35w</td>
<td>92.9</td>
<td>0.850 (0.797, 0.903)</td>
<td>92.5</td>
<td>0.841 (0.797, 0.885)</td>
</tr>
<tr>
<td>36w</td>
<td>94.3</td>
<td>0.883 (0.842, 0.923)</td>
<td>95.4</td>
<td>0.895 (0.867, 0.923)</td>
</tr>
<tr>
<td>37w</td>
<td>97.3</td>
<td>0.936 (0.904, 0.969)</td>
<td>98.6</td>
<td>0.963 (0.945, 0.982)</td>
</tr>
<tr>
<td>38w</td>
<td>97.0</td>
<td>0.929 (0.896, 0.962)</td>
<td>96.9</td>
<td>0.909 (0.884, 0.934)</td>
</tr>
<tr>
<td>39w</td>
<td>99.7</td>
<td>0.993 (0.98, 1.000)</td>
<td>99.5</td>
<td>0.987 (0.975, 1.000)</td>
</tr>
<tr>
<td>40w</td>
<td>95.8</td>
<td>0.904 (0.851, 0.957)</td>
<td>96.3</td>
<td>0.899 (0.861, 0.938)</td>
</tr>
</tbody>
</table>
6.5.2 SGA by gestational-age

This is the first study to explore the application of INTERGROWTH-21st to local growth curves at each gestational age. INTERGROWTH-21st classified more SGA stillbirths at younger gestations and fewer at later gestations. Observed agreement and concordance were also lower at these gestations. The largest discrepancies for 10th centile cut-points between the two charts were at the younger gestations. At these gestations INTERGROWTH-21st identified a much large proportion of SGA stillbirths than Theron-Thompson. Previous studies have not considered the impact of gestational age on observed agreement for different methods of SGA identification. In the current study this observation would have been masked if comparisons were only made overall across pregnancy indicating the importance of assessment by specific gestational age.

The reasons for the differences between classification by INTERGROWTH-21st and Theron-Thompson at different gestations are unclear, however ethnicity, population-specific growth differences and inaccuracies in gestational age/weight may all play a role.

Differences in the composition of ethnicities within the samples used to develop Theron-Thompson and INTERGROWTH-21st may contribute to the differences seen in the fetal growth charts in identifying SGA. INTERGROWTH-21st was developed based on women from eight countries aged 15-35 years, with no diagnosed morbidity, who were well-nourished, lived in urban areas and did not smoke (270). The premise was that these women were ‘low-risk’ healthy women that represent ‘normal physiological growth’ and represented a multi-ethnic sample (270). South Africa also has a multi-ethnic population with more than 10 ethnic groups, none that were included in the development of INTERGROWTH-21st. Several studies have observed ethnic differences in the application of INTERGROWTH-21st. A NZ study found that customized criteria identified 2-3 times as many SGA infants in Maori, Pacific, European and Asian pregnancies compared to INTERGROWTH-21st (221). The National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies (NCHID study) found significant differences in fetal growth by race/ethnicity in American women and has since
developed race-specific charts (222). It is possible that racial/ethnic differences in fetal growth across pregnancy are present and may account for the differences seen at specific gestational ages.

The differences observed may also extend to a population level. There are recognised differences in optimal perinatal outcome achieved at different births weights in different populations (223, 224). Different populations have different birth weight distributions and optimal fetal growth standards as well as perinatal mortality curves (223, 224). The mortality curves are shifted in the same direction as birth weight (223). The findings of the current study also support the notion that differences in fetal growth patterns resulting in adverse outcome (stillbirth) are present when using population-specific growth charts as compared with internationally derived charts.

A possible alternative explanation is that there are greater in-accuracies in the determination of gestational age and weight at younger gestations leading to higher levels of disagreement between INTERGROWTH-21st and Theron-Thompson (larger differences at smaller gestations). Using ultrasound to determine intrauterine estimates of fetal weight are known to be less accurate at <2000g (271) and symphysis fundal height and LMP have known inherent issues in determining gestational age and size (230). We sought to reduce these issues by including only cases where gestational age determination was ‘certain’. One would expect that symphysis fundal height/LMP would have a greater number of inaccuracies in determining gestational age and more difficulty determining fetal weight given small fetal size. However, this was not reflected in our data with greater agreement between the charts for gestational age determined by LMP/clinical examination at most gestations. We also had a large sample size (>1900 stillbirths) at gestations 28-29 weeks therefore not compromising the power. Overall it is unlikely that the differences seen at earlier gestations are an artefact of inaccuracies in gestational age or weight determination at younger gestations.
6.5.3 Public health implications

If INTERGROWTH-21st charts were to be adapted clinically in South Africa as a method to identify ‘high-risk’ women based on fetal growth, this would have implications for maternal health service systems. Women in South Africa receive antenatal care at the community level with a nurse/midwife and are up-referred to obstetric specialist care at the district level if identified as ‘high-risk’ (191). One of the criteria for high-risk is SGA and/or slowing growth velocity as classified through growth charts. Specialised obstetric care and serial ultrasound are only available in high-risk pregnancies. The adaption of INTERGROWTH-21st would increase the number of women classified as ‘high-risk’ and up-referred for obstetric antenatal at lower gestations (28-30 weeks) increasing demand on already under-resourced obstetric services. Increased medicalisation without prevention of adverse perinatal outcomes due to suboptimal diagnostic accuracy of antenatal growth charts has been highlighted previously (220). It is unclear if identifying more pregnancies as SGA at lower gestations would result in a decrease in stillbirths or increased medicalization without prevention of adverse outcome.

Conversely, based on our findings, the application of INTERGROWTH-21st classification to the South African population would decrease the proportion of women classified as ‘high-risk’ due to SGA at gestations 34-36 weeks. This gestational period has been identified as a crucial period for stillbirths in South Africa (84), and has also been identified as a high-risk period for women who do not receive antenatal care during this time (244). It is possible that not recognising these pregnancies as SGA and therefore continuing to consider these pregnancies as ‘low-risk’ would result in an increased stillbirth rate during this period. Further the timing of ultrasound assessment (only available to high-risk women in South Africa) for SGA in late pregnancies becomes important due to the slowing of growth velocity for some fetuses near term, thus meeting the criteria for SGA for the first time in late pregnancy (272). An increased number of these fetuses may be missed if a less-sensitive INTERGROWTH-21st growth chart is used at this time point.
From a public health perspective an optimal fetal growth standard is one that most accurately identifies fetuses at risk of poor perinatal outcome (223). Arguably population-specific growth standards and customized growth charts are more appropriate than generalised growth standards due to their ability to take into account that optimal perinatal outcomes are achieved at different birth weights for different populations. The current study observed differences in the population-specific charts in recognising SGA fetuses where adverse outcome occurred (all stillbirths and IUGR stillbirths) compared to international-standards at different gestational ages. The impact of this on adverse perinatal outcomes would need to be considered if South Africa were to adopt INTERGROWTH-21st in place of local standards as a method of classifying SGA pregnancies. Currently customised growth charts are not available based on a South African population.

6.5.4 Strengths and weaknesses

While it is important to identify SGA fetuses it must also be recognised that this only identifies pregnancies requiring further investigation. A fetus who is classified as SGA may not necessarily be pathologically growth restricted and may be healthy with normal growth that just happens to fall in the lowest 10th centile on growth charts (47). In addition to this it must be acknowledged that growth restriction may also occur in AGA pregnancies (273). This was observed in our study where one-fifth of stillbirths with IUGR as the primary cause of death were AGA (using either growth chart). In these cases umbilical artery Doppler measurements using an inexpensive hand-held device such as Umbiflow™ can be used to identify such cases (273).

This study focused on stillbirths only, representing pathological pregnancies. It is likely that SGA estimates for macerated stillbirths are over-estimated using all criteria as the death may have occurred up to three weeks prior (254) thus the fetus may have been appropriate-for-gestational age at the time of death. Fresh stillbirths are likely to represent more accurate estimates for SGA as the time difference between fetal demise and delivery is not considerable. Future studies should consider the prevalence of SGA in live births to reduce the over-estimation of SGA. We were also only able to
examine pregnancies 28-40 weeks as Theron-Thompson growth charts are not reliable for gestations <28 weeks (227) and INTERGROWTH-21st estimated fetal weight is only available up to 40 weeks gestation.

This was one of the largest studies in low-to-middle-income-countries examining the proportion of SGA stillbirths using INTERGROWTH-21st standards. It is unclear how these results can be generalised to other LMICs populations due to differences in ethnicity and fetal growth at a population level which may influence the classification of SGA in stillbirth (221, 222). This study has highlighted the need for each country to carefully examine and consider the application of INTERGROWTH-21st within their own context specifically at each gestational age before adapting for clinical or use in epidemiology.

6.5.5 Conclusion

Our findings show differences in the estimated proportion of stillbirths considered SGA at each gestational age depending on the growth chart used which have not been previously considered in other studies. This highlights the importance of future studies to consider SGA at each gestational age and not simply compare proportions across the entire pregnancy period. The development of an international standard is essential to compare the prevalence of SGA between countries. The results of the current study have public health implications for identifying infants at risk of stillbirth antenatally in a low-resource setting. Each country must carefully consider the impact of using INTERGROWTH-21st due to the issues raised in this study pertaining to gestational age and potential ethnic and population differences in optimal fetal growth.
CHAPTER 7: Does antenatal care timing influence stillbirth risk in the third trimester?: a secondary analysis of perinatal death audit data in South Africa

PUBLISHED PAPER

This chapter is the published version of the following paper:


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Keywords: stillbirth, antenatal care, South Africa, perinatal mortality
**PREAMBLE**

During the PhD candidature the World Health Organization conducted a revision of Antenatal Care guidelines. One of the aspects that was reviewed was the timing of antenatal care contacts due to recent evidence indicating that more frequent contacts were required in the third trimester. There was a unique opportunity to use the South African data to compare stillbirth risk across pregnancy between provinces with different antenatal care schedules. This following paper was presented at the Guidelines Development Group Meeting, WHO Recommendations on Antenatal Care Panel 2 (Geneva, Switzerland, Chateau de Penthes, 21-23 March 2016).
CHAPTER 7 ANC TIMING AND STILLBIRTH RISK

7.1 Abstract

Objective: To explore stillbirth risk across gestation in three provinces of South Africa with different antenatal care schedules.

Design: Retrospective audit of perinatal death data using South Africa’s Perinatal Problem Identification Program.

Setting: In 2008, the Basic Antenatal Care Programme was introduced in Limpopo and Mpumalanga provinces, reducing appointments to five visits at booking, 20, 26, 32, 38 weeks and 41 weeks if required. In the Western Cape province seven appointments remained at booking, 20, 26, 32, 34, 36, 38 and 41 weeks if required.

Population: All audited stillbirths (n=4211) between October 2013 to August 2015 in Limpopo, Mpumalanga and Western Cape.

Methods: Stillbirth risk (26-42 weeks gestation, >1000g) across gestation was calculated using Yudkin’s method. Stillbirth risk was compared between provinces and relative risks calculated between Limpopo/ Mpumalanga and Western Cape.

Main Outcome measures: Stillbirth risk across gestation

Results: Stillbirth risk peaked at 38 weeks gestation in Limpopo (relative risk (RR) 3.11; 95% CI 2.40-4.03; p<0.001) and Mpumalanga (RR 3.09; 95% CI 2.37-4.02; p<0.001) compared to Western Cape where no peak was observed. Stillbirth risk at 38 weeks in Limpopo and Mpumalanga were statistically greater than both 37 and 39 weeks stillbirth risk within provinces (p<0.001). As expected a peak at 41 weeks was observed in all provinces.

Conclusions: The increased period of stillbirth risk occurs after a six week absence of antenatal care. This calls for a refocus on the impact of reduced antenatal care visits during the third trimester.
7.1 Background

High on the global health agenda is accelerating progress to end preventable stillbirths (6, 7). In 2014, the Every Newborn Action Plan set a target of 12 or fewer stillbirths per 1000 in every country by 2030 (8). South Africa is still above this target with a rate of 17.6 per 1000 births (9). The provision of antenatal care is crucial in reducing stillbirths (274). It is estimated that 50% of stillbirths have a maternal complication (12). Resource limitations in many low-and-middle-income countries, where the majority of deaths take place (8), make the correct timing and frequency of appointments important in preventing avoidable deaths.

In 2001, the World Health Organization (WHO) conducted the Antenatal Care Trial across clinics in four countries with 22000 women. This randomised controlled trial suggested that five focused antenatal care visits were adequate to ensure good birth outcomes for both mother and baby and avoid adverse outcomes such as low birth weight and postpartum anaemia (137). After the publication of this data many countries reduced their antenatal schedules to four or five visits. The current WHO model for antenatal care for low risk pregnancies, as informed by the WHO Antenatal Care Trial is a schedule of five focused visits: at booking, 20, 26, 32, 38 weeks with an appointment at the hospital at 41 weeks (137). Recent analyses in the literature are beginning to re-examine the issue of third trimester antenatal care visits in relation to stillbirth (149, 150). An updated Cochrane review published in 2015 found that in low-and-middle-income countries perinatal mortality was significantly higher in reduced antenatal care visit groups receiving five or fewer visits compared to standard antenatal care visits (150). A secondary analysis of the WHO Antenatal Care Trial also found an increased relative risk of fetal death of 27% between 32 and 36 weeks gestation in populations with reduced antenatal care schedules (149).

In South Africa, in 2008 all provinces but one adopted the reduced antenatal care schedule, giving us the unique opportunity to evaluate the impact of reduced antenatal care visits in the third trimester...
on stillbirth risk across gestation by comparing perinatal mortality data from three selected provinces: Limpopo, Mpumalanga, Western Cape. In Limpopo and Mpumalanga antenatal care visits occurred at booking and 20, 26, 32, 38 weeks (+41 weeks if required), while in Western Cape visits occurred at booking, 20, 26, 32, 34, 36, 38 weeks (+41 weeks if required).

7.2 Methods

Evaluation of stillbirth risk and antenatal care timing

Secondary analysis of the South African Perinatal PPIP database allowed for the analysis stillbirth risk across gestation, which could be compared between the three provinces between October 2013 and August 2015 inclusive. PPIP is a perinatal quality audit system that has been described in detail elsewhere (12, 63). Briefly, at each clinical site across the three provinces the clinical team perform a death review shortly after a death has occurred. The primary obstetric cause of death was defined by the PPIP technical team as the main obstetric event or pregnancy occurrence which was integral in the pathway to perinatal death, as described in other published work (275). Macerated stillbirth was clinically diagnosed as a baby where the skin was discoloured, blotchy and friable to touch; a fresh stillbirth was clinically diagnosed as a baby with the skin intact and ‘normal’ in appearance. These dates and provinces were chosen as they introduced the PPIP V3 in the middle of 2013; this new version included the gestational age and the maternal condition at birth for all perinatal deaths for the first time. In all three provinces over 90% of perinatal deaths were audited by PPIP. Gestational age was calculated based on date of last menstrual period, ultrasound or clinical examination and cases were excluded if the gestation age was unknown or if the estimated age was considered ‘uncertain’. No hierarchy was employed in determining gestational age. Using PPIP we extracted detailed data on all stillbirths weighing >1000g and >26 weeks gestation. Only women who had reported receiving antenatal care were included.
CHAPTER 7 ANC TIMING AND STILLBIRTH RISK

The PPIP program has ethical approval from the University of Pretoria. The data is collected with permission from the South African Department of Health. This secondary analysis was approved by the PPIP technical task team and UWA Human Ethics Committee.

Statistical Analysis

Stillbirth rate

Stillbirth rate was calculated using the number of stillbirths/the number of births and expressed as stillbirths per 1000 live births. Overall incidence of stillbirth for the study period was conducted as well as cumulative stillbirth rate at each gestational age.

Stillbirth risk

A fetuses-at-risk (FAR) approach was adopted using Yudkin’s (1987) method of stillbirth risk calculation. This approach considers the number of fetuses still in-utero as the population at risk (260). As there were no live birth data available for Limpopo, Mpumalanga or Western Cape with information on gestational age an alternative approach had to be used. Therefore data on live births with information on gestational age was used from Mamelodi subdistrict. Several steps were undertaken: 1) The proportion of live births in each birth weight category (500-999g; 1000-1499g; 1500-1999g; 2000-2499g, 2500+g) for Mpumalanga, Limpopo and Western Cape were compared with the proportion of live births in each birth weight category for Mamelodi. There were no significant differences in the proportion of live births occurring in each birth weight category between the provinces and Mamelodi so we were able to assume that the distribution across gestation would also be similar; 2) The distribution of live births across gestation from Mamelodi was plotted i.e. the proportion of all live births for Mamelodi that occurred at each gestational age (e.g. at 26 weeks 0.49% of infants were born, at 38 weeks 17.67 % of infants were born); 3) The proportion of live births at each gestational age in Mamelodi was applied to the number of known births in Mpumalanga, Limpopo and Western Cape (e.g. at 26 weeks 0.49% of infants were born, at 38 weeks 17.67 % of infants were born); 4) Sensitivity analysis was conducted by as outline below. At each gestational age
stillbirth risk was calculated using the number of stillbirths divided by the total number of unborn fetuses for each province (separately) as expressed as the number of stillbirths per 1000 fetuses still in utero.

Relative Risk

Relative risk was calculated between Limpopo/ Mpumalanga and Western Cape at each gestation age critical such as 32, 38 and 41 weeks. Relative risk was also calculated within provinces between large increases/decreases, for example between 37-38 weeks and 38-39 weeks. A p-value of <0.01 was considered statistically significant.

Hazard ratio

A proportional hazard approach was adopted to compare stillbirth risk across gestation between Limpopo/Mpumalanga with Western Cape. The Cox regression model used an interaction term for province*time across gestation (grouped as a factor) across the gestational period. The time periods adopted were <33 weeks, 34-36 weeks, 37 weeks, 38 weeks, 39 weeks, 40+ weeks. Hazard Ratios and 95% Confidence Intervals were calculated at each time point for the comparisons between provinces.

Primary Cause of Death

Pearson’s chi-squared was used to test statistical differences in the proportion of deaths for primary cause of death between provinces, for example hypertensive disorders. The difference in the proportion of stillbirths by mothers condition (mother complication Y/N) was also tested using Pearson’s chi-squared.

Sensitivity Analysis

As live birth data was derived from Mamelodi subdistrict rather than Limpopo, Mpumalanga or Western Cape we conducted a sensitivity analysis to ensure that the use of live birth data from Mamelodi was a reasonable and valid approach. A series of hypothetical changes to the distribution of live births across gestational age were implemented and the impact on the risk estimates assessed.
7.3 Results

There were 528727 births over 1000g in the study period between October 2013-August 2015 (Limpopo =209768; Mpumalanga =145362; Western Cape= 173597), of these births 8111 were stillbirths (Limpopo=3808; Mpumalanga =2501; Western Cape=1802). After exclusion of stillbirths prior to 26 weeks, stillbirths with unknown or uncertain gestation and women who had not received antenatal care, the number of stillbirths used for analysis was 4211 (Limpopo n=1968; Mpumalanga n=1533; Western Cape n=710). There were no statistically significant differences in the proportion of women between ‘certain’ gestational age and ‘uncertain’ gestational age groups in terms of maternal age, parity, HIV status or syphilis status. The only exception was in Western Cape where the ‘uncertain’ gestational age group was younger than the ‘certain’ gestational age group (15-24 years uncertain 49.6%, certain 40.5%, p=0.0369).

The cumulative incidence of stillbirth for the study period was highest in Limpopo (18.5 per 1000 live births) and Mpumalanga (17.5/1000) compared to Western Cape (10.5/1000). In terms of the stillbirth rate across gestation, although Western Cape had a lower stillbirth rate consistently across gestation compared to the other two provinces the pattern was the same for all three provinces. The cumulative stillbirth rate increased between 26 to 31 weeks gestation then declined steadily after 31 weeks gestation (Figure 7.1). At 38 weeks the stillbirth rate for Limpopo was 17.2/1000 live births, Mpumalanga 17.1/1000 and Western Cape 5.44/1000.
Figure 7.1 Cumulative stillbirth rate/1000 births (stillbirths and live births) for Western Cape, Mpumalanga and Limpopo across gestational age.

When examining stillbirth risk (number of stillbirths/number fetuses still in-utero), Limpopo and Mpumalanga showed increased stillbirth risk at 38 weeks which was significantly different to both Western Cape 38 week stillbirth risk (p<0.001) and also stillbirth risk at 37 and 39 weeks (p<0.001) within each province (Figure 7.2). In Western Cape no peak was observed at 38 weeks. At 38 weeks stillbirth risk was 3.63 per 1000 fetuses still in-utero for Limpopo, 3.61 per 1000 for Mpumalanga and 1.16 per 1000 for Western Cape. The relative risk of stillbirth at 38 weeks was 3.11 (95% CI 2.40-4.03; p<0.001) for Limpopo and 3.09 (95% CI 2.37-4.02; p<0.001) for Mpumalanga compared to Western Cape. The relative risk for stillbirth at 38 weeks compared to 37 weeks and 39 weeks was 1.76 (95% CI 1.47-2.09; p<0.001) and 1.50 (95% CI 1.24-1.80; p<0.001), respectively for Limpopo. In Mpumalanga the RR was 2.15 (95% CI 1.76-2.63; p<0.001) at 38 weeks compared to 37 weeks and 2.41 (95% CI 1.90-3.05; p<0.001) compared to 39 weeks. In all provinces an increase in stillbirth risk was also observed at 41 weeks: Limpopo stillbirth risk 10.2/1000; Mpumalanga 5.6/1000; Western Cape 5.5/1000. The relative risk between Limpopo and Western Cape for stillbirth risk at 41 weeks was 1.8 (1.0-3.4; p=0.048), while for Mpumalanga the difference was not statistically different (RR 1.0; 95% CI 0.5-2.1; p=0.920).
Figure 7.2 Comparison of stillbirth risk by weekly gestation between provinces and primary cause of stillbirth. (A) Stillbirth risk (all); (B) stillbirth risk (macerated); (C) stillbirth risk (fresh). *P < 0.05 with Western Cape 38 weeks; ^P < 0.05 with 37 and 39 weeks within-province data.
The proportional hazards models showed similar results to the approach using Yudkin’s methods of stillbirth risk calculation (Figure 7.3). There was an increased Hazard Ratio at 38 weeks for both Limpopo (HR 3.1; 95% CI 2.4-4.1) and Mpumalanga (HR 3.1; 95% CI 2.4-4.0).

Limpopo and Mpumalanga both had statistically greater proportions of deaths due to hypertension than Western Cape (p<0.001). Stillbirth from hypertension peaked at 32 weeks (12% of hypertensive deaths) and 38 weeks (11% of hypertensive deaths) in Limpopo and Mpumalanga but in Western Cape there were several peaks across gestation (at 33, 35, 36 weeks). The difference in the proportion of hypertensive related deaths occurring at 32 weeks was significantly higher for Mpumalanga (p<0.001) and Limpopo (p<0.001) compared to Western Cape. The difference seen at 38 weeks was not statistically significant between provinces but neared significance for the Limpopo (p=0.064) compared to Western Cape. Maternal complication occurred in 37.9% of stillbirths in Limpopo; 50% in Mpumalanga, and 45% in Western Cape. The lower proportion of stillbirths with a maternal condition in Limpopo was statistically significant compared to both Western Cape (p<0.001) and Mpumalanga (p<0.001). Maternal hypertension was present in 23.9% of stillbirths (Limpopo 21.8%; Mpumalanga 28.8%; Western Cape 18.9%).
Figure 7.3. Estimated hazard ratio for stillbirth (dark grey solid line, Mpumalanga; light grey solid line, Limpopo) and 95% confidence intervals (dotted lines) for provinces (relative to Western Cape).

*P < 0.05 with Western Cape.
Sensitivity Analysis

There were no significant differences between the proportion of live births by weight categories (1000-1499g, 1500-1999g, 2000-2499g and 2500+g) between Mamelodi and the three provinces. The largest difference in the proportion of live births occurring in a single weight category was 2.4% between Western Cape and the Mamelodi subdistrict for the 2500g+ category. Therefore a sensitivity analysis was performed by increasing the proportion of live births at each gestational age one at a time by 5% and 20% in individual analyses. Decreasing the proportion of live births by 5% and 20% was also performed in the same manner. There were no significant differences between stillbirth risk prior to adjustment and after adjustment at any gestational age with the increases/decreases implemented. The greatest change in stillbirth risk at 38 weeks was <1%, when a 20% change in the number of live born neonates was implemented at 38 weeks (e.g. in Mpumalanga stillbirth risk changed from 3.61/1000 fetuses in-utero to 3.58/1000). With a 20% increase in the proportion of live births occurring at 38 weeks in Limpopo (Western Cape remained unchanged) the relative risk between Limpopo and Western Cape was 3.09 (95% CI 2.38-4.00; p<0.001) compared to 3.11 (95% CI 2.40-4.03; p<0.001) in the original analysis. For Mpumalanga the relative risk was 3.07 (95% CI 2.36-3.99; p<0.001) compared to 3.09 (95% CI 2.37-4.02; p<0.001) in the original analysis. Therefore it was concluded that if even if there was a difference in the distribution of live births at any gestational age at eight times the variation observed in our data it would be unlikely for any substantial changes to occur to our risk estimates.

7.4 Discussion

Main findings

This secondary analysis of more than 4000 stillbirths found an unexpected peak in stillbirth risk at 38 weeks in the two provinces with reduced antenatal care schedules. This coincides with the first antenatal care visit after a six week absence of antenatal care. The risk of stillbirth at 38 weeks in both Limpopo and Mpumalanga was around three times that of Western Cape. In all provinces a peak was
observed at 41 weeks as expected (260). In addition a larger proportion of deaths were due to hypertension in both Limpopo and Mpumalanga with a peak in deaths at 32 weeks compared to Western Cape.

**Strengths and Limitations**

This study used data from a real-world setting that retrospectively evaluated the timing of stillbirths across gestation in relation to antenatal care schedule. Each death was evaluated rigorously by a clinical team. The results from this ecological study must be interpreted with caution. Firstly, these results are for unadjusted statistical models where known confounders such as socioeconomic status (SES) and rural location have not been controlled for. These data were aggregate clinical data, which did not contain information on SES or proxy indicators for SES. This limited our ability to adjust for confounding in our models and apply sensitivity analyses such as the principle-stratification approach as published in other studies (265, 276). While it is recognised that Western Cape is a wealthier province which would likely influence stillbirth rate (as shown in Figure 7.1), SES should not affect the patterns observed in stillbirth risk across gestation i.e. there is no specific gestation at which one would expect stillbirth risk to be increased in a higher SES population compared to a lower SES population. Not adjusting for SES across provinces would also not influence stillbirth risk across gestation in each province i.e. the increased stillbirth risk specifically at 38 weeks.

Secondly, the study was limited by not having live birth data with gestational age for Limpopo, Mpumalanga and Western Cape, therefore data from Mamelodi subdistrict was used to inform our analysis around stillbirth risk. However, the sensitivity analysis revealed that even large, unrealistic changes to the proportion of live births at any gestational age would not be likely confer a large change to our estimates.
Interpretation

We used Yudkin’s method which is a fetuses-at-risk (FAR) approach to calculate stillbirth risk. In our data examining stillbirth risk using the FAR approach revealed a critical period at 38 weeks gestation, which would not have been revealed if using stillbirth rate as a measure of risk. An extension on Yudkin’s method of stillbirth risk calculation is to use a modified Cox regression model designed for perinatal mortality studies adopting the FAR approach, where time-dependant effects such as gestational age must be considered (259). This model has been used in numerous studies that examine fetal death using the FAR approach (277, 278). Due to the nature of our data, issues with convergence prevented us from using this method. This method had it worked would arguably have been a more appropriate method to use.

Interestingly our analysis found similar findings to the Cochrane review and WHO Antenatal Care Trial secondary analysis when observing the peak at 38 weeks gestation. Our main observation was an unexpected peak in stillbirth risk at 38 weeks in the two provinces that had reduced antenatal care schedules. The peak in stillbirth risk observed at 38 weeks in the provinces with reduced antenatal care schedules is consistent with the secondary analysis of the WHO Antenatal Care Trial. The trial revealed an increased relative risk of 24% for fetal death between 32 and 36 weeks gestation in countries with reduced antenatal care schedules in both low and high risk groups (149). In both studies the risk of death increased specifically during the period when no antenatal care was delivered. The recent Cochrane review found that in low-and-middle-income countries perinatal mortality was significantly higher in the reduced antenatal care visit groups, with an increased risk ratio of 15% (150). This was largely attributed to the WHO Antenatal Care Trial were an increase in stillbirths amongst the reduced visit group was observed (150).

The reason for the observed peak at 38 weeks in the provinces with reduced antenatal care but not Western Cape where antenatal care continues fortnightly is unclear. Western Cape has better maternal and perinatal outcomes, as reflected by the lower stillbirth rate observed in the province.
which may account in part for the absence of a peak in stillbirth risk at 38 weeks. It is also notable that the peak in stillbirth risk at 41 weeks occurs as with the other two provinces. Although a lack of antenatal care during this time is a plausible explanation for the higher stillbirth risk seen in Limpopo and Mpumalanga at 38 weeks (149) it is unclear if the absence of a peak in stillbirth risk at 38 weeks in Western Cape is due to more frequent antenatal care in the third trimester or due to better quality antenatal care or another unknown reason. The combination of frequent antenatal care as well as better quality antenatal care is likely to contribute as any fetuses at risk of stillbirth may be identified at antenatal care appointments but also managed clinically. It is also important to remember that the peak at 38 weeks is likely to reflect diagnosis of stillbirth rather than time of fetal demise, however it is interesting that the diagnosis of stillbirth for both fresh and macerated stillbirths was increased at 38 weeks. This indicates that deaths occurred during the period between 35-38 weeks (macerated stillbirth) (254) or closer to 38 weeks (fresh stillbirths), both during a period when no antenatal care visits were scheduled. Recently a critical period for small-for-gestational age babies has been observed between 33-37 weeks gestation, with the largest proportion of stillbirths occurring during this period (275). This critical period falls during a time when no antenatal care is delivered in Limpopo or Mpumalanga. Other studies exploring the timing of antenatal care and stillbirth risk have also concluded that lack of antenatal care is a plausible explanation (149, 150). The WHO Antenatal Care Trial secondary analysis concluded that the peak in deaths during this period may be due to the reduced number of visits (149), while the Cochrane review concluded that having only two or three visits scheduled in the third trimester would not be sufficient to detect fetuses at risk or provide treatment to prevent stillbirth, thus contributing the increased risk of perinatal death in the reduced antenatal care group (150). It is unknown if visits during this time at 34 weeks and 36 weeks gestation (as in Western Cape) would precede the peak in stillbirth diagnosis at 38 weeks and allow time for intervention. The average time between the last antenatal care visit and a maternal near miss event due to hypertension is 2.6 weeks (279) this is around the same time frame for fetal demise in macerated
stillbirths. Perhaps additional antenatal care appointments scheduled should consider this lead time to identify maternal complications and potentially decrease stillbirth risk.

7.5 Conclusion

It is difficult to determine from the current study’s findings if stillbirth risk increases when antenatal care appointments are reduced in the third trimester, however it appears to be a plausible explanation for the increase in stillbirth risk seen in the current study. Perhaps there is a need to re-focus attention on third trimester antenatal care visits and the impact on stillbirth given the recent advances in the literature. Further research is needed in this area given the large number of stillbirths occurring in the third trimester globally every year (8).
CHAPTER 8: Applying the international classification of diseases to perinatal mortality data, South Africa

PUBLISHED PAPER

This chapter is the published version of the following paper:


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Keywords: ICD-PM, perinatal mortality, stillbirth, South Africa
PREAMBLE

During the PhD candidature the development of ICD-PM occurred and was published. Although piloted before its’ release the application of ICD-PM to a LMIC setting had not yet been conducted. This was a unique opportunity to use the South African PPIP data available to test the application in a LMIC setting. This was a necessary and crucial step as any mortality coding system must be tested in an environment where the majority of deaths are occurring such as in LMICs.
8.1 Abstract

Objective: To examine the feasibility of applying the International Classification of Diseases-perinatal mortality (ICD-PM) coding to an existing data set in the classification of perinatal deaths.

Methods: One author, a researcher with a non-clinical public health background, applied the ICD-PM coding system to South Africa’s national perinatal mortality audit system, the Perinatal Problem Identification Program. The database for this study included all perinatal deaths ($n = 26,810$), defined as either stillbirths (of birth weight $> 1000\, \text{g}$ and after 28 weeks of gestation) or early neonatal deaths (age 0–7 days), that occurred between 1 October 2013 and 31 December 2016. A clinical obstetrician verified the coding.

Findings: The South African classification system does not include the timing of death; however, under the ICD-PM system, deaths could be classified as antepartum ($n = 15,619; 58.2\%$), intrapartum ($n = 3725; 14.0\%$) or neonatal ($n = 7466; 27.8\%$). Further, the South African classification system linked a maternal condition to only 40.3% ($10,802/26,810$) of all perinatal deaths; this proportion increased to 68.9% ($18,467/26,810$) under the ICD-PM system.

Conclusion: The main benefit of using the clinically relevant and user-friendly ICD-PM system was an enhanced understanding of the data, in terms of both timing of death and maternal conditions. We have also demonstrated that it is feasible to convert an existing perinatal mortality classification system to one which is globally comparable and can inform policy-makers internationally.
8.2 Background

High on the global health agenda is the need to accelerate progress towards ending preventable perinatal deaths, defined by the WHO as either a stillbirth of weight > 1000 g or after at least 28 weeks gestation, or an early neonatal death in the first 7 days after birth (6). In developing appropriate intervention strategies to reach this target, the causes of perinatal deaths must be classified in a globally comparable way (280, 281). A recent systematic review identified no less than 81 different systems used to classify perinatal deaths globally, with only 17 systems using the International Classification of Diseases and Related Health Problems (ICD) codes (64). Other studies have recognized that multiple, disparate systems impede the ability to understand and achieve accurate estimates of cause of death, hindering effective prevention strategies (65, 66). Of particular importance is the need to focus on the mother–infant dyad, as maternal condition is closely related to perinatal death (6).

The Every Newborn Action Plan recommends that maternal complications be recorded as part of perinatal death registration; however, challenges existed in applying the 10th edition of the ICD (ICD-10) classification system as maternal condition was not linked to perinatal condition (69). To address these issues, the WHO application of ICD-10 to perinatal deaths (ICD-perinatal mortality or ICD-PM) was published in 2016 (70), the first perinatal death classification system developed for application globally (71). ICD-PM is modelled on the WHO application of the ICD-10 system to deaths during pregnancy, childbirth and the puerperium (ICD-maternal mortality or ICD-MM)(72), and follows all coding rules of ICD-10 (73). Importantly, the ICD-PM system identifies the timing of perinatal death (i.e. antepartum, intrapartum or neonatal), links causes of death to existing ICD-10 codes and connects maternal condition with perinatal death (70). One of the aims of ICD-PM is to group ICD-10 codes into clinically relevant and easy-to-use categories (71).
We demonstrate the benefits achieved, in terms of an improved understanding of the data, from the application of ICD-PM codes to perinatal deaths that were previously classified using the South African perinatal mortality audit system, called Perinatal Problem Identification Program.

### 8.3 Methods

**Data Source**

South Africa’s perinatal mortality audit system (12) records and classifies perinatal deaths at all 588 clinics across the country. Each clinical team performs a mortality review shortly after death and reports the cause of perinatal death (and associated maternal condition) to the classification system. For the purposes of the system, perinatal deaths are defined as either fresh or macerated stillbirth or early neonatal death (age 0–7 days). The primary obstetric cause of death is classified in terms of both lead categories and subcategories according to Table 8.1. Maternal condition is also recorded, and classified as either healthy (where the examining clinician did not identify any clinical problems) or as one of the medical/obstetric conditions listed in Table 8.2. Classifications of perinatal death are linked to maternal condition lead categories, but not to subcategories. Data are joined into a national database at the Medical Research Council Unit for Maternal and Infant Health Care Strategies, Pretoria. Regular auditing of individual clinics is conducted to ensure the completeness and accuracy of the database.

We used all 26 810 perinatal deaths, which occurred during the period between 1 October 2013 and 31 December 2016, recorded in the classification system’s database Table 8.3. The start date coincided with the launch of the third version of the system, which had been improved to include gestational age at death.
Table 8.1. Classification of primary cause of death for perinatal deaths in Perinatal Problem Identification Program (PPIP) in South Africa

<table>
<thead>
<tr>
<th>INTRAUTERINE DEATH</th>
<th>FETAL ABNORMALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained intrauterine death - macerated</td>
<td>Fetal chromosomal abnormality</td>
</tr>
<tr>
<td>Unexplained intrauterine death - fresh</td>
<td>Abnormality of multiple systems</td>
</tr>
<tr>
<td>Unexplained IUD due to lack of notes</td>
<td>Neural tube defects</td>
</tr>
<tr>
<td>SPONTANEOUS PRETERM LABOUR</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Ideopathic preterm labour</td>
<td>Non-specific fetal abnormality - FLK</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes</td>
<td>Cardiovascular system abnormality</td>
</tr>
<tr>
<td>Iatrogenic preterm delivery for no real reason</td>
<td>Non-immune hydrops fetalis</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes with chorioamnionitis</td>
<td>Renal system abnormality</td>
</tr>
<tr>
<td>Preterm labour with chorioamnionitis with intact membranes</td>
<td></td>
</tr>
<tr>
<td>Cervical incompetence</td>
<td></td>
</tr>
<tr>
<td>HYPERTENSIVE DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Proteinuric hypertension</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td></td>
</tr>
<tr>
<td>Pregnancy-induced hypertension without proteinuria</td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td></td>
</tr>
<tr>
<td>INTRAPARTUM ASPHYXIA</td>
<td></td>
</tr>
<tr>
<td>Labour related intrapartum asphyxia</td>
<td></td>
</tr>
<tr>
<td>Meconium aspiration</td>
<td></td>
</tr>
<tr>
<td>Cord around the neck</td>
<td></td>
</tr>
<tr>
<td>Cord prolapse</td>
<td></td>
</tr>
<tr>
<td>Ruptured uterus</td>
<td></td>
</tr>
<tr>
<td>Traumatic breech delivery</td>
<td></td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td></td>
</tr>
<tr>
<td>Precipitous labour</td>
<td></td>
</tr>
<tr>
<td>Traumatic assisted delivery</td>
<td></td>
</tr>
<tr>
<td>ANTEPARTUM HAEMORRHAGE</td>
<td></td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td></td>
</tr>
<tr>
<td>Abruptio placenta with hypertension</td>
<td></td>
</tr>
<tr>
<td>Antepartum haemorrhage of unknown origin</td>
<td></td>
</tr>
<tr>
<td>Placenta praevia</td>
<td></td>
</tr>
<tr>
<td>INTRAUTERINE GROWTH RETARDATION</td>
<td></td>
</tr>
<tr>
<td>Idiopathic intrauterine growth retardation</td>
<td></td>
</tr>
<tr>
<td>Postmaturity</td>
<td></td>
</tr>
<tr>
<td>IUGR with histological features of ischaemic placental disease</td>
<td></td>
</tr>
</tbody>
</table>

Bold – lead categories; normal – sub-categories;
Table 8.2. Classification of maternal conditions in Perinatal Problem Identification Program (PPIP) in South Africa *

<table>
<thead>
<tr>
<th>NO OBSTETRIC CONDITION</th>
<th>NON-PREGNANCY-RELATED INFECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy mother</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td><strong>HYPERTENSION</strong></td>
<td>Other non-pregnancy-related infections</td>
</tr>
<tr>
<td>Proteinuric hypertension</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension without proteinuria</td>
<td>Complications of antiretroviral therapy</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Wasting syndrome</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Other pneumonia</td>
</tr>
<tr>
<td>HELLP</td>
<td>PCP pneumonia</td>
</tr>
<tr>
<td>Liver rupture</td>
<td>Malaria</td>
</tr>
<tr>
<td>Acute fatty liver</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td><strong>OBSTETRIC HAEMORRHAGE</strong></td>
<td>Other meningitis</td>
</tr>
<tr>
<td>Abruption with hypertension</td>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td>Abruption without hypertension</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Other APH not specified</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Ruptured uterus with previous c/s</td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Ruptured uterus without previous c/s</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td><strong>MEDICAL AND SURGICAL DISORDERS</strong></td>
<td><strong>COINCIDENTAL CONDITIONS</strong></td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Herbal medicine</td>
</tr>
<tr>
<td>Other medical and surgical disorders</td>
<td>Other coincidental conditions</td>
</tr>
<tr>
<td>Auto-immune disease</td>
<td>Other accidents</td>
</tr>
<tr>
<td>Haematological disease</td>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>Genito-urinary disease</td>
<td>Assault</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Rape</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td><strong>ANAESTHETIC COMPLICATIONS</strong></td>
</tr>
<tr>
<td>CNS disease</td>
<td>Complications of general anaesthetic</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>Complications of spinal anaesthetic</td>
</tr>
<tr>
<td>GiT disease</td>
<td>Complications of epidural anaesthetic</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td><strong>EXTRA-UTERINE PREGNANCY</strong></td>
</tr>
<tr>
<td>Skeletal disease</td>
<td>Extra-uterine pregnancy</td>
</tr>
<tr>
<td><strong>PREGNANCY-RELATED SEPSIS</strong></td>
<td><strong>EMBOLISM</strong></td>
</tr>
<tr>
<td>Chorioamnionitis with ruptured membranes</td>
<td>Amniotic fluid embolism</td>
</tr>
<tr>
<td>Chorioamnionitis with intact membranes</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td><strong>ACUTE COLLAPSE - CAUSE UNKNOWN</strong></td>
<td></td>
</tr>
<tr>
<td>Acute collapse - cause unknown</td>
<td></td>
</tr>
</tbody>
</table>

Bold – lead categories; normal – sub-categories; * Only lead categories can be linked to perinatal death
Table 8.3. Primary cause of death as classified by South Africa’s existing perinatal audit data (PPIP) for perinatal deaths (>1000g and =>28 weeks gestation) between 1st October 2013 and 31st December 2016 (n=26810) (FSB – fresh stillbirths, MSD – macerated stillbirths, END – early neonatal deaths).

<table>
<thead>
<tr>
<th>Perinatal cause of death</th>
<th>Maternal cause of death</th>
<th>No maternal condition</th>
<th>Coincidental conditions</th>
<th>Medical and surgical disorders</th>
<th>Non-pregnancy related infections</th>
<th>Pregnancy-related sepsis</th>
<th>Obstetric haemorrhage</th>
<th>Hypertension</th>
<th>Other maternal condition *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FSB</td>
<td>MSB</td>
<td>END</td>
<td>FSB</td>
<td>MSB</td>
<td>END</td>
<td>FSB</td>
<td>MSB</td>
<td>END</td>
</tr>
<tr>
<td>Unexplained intrauterine death</td>
<td>632</td>
<td>4729</td>
<td>(19.3)</td>
<td>77</td>
<td>0</td>
<td>(0.0)</td>
<td>25</td>
<td>169.9</td>
<td>93</td>
</tr>
<tr>
<td>Intrapartum asphyxia</td>
<td>1478</td>
<td>421</td>
<td>45.1</td>
<td>2430</td>
<td>0</td>
<td>(42.4)</td>
<td>67</td>
<td>45.3</td>
<td>17</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>56</td>
<td>252</td>
<td>(1.7)</td>
<td>53</td>
<td>0</td>
<td>(0.9)</td>
<td>6</td>
<td>4.1</td>
<td>8</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>370</td>
<td>206</td>
<td>(11.3)</td>
<td>105</td>
<td>0</td>
<td>(2.9)</td>
<td>13</td>
<td>8.8</td>
<td>7</td>
</tr>
<tr>
<td>Spontaneous preterm labour</td>
<td>263</td>
<td>384</td>
<td>(8.0)</td>
<td>1772</td>
<td>0</td>
<td>(31.0)</td>
<td>5</td>
<td>5.1</td>
<td>9</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>252</td>
<td>263</td>
<td>(7.7)</td>
<td>661</td>
<td>0</td>
<td>(11.5)</td>
<td>3</td>
<td>2.0</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>55</td>
<td>162</td>
<td>(5.5)</td>
<td>139</td>
<td>0</td>
<td>(2.4)</td>
<td>12</td>
<td>3.4</td>
<td>14</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>76</td>
<td>355</td>
<td>(2.3)</td>
<td>91</td>
<td>0</td>
<td>(1.6)</td>
<td>3</td>
<td>0.7</td>
<td>3</td>
</tr>
<tr>
<td>No obstetric cause</td>
<td>32</td>
<td>68</td>
<td>(1.0)</td>
<td>345</td>
<td>0</td>
<td>(1.0)</td>
<td>15</td>
<td>8.4</td>
<td>0</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>13</td>
<td>69</td>
<td>(0.4)</td>
<td>33</td>
<td>0</td>
<td>(1.0)</td>
<td>3</td>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>Misc.</td>
<td>40</td>
<td>98</td>
<td>(1.2)</td>
<td>110</td>
<td>0</td>
<td>(1.9)</td>
<td>1</td>
<td>0.2</td>
<td>3</td>
</tr>
<tr>
<td>Trauma</td>
<td>11</td>
<td>18</td>
<td>(0.3)</td>
<td>16</td>
<td>0</td>
<td>(10.8)</td>
<td>16</td>
<td>7.3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>3278</td>
<td>7005</td>
<td>(100)</td>
<td>5725</td>
<td>0</td>
<td>(100)</td>
<td>148</td>
<td>178</td>
<td>178</td>
</tr>
</tbody>
</table>

* extra-uterine pregnancy, anaesthetic complications, embolism, acute collapse combined
Conversion to ICD-PM Coding

The first author, a non-clinical researcher with a background in public health, studied *The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM* to learn to apply ICD-PM codes to the classification system’s database. The coding conversion took place between November 2017 and January 2018. The second author, a consulting obstetrician, provided guidance and verification on a voluntary basis. The ICD-PM system (72, 280, 282) classifies mortality according to: (i) time of death, whether antepartum (A1–A6), intrapartum (I1–I7) or neonatal (N1–N11); (ii) the primary cause of perinatal death (e.g. loss of fetal blood: P50); and (iii) the main maternal condition (M1–M4 to describe various complications and conditions, and M5 for healthy mother) at the time of perinatal death.

Ethics

Data were collected with the permission of the South African Department of Health. This analysis was approved by the technical task team who run the database and produce the reports from the South African Medical Research Council/University of Pretoria Maternal and Infant Health Care Strategies unit. This was a secondary analysis and all identifiers of the cases were removed. Ethics approval was given by the University of Western Australia Human Ethics Committee (RA/4/1/7955, 20 November 2015).

8.4 Results

Table 8.4 shows the reclassification of perinatal deaths using the ICD-PM and the primary causes of death are linked to maternal condition. Most deaths were antepartum in timing (15 619/26 810; 58.3%), followed by neonatal (7466/26 810; 27.8%) and intrapartum (3725/26 810; 13.9%). Of the total number of perinatal deaths, 8.8% (2368) were associated with a maternal death.
Table 8.4. Application of ICD-PM codes to South Africa’s perinatal audit data (PPIP) for perinatal deaths (>1000g and =>28 weeks gestation) between 1st October 2013 and 31st December 2016 (n=26810).

<table>
<thead>
<tr>
<th>Perinatal condition</th>
<th>Maternal condition</th>
<th>M1: Complications of placenta, cord and membranes</th>
<th>M2: Maternal complications of pregnancy</th>
<th>M3: Other complications of labour and delivery</th>
<th>M4: Maternal and medical surgical conditions</th>
<th>M5: No maternal condition</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1: Congenital malformations, deformations and chromosomal abnormalities</td>
<td>5</td>
<td>0</td>
<td>75</td>
<td>334</td>
<td>414 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2: Infection</td>
<td>83</td>
<td>1</td>
<td>310</td>
<td>52</td>
<td>446 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3: Antepartum hypoxia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A4: Other specified antepartum disorder</td>
<td>2342</td>
<td>10</td>
<td>595</td>
<td>0</td>
<td>2947 (18.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5: Disorders related to fetal growth</td>
<td>122</td>
<td>518</td>
<td>283</td>
<td>347</td>
<td>1270 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A6: Fetal death of unspecified cause</td>
<td>246</td>
<td>45</td>
<td>4573</td>
<td>5678</td>
<td>10542 (67.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>2798 (17.9)</td>
<td>574 (3.7)</td>
<td>5819 (37.3)</td>
<td>6428 (41.2%)</td>
<td>15619 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapartum death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I1: Congenital malformations, deformations and chromosomal abnormalities</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>161</td>
<td>190 (5.1)</td>
<td></td>
</tr>
<tr>
<td>I2: Birth trauma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I3: Acute intrapartum event</td>
<td>919</td>
<td>8</td>
<td>932</td>
<td>518</td>
<td>199</td>
<td>2476 (65.2)</td>
<td></td>
</tr>
<tr>
<td>I4: Infection</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>32</td>
<td>0</td>
<td>43 (1.2)</td>
<td></td>
</tr>
<tr>
<td>I5: Other specified intrapartum disorder</td>
<td>350</td>
<td>52</td>
<td>0</td>
<td>77</td>
<td>0</td>
<td>479 (12.9)</td>
<td></td>
</tr>
<tr>
<td>I6: Disorders related to fetal growth</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>20</td>
<td>28</td>
<td>64 (1.7)</td>
<td></td>
</tr>
<tr>
<td>I7: Intrapartum death of unspecified cause</td>
<td>4</td>
<td>9</td>
<td>0</td>
<td>337</td>
<td>23</td>
<td>373 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>1299 (34.8)</td>
<td>70 (1.9)</td>
<td>932 (25.0)</td>
<td>1013 (27.2)</td>
<td>411 (11.0)</td>
<td>3725 (100)</td>
<td></td>
</tr>
<tr>
<td>Neonatal death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1: Congenital malformations, deformations and chromosomal abnormalities</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>133</td>
<td>583</td>
<td>724 (9.7)</td>
<td></td>
</tr>
<tr>
<td>N2: Disorders related to fetal growth</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>45</td>
<td>77</td>
<td>136 (1.8)</td>
<td></td>
</tr>
<tr>
<td>N3: Birth trauma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N4: Complications of intrapartum events</td>
<td>200</td>
<td>1</td>
<td>1660</td>
<td>323</td>
<td>0</td>
<td>2184 (29.3)</td>
<td></td>
</tr>
<tr>
<td>N5: Convulsions and disorders of cerebral status</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N6: Infection</td>
<td>50</td>
<td>2</td>
<td>0</td>
<td>164</td>
<td>54</td>
<td>270 (3.6)</td>
<td></td>
</tr>
<tr>
<td>N7: Respiratory and cardiovascular disorders</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>756</td>
<td>674</td>
<td>1434 (19.2)</td>
<td></td>
</tr>
<tr>
<td>N8: Other neonatal conditions</td>
<td>334</td>
<td>2</td>
<td>0</td>
<td>79</td>
<td>0</td>
<td>415 (5.6)</td>
<td></td>
</tr>
<tr>
<td>N9: Low birthweight and prematurity</td>
<td>51</td>
<td>226</td>
<td>1458</td>
<td>331</td>
<td>62</td>
<td>2128 (28.5)</td>
<td></td>
</tr>
<tr>
<td>N10: Miscellaneous</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>96</td>
<td>71</td>
<td>175 (2.3)</td>
<td></td>
</tr>
<tr>
<td>N11: Neonatal death of unspecified cause</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>665 (8.9)</td>
<td>235 (3.1)</td>
<td>3118 (41.7)</td>
<td>1927 (25.8)</td>
<td>1521 (20.4)</td>
<td>7466 (100)</td>
<td></td>
</tr>
</tbody>
</table>
Antepartum deaths

Antepartum deaths were largely due to fetal deaths of an unspecified cause (10,542 deaths; 67.5%; ICD-PM code A6), other specified antepartum disorder (2,947 deaths; 18.9%; A4) or disorders related to fetal growth (1,270 deaths; 8.1%; A5; Table 8.4). Of the 15,619 antepartum deaths recorded, 41.0% (6,411) of the mothers had no maternal condition. For most of antepartum deaths classified as fetal death of unspecified cause, the mothers were free from any maternal complication (53.9%; 5,678/10,542; A6 M5): 5,537 (97.5%) deaths were due to an unexplained intrauterine death (A6 P95), 56 deaths (1.0%) were described as miscellaneous or other causes not described by the South African classification (A6 P95), and 85 (1.5%) deaths had no obstetric cause (M5).

Antepartum deaths classified as other specified antepartum disorder (2,947 deaths; 18.9%; A4) were further classified under fetal blood loss (2,342 deaths; P50), with the main causes being abruptio placentae (1,124 deaths; 38.1%; A4 P50 M1 P02.1), abruptio placentae with hypertension (928 deaths; 31.5%; A4 P50 M1 P02.1), antepartum haemorrhage of unknown origin (106 deaths; 3.6%; A4 P50 M1 P02.1), placenta praevia (69 deaths; 2.3%; A4 P50 M1 P02.0) and twin-to-twin transfusion (115 deaths; 3.9%; A4 P50 M1 P02.3). Where fetal blood loss was the primary cause of perinatal death, 595 deaths were related to maternal medical and surgical conditions (M4), including: hypertension (406 deaths), medical and surgical complications (114 deaths), non-pregnancy-related infections (21 deaths), coincidental (14 deaths), sepsis (4 deaths), anaesthetic (4 deaths) and acute collapse (3 deaths), all coded as A4 P50 M4; and rhesus isoimmunisation (29 deaths), coded as A4 P55.0 M4 P00.9. There were 10 antepartum haemorrhages with ectopic pregnancies, coded as A4 P50 M2 P01.4. Causes of death relating to haemorrhage described by code P52 are not categorized in the South African database, so we could not utilize this code during our conversion.

Intrapartum deaths

The main causes of the 3,725 intrapartum deaths (Table 8.4) were acute intrapartum event (2,576 deaths; 69.2%; I3), other specified intrapartum disorder (479 deaths; 12.9%; I5) or intrapartum death
of unspecified cause (373 deaths; 10.0%; I7). The other 297 deaths were classified as congenital malformations, deformations and chromosomal abnormalities (190 deaths; 5.1%; I1), infection (43 deaths; 1.7%; I4) and disorders related to fetal growth (64 deaths; 1.7%; I6). All deaths due to acute intrapartum events were classified as I3 P20.10 intruterine hypoxia, first noted during labour and delivery. Of the intrapartum deaths of unspecified cause, most were due to hypertensive disorders (269 deaths; 72.1%) or maternal disease (46 deaths; 12.3%). Of all the intrapartum deaths; 11.0% (411 deaths) were not associated with any maternal complication.

Neonatal deaths

The main causes of the 7466 neonatal deaths were complications of intrapartum events (2184 deaths; 29.3%; N4) or low birth weight and prematurity (2128 deaths; 28.5%; N9). All neonatal deaths classified as complications of intrapartum events were due to severe birth asphyxia (N4 P21; Table 8.4). Of all neonatal deaths, 1521 (20.4%) were not associated with any maternal complication. A large proportion (3118 deaths; 41.8%) of neonatal deaths were attributed to other complications of labour and delivery (M3). Of those deaths coded as M3, 1550 (49.7%) were due to labour-related intrapartum asphyxia (P03.9), 1456 (46.7%) were due to idiopathic preterm labour (P03.8 O60.0), 31 (1.0%) occurred as a result of traumatic breech delivery (P03.0), 25 (0.8%) were due to a precipitous labour (P03.5), 25 (0.8%) resulted from shoulder dystocia (P03.8 O66.0), 19 (0.6%) were due to traumatic assisted delivery (P03.2, P03.3) and 12 (0.4%) were due to a ruptured uterus (P03.8 O71.1).

Table 8.5 provides an example of how ICD-PM codes were applied to neonatal deaths classified by the South African classification system as being due to preterm labour. According to the classification system, most (83.5%, 1772/2121) of the deaths due to preterm labour were associated with a healthy maternal condition. Under the ICD-PM classification, however, 96.5% of these (1710/1772) were associated with a non-healthy maternal condition. For example, cases of perinatal death due to idiopathic preterm labour, premature rupture of membranes, premature rupture of membranes with chorioamnionitis, cervical incompetence and premature rupture of membranes with chorioamnionitis
and intact membranes were assigned the codes M3 P03.8, M2 P01.1, M2 P01.1, M2 P01.0 and M1 P02.7, respectively. Only 3.5% (62/1772; iatrogenic preterm delivery for no real reason) of neonatal deaths due to preterm labour associated with a healthy mother, according to the South African classification, are coded as M5 under the ICD-PM system.
### Table 8.5. Example of application of ICD-PM codes to existing PPIP neonatal deaths due to spontaneous preterm labour (n=2121) *

<table>
<thead>
<tr>
<th>Maternal Condition (PPIP)</th>
<th>Healthy</th>
<th>Coincidental conditions</th>
<th>Medical and surgical disorders</th>
<th>Non-pregnancy related infection</th>
<th>Extra-uterine pregnancy</th>
<th>Pregnancy-related sepsis</th>
<th>Obstetric haemorrhage</th>
<th>Hypertension</th>
<th>Anaesthetic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Condition (PPIP)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ICD-PM code, n(%total)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>N9 M3 P03.8, 1458 (68.5)</td>
<td>N9 M4 P00.5, 33(1.6)</td>
<td>N9 M4 P00.0-P00.4, 67(2.8)**</td>
<td>N9 M4 P00.2, 61(2.8)</td>
<td>N9 M2 P01.4, 1(0.05)</td>
<td>N9 M1 P02.7, 9(0.4)</td>
<td>N9 M1 P02.1 10(0.5)</td>
<td>N9 M4 P00.0 50(2.3)</td>
<td>N9 M4 P04.0 1(0.05)</td>
</tr>
<tr>
<td></td>
<td>N9 M2 P01.1, 205(9.6)</td>
<td>N9 M4 P00.5, 6(0.3)</td>
<td>N9 M4 P00.0-P00.4, 21(1.0)</td>
<td>N9 M4 P00.2, 6(0.3)</td>
<td>N9 M2 P01.4, 1(0.05)</td>
<td>N9 M1 P02.7, 9(0.4)</td>
<td>N9 M1 P02.1, 5(0.2)</td>
<td>N9 M4 P00.0, 11(0.5)</td>
<td>N9 M4 P04.0, 1(0.05)</td>
</tr>
<tr>
<td></td>
<td>N9 M5, 62(2.9)</td>
<td>N9 M4 P00.0 1(0.05)</td>
<td>N9 M4 P00.0-P00.4, 2(0.1)</td>
<td>N9 M4 P00.2, 3(0.1)</td>
<td>N9 M2 P01.4, 0(0)</td>
<td>N9 M1 P02.7, 2(0.1)</td>
<td>N9 M1 P02.1, 5(0.2)</td>
<td>N9 M4 P00.0, 1(0.05)</td>
<td>N9 M4 P04.0, 1(0.05)</td>
</tr>
<tr>
<td></td>
<td>N9 M2 P01.1, 21(0.9)</td>
<td>N9 M4 P00.0, 0(0)</td>
<td>N9 M4 P00.0-P00.4, 3(0.1)</td>
<td>N9 M4 P00.2, 3(0.1)</td>
<td>N9 M2 P01.4, 0(0)</td>
<td>N9 M1 P02.7, 18(1)</td>
<td>N9 M1 P02.1, 1(0.5)</td>
<td>N9 M4 P00.0, 0(0)</td>
<td>N9 M4 P04.0, 0(0)</td>
</tr>
<tr>
<td></td>
<td>N9 M2 P01.0, 15(0.7)</td>
<td>N9 M4 P00.5, 0(0)</td>
<td>N9 M4 P00.0-P00.4, 3(0.1)</td>
<td>N9 M4 P00.2, 2(0.1)</td>
<td>N9 M2 P01.4, 0(0)</td>
<td>N9 M1 P02.7, 1(0.05)</td>
<td>N9 M1 P02.1, 1(0.5)</td>
<td>N9 M4 P00.0, 0(0)</td>
<td>N9 M4 P04.0, 0(0)</td>
</tr>
<tr>
<td></td>
<td>N9 M1 P02.7, 11(0.5)</td>
<td>N9 M4 P00.5, 0(0)</td>
<td>N9 M4 P00.0-P00.4, 1(0.05)</td>
<td>N9 M4 P00.2, 0(0)</td>
<td>N9 M2 P01.4, 0(0)</td>
<td>N9 M1 P02.7, 6(0.3)</td>
<td>N9 M1 P02.1, 0(0)</td>
<td>N9 M4 P00.0, 0(0)</td>
<td>N9 M4 P04.0, 0(0)</td>
</tr>
</tbody>
</table>

* as only deaths >1000g and =>28weeks were analysed the only categories applicable for N9 were P07.1 Other low birth weight (n=2051) and P07.3 Other preterm infants (n=70), due to low numbers in P07.3 we combined these groups to demonstrate how maternal codes can be applied to these deaths.

** PPIP maternal condition (ICD-PM code): cardiac disease (M4 P00.3), endocrine disease (M4 P00.9), GIT disease (M4 P00.9), CNS disease (M4 P00.9), respiratory disease (M4 P00.3), haematological disease (M4 P070520.9), genito-urinary disease (M4 P00.1), auto-immune disease (M4 P00.9), skeletal disease (M4 P00.9), psychiatric disease (M4 P00.9), neoplastic disease (M4 P00.9), other medical and surgical disorders (M4 P00.9).
8.5 Discussion

Here we show that ICD-PM coding improve consideration of maternal complication when classifying perinatal deaths. Previous research in South Africa reported that maternal complications were linked to around one half of all stillbirths and one quarter of early neonatal deaths. According to the South African classification system, 45.7% (8644/18,927) of stillbirths and 27.4% (2158/7883) of early neonatal deaths were classified as being linked to a maternal complication; this is equivalent to 40.3% (10,802/26,810) of all deaths. In contrast, our analysis of ICD-PM classifications identified a much higher proportion of maternal conditions for these outcomes. Maternal complications were associated with 59.0% (9,208/15,619) of antepartum deaths, 89.0% (3,314/3,725) intrapartum deaths and 79.6% (5,945/7,466) of neonatal deaths; this is equivalent to 68.9% (18,467/26,810) of all deaths.

We managed to classify all neonatal deaths with a primary cause of intrapartum asphyxia with an associated maternal condition using the ICD-PM codes, while the South African classification system only classified 17.4% (512/2942). Several subcategories such as labour-related intrapartum asphyxia, cord around neck and others as outlined in Table 8.1 are classified according to the South African classification system as perinatal complications with a healthy mother. Using the ICD-PM system, however, these deaths can be categorised as the result of a maternal condition. Antepartum haemorrhage because of abruptio placentae or placenta praevia is considered a perinatal condition under the South African classification system, but classified as a maternal condition by the ICD-PM system.

We also show that ICD-PM coding improve consideration of timing of death. A recent systematic review found that 59% of globally reported stillbirths had no information regarding the timing of death (283), making the appropriate timing of interventions difficult to identify. Further, in some resource-poor settings the timing of a perinatal death may be the only piece of information captured. This information should therefore be a part of any classification system (41).
The application of the ICD-PM coding system to our data revealed a significant burden of deaths occurring during the antepartum period. Further, more than a quarter of early neonatal deaths were due to low birth weight. This highlights the already established importance of investment in antenatal care to reduce perinatal mortality. The 2016 WHO antenatal care recommendations (96) include an increased number of antenatal care contacts in the third trimester. In response to these recommendations and the increased number of third-trimester stillbirths observed when antenatal care visits had not been made during this period, the number of recommended antenatal care visits was changed in South Africa in April 2017 (244).

A commonly cited burden of perinatal mortality is prematurity and prematurity-related causes (236). However, simply identifying that prematurity is an important contributor to deaths gives no information regarding the optimal timing for interventions. From the ICD-PM classification, we see that 36.7% (1270; coded under A5, disorders related to fetal growth) of deaths due to prematurity (3426; the total of deaths classified as A5, I6 or N9) occurred during the antepartum period, and that 72.7% (923/1270) of these deaths were also related to a maternal complication. This information is invaluable to public health workers and policy-makers in targeting interventions; a heightened awareness of the causes of such deaths allows a focus on preterm-related issues, showing that both obstetric and neonatal interventions are required.

For implementing ICD-PM coding, systematic training of data administrators in the classification of deaths using ICD-PM will be required to ensure familiarity with the new system, as well as consistency across settings. Data administrators will also need to have access to clinicians to discuss cases that do not clearly fit a specific ICD-PM classification. In our experience, however, the ICD-PM system is both clinically relevant and easy to use; the coder for this study does not have a clinical background. There was a high level of agreement between the coder and the verifying obstetrician, with differences encountered in only two cases: (i) premature rupture of membranes with chorioamnionitis (M1 P01.1 according to coder, M1 P02.7 according to obstetrician) and (ii) unexplained uterine death (A3 according to coder, A6 according to obstetrician). This demonstrates the feasibility in implementing
the ICD-PM codes to existing data sets by administrators or allied health providers, in consultation with clinicians. Data administrators can be trained in the application of ICD-PM coding under the mentorship of clinicians, an advantage in low-resource settings.

We noted some specific issues with ICD-PM, including mutually exclusive categories, deaths which could be classified under two different ICD-PM codes, multiple contributing factors for cause of death, and causes of death not captured by the South African classification system but considered by ICD-PM codes (or vice versa). Examples of these issues and potential solutions are discussed in Table 8.6.

As maternal and perinatal outcomes are closely related, both mother and infant benefit from intervention (280); this is particularly relevant in the management of hypertension and care during the intrapartum period (281, 284, 285). However, possible challenges exist with the application of the ICD-PM system to data sets which consider perinatal death and maternal condition separately, introducing issues in the integration of the two systems. The adaption of integrated perinatal and maternal data collection systems may be difficult in poorly resourced settings. For countries that do not have well established death classification systems, future developments could consider autopsy review categories aligned with ICD-PM codes for better consistency between death review and coding stages. For example, the South African classification system could be strengthened to align more closely to ICD-PM as described in Table 8.6.
### Table 8.6. Opportunities for improvement in implementing ICD-PM to PPIP data system

<table>
<thead>
<tr>
<th>Issue</th>
<th>Examples from implementation</th>
<th>Outcome implemented/potential solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutually exclusive categories</strong></td>
<td>1. A preterm birth where cause of death is premature rupture of membranes (PROM) with chorioamnionitis (PPIP) could be classified as either M1 P02.7 fetus and newborn affected by chorioamnionitis or M2 P01.1 fetus and newborn affected by PROM.</td>
<td>1. These deaths were classified under M1 P02.7 fetus and newborn affected by chorioamnionitis</td>
</tr>
<tr>
<td><strong>Multiple contributing factors for cause of death</strong></td>
<td>2. In PPIP abruptio placenta also complicated by maternal hypertension can be classified as abruptio placenta or abruptio placenta with hypertension. ICD-PM can classify abruptio placenta as fetal blood loss, fetus and newborn affected by other forms of placental separation and haemorrhage – abruptio placenta (A4 P50 M1P02.1) or fetus or newborn affected by maternal hypertensive disorders (A4 P50 M4 P00.0). Here the coder must make a decision as to which is the most important maternal condition by which to classify – i.e., the abruptio placenta or hypertension.</td>
<td>2. These deaths were coded as A4 P50 M1P02.1 (abruptio placenta).</td>
</tr>
<tr>
<td></td>
<td>3. In PPIP deaths due to antepartum haemorrhage where another maternal condition was present simultaneously can be classified with both conditions present. This occurs as the defining cause of death for haemorrhage lies under the maternal condition rather than fetal condition. The fetal condition is classified as P50 (fetal blood loss) and the maternal condition under abruptio placenta (M1P02.1), placenta praevia (M1P02.0) or twin-to-twin transfusion (M1P02.3). Competing interests arise where multiple maternal conditions are present such as sepsis, anaesthetic complications, hypertension, medical and surgical complications or non-pregnancy-related infections in addition to abruptio placenta or placenta praevia. The coder must make a decision whether to code under M4 or M1.</td>
<td>3. Where no other maternal condition was present antepartum haemorrhage was coded under M1. M4 was used for antepartum haemorrhage with another maternal condition also present concurrently.</td>
</tr>
<tr>
<td><strong>Two different ICD-PM codes for same cause of death</strong></td>
<td>4. Unexplained intrauterine death could have been coded as either A3 or A6. A3 and A6 coding are essentially explaining the same end cause of death (antenatal asphyxia).</td>
<td>4. These deaths were coded as A6 with no deaths being classified under A3.</td>
</tr>
<tr>
<td><strong>Conditions not captured in PPIP but included in ICD-PM</strong></td>
<td>5. M3 P03.4 fetus and newborn affected by caesarean section delivery not captured in PPIP. In PPIP caesarean section delivery is not a classifiable cause of death, with some deaths captured under maternal condition ‘complications of anaesthesia’ or ‘medical and surgical disorders’.</td>
<td>5. More detailed information for these categories in PPIP would enhance the alignment of the existing data collection system to ICD-PM.</td>
</tr>
<tr>
<td></td>
<td>6. Birth trauma (I2) is not captured in PPIP. In PPIP most deaths due to birth trauma would be classified as ‘traumatic assisted delivery’ or ‘other cause of death not described in classification’.</td>
<td>6. More detailed information for these categories in PPIP would enhance the alignment of the</td>
</tr>
</tbody>
</table>

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### CHAPTER 8 APPLICATION OF ICD-PM TO PPIP

| **PPIP maternal condition classifications too broad** | **For maternal conditions in PPIP, only Lead categories are able to be linked to perinatal death (i.e. hypertension, obstetric haemorrhage, medical and surgical disorders) without more specific detail (proteinuric hypertension, eclampsia, chronic hypertension etc.) being linked.** |
| **7.** For deaths related to other complications of labour and delivery (M3 - *other complications of labour and delivery*), a large proportion of cases were classified as unspecified under the code P03.9 *Fetus and newborn affected by complication of labour and delivery, unspecified*. In PPIP these deaths were classified as ‘labour related intrapartum asphyxia’ with no further detail as to the exact labour-related maternal cause of these deaths. |
| **8.** It may be possible to reduce the number of deaths falling under this unspecified category if PPIP mortality audits were able to capture more detailed information around maternal causes for complications of labour and delivery such as those conditions falling under M3 *P03.1 fetus and newborn affected by other malpresentation, malposition, disproportion during labour and delivery*, P03.6 *fetus and newborn affected by abnormal uterine contractions* and conditions classifiable under O60-O75. |

| **High proportion of antepartum deaths classified as unspecified causes with no maternal complication (A6;M5)** | **Initially it appeared as though ICD-PM coding was not sufficiently sensitive to identify the causes of these antepartum deaths accurately, however these deaths were at the highest descriptive level in PPIP without more detailed available information regarding the cause of death.** |
| **9.** These deaths were ‘truly’ due to unexplained or unknown causes. There could be no improvement in the ICD-PM classification system that would decrease the number of deaths falling under A6; M5. |
In conclusion, by allowing for an increased recognition of the role of maternal condition and the timing of death in perinatal mortality, our conversion of an existing national perinatal mortality data set to ICD-PM codes enhanced our understanding of the data. This work is part of a larger work investigating perinatal deaths in South Africa and the required interventions (84, 244). Our new classification of perinatal deaths could inform the allocation of resources and the timing of interventions. Adopting the ICD-PM coding system internationally would lead to a consistent global perinatal death classification system, which would create comparable data that could inform policy-makers globally.
CHAPTER 9. OVERVIEW OF KEY FINDINGS, DISCUSSION AND CONCLUSIONS

9.1 Original contributions and key findings

This thesis has systematically explored several key public health issues concerning the prevention of stillbirths in South Africa. The majority of previous research in these areas has been conducted in high income settings limiting the generalisability of these findings to contexts such as South Africa and LMICs. This doctorate utilised rich, population-based data to explore these issues in a LMIC setting.

A series of analyses pertaining to antenatal stillbirths and growth-restricted pregnancies were conducted. This body of work has described the causes of death, condition of mother and timing of deaths in growth restricted fetuses in South Africa, showing that nearly half of all antenatal stillbirths have no maternal complication and there is no increase in this proportion for growth restricted pregnancies (Chapter 4). The Chapter 5 analysis demonstrated that many growth restricted pregnancies are missed with current methods and that there are increased periods of stillbirth risk in the third trimester for growth restricted pregnancies as compared to normally growing pregnancies. The importance of frequent antenatal care in the third trimester was highlighted in Chapter 7 showing that stillbirth risk is increased after periods of no ANC likely due to an increase in diagnosed stillbirths after a period of absent ANC.

In relation to measurement and data, Chapter 6 found that INTERGROWTH-21st and Theron-Thompson growth charts identified the same proportion of stillbirths as SGA (~31.5%). However, differences by gestational-age were present, with INTERGROWTH-21st more sensitive at younger gestations and Theron-Thompson more sensitive at older gestations. In terms of categorising deaths, it is feasible to implement ICD-PM to existing perinatal mortality data collection systems in LMICs (Chapter 8). The main advantage of ICD-PM was increased ability to identify time of death, with most deaths (58.2%) occurring in the antenatal period.
9.2. Medical causes of death and timing of deaths for SGA

9.2.1 Key findings

Chapter 4 was able to address some of the limitations with research to date in LMICs exploring maternal condition in perinatal mortality cases. These limitations were small sample sizes, limited generalisability of study data (mainly hospital) to a wider obstetric population, inability to separate stillbirth and early neonatal death as primary outcomes, and the inability to examine SGA specifically. This study overcame these limitations by using national mandatory mortality data with linked data on maternal condition at the time of death.

This study found that in 40% of stillbirths, no maternal complication was present, with the mother presenting as clinically healthy. This was lower than global estimates showing no maternal complication present in 74.7% of stillbirths (286). Most importantly, it was revealed that there was no increase in maternal complications for SGA pregnancies as compared to AGA pregnancies (Chapter 4).

The implications of this in a community antenatal care setting are significant as women with identified maternal conditions are up-referred, however current methods miss approximately half the stillbirths that occur in the so-called ‘low-risk’ pregnancy. This is the case for both normally growing and growth restricted pregnancies.

In addition to this finding, it was also revealed that most SGA stillbirths occur between 33 and 37 weeks (Chapter 4). This also coincided with an increased risk of stillbirth for SGA pregnancies (Chapter 5) as compared to appropriately growing fetuses. The women in the Chapter 5 study continued to receive fortnightly ANC during this period of increased risk, however the current ANC model was not adequate to detect these SGA pregnancies at risk of stillbirth. This is consistent with the literature from HICs estimating that at least three-quarters of pregnancies with growth failure are not detected during routine antenatal care (180, 189).
9.2.2 Implications for policy and practice

These studies highlighted the challenges with detecting pregnancies at risk of stillbirth, particularly growth restricted pregnancies that are at 8-fold increased risk of stillbirth (87). This emphasises the need for new methods to detect pregnancies at risk of stillbirth in addition to the use of risk-profiling based on the mother’s condition. This is particularly paramount for community-led antenatal care where low-risk women continue care in a community setting until identified as high-risk. In pregnancies considered low-risk, the detection rate for poorly growing fetuses is low (15%) (189). In addition to identification of maternal complications, which is not a good indicator of SGA, the use of symphysis-fundal height (also a poor predictor of SGA) is also used to identify women who require up-referral (230).

These underlying clinical practice issues are reflected in the findings from Chapter 4 and 5 which demonstrate that current methods of determining pregnancies requiring up-referral are inadequate to prevent all stillbirths (regardless of mother’s condition). There is strong evidence that maternal-risk profiling is an effective and inexpensive method to detect around half of pregnancies that will have adverse outcomes (175, 176), however, other options for investigation in pregnancies with undetectable complications are limited and highlight the need for further research to improve current clinical practice.

9.2.3 Future research directions

Future research needs to explore alternative, in-expensive methods to detect pregnancies requiring up-referral and at risk of stillbirth in community settings. The WHO in its new antenatal care guidelines (2016) states “accurate low-cost methods for detecting abnormal growth are desirable because ultrasound, the most accurate screening tool, is resource-intensive and not widely available in LMICs” (96). A recent cluster RCT in LMICs found that ultrasound is not effective at reducing maternal or perinatal deaths in low-resource settings or increasing attendance at antenatal clinic, and is therefore a not an effective use of limited resources (209). The results from the Chapter 4 and 5
support the need for investigation of new methods to detect pregnancies at risk of perinatal mortality and morbidity.

One new method that has the potential to overcome the barriers discussed previously is a technology called Umbiflow™. Umbiflow™ is a mobile-connected Doppler device that uses a continuous-wave waveform to detect blood flow within the fetal umbilical cord, with any abnormalities indicating placental problems and pregnancies at risk of stillbirth. Umbiflow™ can be operated by nurses and midwives in a community primary care setting and is inexpensive (<USD $300 per unit) (287). Umbiflow does not rely on symphysis fundal height to determine growth failure or risk-profiling of the mother. The potential future implementation of this device in clinical practice is that all women receiving antenatal care in community settings receive one Umbiflow screening irrespective of risk-profile.

The most recent Umbiflow trial was conducted in Mamelodi, South Africa targeting an unselected population (general populations with low-risk and high-risk women) who would normally receive care in the community setting. The non-randomized study (n=21,942) found a 46% reduction (Risk Ratio 0.54, 95% CI 0.31-0.94) in stillbirths (perinatal mortality rate 20/1000 to 11.4/1000; macerated stillbirth rate 10.2/1000 to 4.3/1000) when Umbiflow™ was used to identify women requiring up-referral to the district level (273) as compared to routine care (i.e., maternal risk profiling, growth charts, ultrasound if available).

Based on the available limited evidence, the WHO does not currently recommend the routine use of Doppler velocimetry for low-risk populations. A new multi-country multicentre uncontrolled pre-post quasi-experimental trial study including participants from South Africa, Kenya, India, Ghana and Rwanda has been set up through the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP). The two main objectives of the Umbiflow International Study are: (1) to determine the prevalence of abnormal umbilical flow indices in unselected obstetric populations; (2) to ascertain whether a single screening
with the Umbiflow device in the third trimester of pregnancy can identify women at risk of stillbirth and subsequently up-refer these women for specialised obstetric care leading to a reduction in stillbirths. Importantly, the chosen period is in the third trimester which was identified as a high risk period in Chapter 4 and Chapter 5.

9.3 Growth charts to detect SGA pregnancies

9.3.1 Key findings

Chapter 6 compared newly developed global fetal growth charts with population developed charts. It was revealed that there are large discrepancies in the ability of fetal growth charts to identify SGA fetuses depending on the gestational age (Chapter 6). This study added to the growing debate as to whether standardised globalised charts are superior to local population developed charts. There are several considerations in this debate including differences in fetal growth based on ethnicity and population differences populations which are discussed below (223, 224).

9.3.2 Implications for policy and practice

Currently a number of growth charts are used across South Africa including Theron-Thompson (227), INTERGROWTH-21st (multi-country) (217) and Solomon (French population) (229). The results from Chapter 6 support the use of either INTERGROWTH-21st or Theron-Thompson in the South African population where in gestational-age considerations are not important, such as exploring the proportion of SGA fetuses in a population. Where gestational is an important factor, such as comparing early preterm to late preterm deaths, it is important to recognise that INTERGROWTH-21st is more sensitive at younger gestations and Theron-Thompson more sensitive at older gestations (288). The INTERGROWTH-21st also allowed for the comparison of proportion of SGA pregnancies between countries, which previously was not possible. South Africa had a similar of proportion of stillbirths that were SGA as an UK study (268).

The limitations of the use of fetal growth charts as a method to predict adverse outcomes must also be considered in light of the current literature. It should be acknowledged that growth restriction may also occur in AGA pregnancies (273). In fact, recent work in South Africa found one-third of antenatal
stillbirths due to placental insufficiency occur in fetuses tracking above the 10th centile (273). Further, serial weight-for-gestational-age plots are rarely achieved (232), therefore it is difficult to distinguish the constitutionally small fetus or the fetus above the 10th centile that has had a significant drop in weight velocity (289).

In LMICs, the application of growth charts in the clinical setting is further challenged. Correct pregnancy dating is required as well as the ability to plot SFH correctly by health care staff, both of which are known issues in South Africa (232).

9.3.3 Future research directions

There has recently been a substantial amount of work invested in developing customised growth charts. Customised growth charts take into account the maternal characteristics (maternal height, weight at booking, parity, ethnic origin) to produce an individualised fetal growth chart for each pregnancy. The customised chart provides an optimal curve and normal ranges achievable in an uncomplicated pregnancy. Customised growth charts have been shown to be a better predictor of adverse outcome in numerous settings including LMICs (221, 290). Co-efficients for different South African ethnicities are currently been developed by the UK Perinatal Institute headed by Professor Gardosi. When the data is available, it will be possible to compare the sensitivity, specificity and positive predictive value of customised growth charts as compared to global standardised and local charts for stillbirth and other adverse outcome. Customised charts have been shown to identify growth restricted pregnancies that would usually be above the 10th centile but are now below the 10th centile, and may decrease the number of pregnancies with placental insufficiency that still track as AGA.

However, as discussed previously, relying on growth charts for full clinical assessment is not adequate and there are implementation challenges such as incorrect SFH plotting and lack of serial plotting (232). Alternative methods such as Umbiflow (as discussed previously) or the use of PEA POD® Infant Body Composition System (Pea-Pod) should also be explored.
The Pea-Pod is a device that estimates neonatal fat mass (kg) using an air displacement plethysmography. The application of Pea-Pod would allow an alternative method of defining growth restriction at time of birth based on body fat composition. The Pea Pod has been optimised for preterm and term births (291, 292). However, differences in body fat percentages between ethnicities have not been examined. If this was optimised it may be possible to replace the gross measure of weight centile with fat mass percentage to classify neonates as growth restricted. However, Pea-Pod would not assist in identifying growth restricted fetuses during pregnancies.

9.4 Temporal targets for timing of antenatal care to reduce stillbirths

9.4.1 Key findings

One of the main findings of Chapter 7 was that reduced antenatal care contacts in the third trimester increased stillbirth risk. This finding was consistent with several other published studies emerging around the same time, including the secondary analysis of WHO-ANC trial (149) and a Cochrane review (150). These studies were the first to separate HICs from LMICs as prior studies pooled all data together (149, 150). The pooled studies had shown no increase in perinatal mortality in the reduced ANC contacts group. This result alone would suggest that the previous recommendation by WHO in 2001 to reduce the antenatal schedule would not increase the risk of perinatal death, as suspected at the time of guideline development.

There are several reasons why an increase in perinatal mortality associated with reduced antenatal care contacts is only seen in LMICs. First, there is considerable variation between HIC and LMIC settings in terms of baseline health risk and health resource availability. Pregnancies in LMICs are at far greater risk of perinatal mortality than in HICs due to socio-economic factors, as is reflected in the disparity in mortality rates between settings. There are also vast differences in the way ANC is delivered between settings, with the majority of ANC in LMICs delivered in community care settings, with limited resources and technology compromising the quality of care delivered. This heterogeneity needs to be considered when interpreting the results around perinatal mortality in any pooled analysis. Second, the number of contacts between ‘reduced-visit’ and ‘standard’ ANC models differed
between HIC and LMIC settings. For HICs, the mean number of contacts in the reduced ANC visit group was 8.2, while in LMICs the mean was 4.8. This renders two very different comparisons been made with the reduced contacts group substantially higher in HICs group, and similar in number to the standard contacts group in the LMICs. It may be that there is a threshold regarding the minimum number of ANC contacts to influence perinatal mortality outcomes which is not reached in the HICs. The reduced visit group in the Chapter 7 study had 4 ANC contacts, similar to the other LMICs, supporting the notion of a minimum threshold in terms of the number of contacts.

Although most recent evidence is consistent with the findings from Chapter 7, it should be noted that there were some earlier studies that presented findings in support of reduced ANC schedules. These studies informed the initial change in ANC recommendations by WHO to reduce the schedule in 2001.

Two of the most important studies were RCTs conducted in neighbouring Zimbabwe (one rural, one urban) with a similar population and local context as South Africa (126, 131). These studies found that perinatal mortality was not increased in the reduced contacts group. At the time the importance of the timing of antenatal care contacts in addition to the number of contacts was not realised. Given the advance in knowledge since the publication of these studies, including the findings of Chapter 7, the reasons for the differences seen in results can be elaborated on.

The first consideration is that in both Zimbabwean studies, the reduced visit group and standard visit group were homogenous in terms of the number of contacts. In the rural study, the mean number of contacts in the reduced contact group was the same as the standard visit group (mean number contacts 4). In Chapter 7 there was a difference of 4 contacts between the reduced visit and standard group, therefore representing two different care schedules. This is likely one reason why an increase in perinatal mortality in the reduced care group was observed only in the Chapter 7 study, despite similar populations and local contexts as in the other Zimbabwean studies.

Secondly, there were substantial differences in the timing of the contacts between the Zimbabwean studies and the Chapter 7 study. The Zimbabwean studies had a reduced visit schedule that was very
similar to the high visit group in South Africa with contacts at booking, 24-28, 32-34, 36-38, and 40 weeks. In Chapter 7 there was a tripling of stillbirth risk at 38 weeks. One hypothesis is that as the Zimbabwean women were still receiving antenatal care during this high-risk period for stillbirth, stillbirth risk was not increased, the findings from Chapter 4 and 5 also identify this period as a high-risk period for stillbirth especially for SGA infants. However, it is necessary to examine if there were more inductions and referrals in the Zimbabwean reduced-visit group to see if the additional ANC contacts had an impact on management.

Chapter 7 was also the first study to examine the causes of death during periods of stillbirth risk. The increase in proportion of deaths due to hypertension during the absence of antenatal care supports the hypothesis suggested by Hofmeyr and Hodnett (293), that the increase in perinatal mortality between 32 and 36 weeks, as observed in the secondary analysis of WHO ANC Trial (149), was potentially due to treatable and detectable conditions in the third trimester, such as eclampsia and hypertension. This was the first time this hypothesis was able to be tested simultaneously with the impact of ANC timing on stillbirth risk.

Complete blinding in trials of antenatal care is impossible, increasing the chance of selection or information bias in previous RCTs. It is also a challenge to avoid co-interventions in such trials unlike classic therapeutic trials, as demonstrated with many ANC RCTs to date (130). Although the Chapter 7 study was not as robust in terms of study design, the strength was that it was a ‘real-life’ reflection of the situation in South Africa and a ‘natural experiment’ removing the issues of selection and information bias present in previous RCTs. The data from the Chapter 7 study aligned consistently with findings from the Cochrane review (150) and secondary analysis of WHO ANC study (149). This consistent evidence which adopted a range of methodology was presented as evidence in the revisions of antenatal care guidelines at a national and international level.
9.4.2 Implications for policy and practice

In 2016 a revision of the Antenatal Care Guidelines was conducted by WHO. The findings from Chapter 7 were part of the evidence reviewed by the Guidelines Development Group Meeting, WHO Recommendations on Antenatal Care Panel 2 (Geneva, Switzerland, Chateau de Penthes, 21-23 March 2016). In December 2016, WHO increased the number of recommended antenatal care contacts in the third trimester under the WHO recommendations on antenatal care for a positive pregnancy experience - Recommendation E.7: Antenatal care models with a minimum of eight contacts are recommended to reduce perinatal mortality and improve women’s experience of care (96). The recommended visit schedule is <12 weeks, 20, 26, 30, 34, 36, 38 and 40 weeks.

The decision by the WHO Antenatal Care Guideline Development Group to increase the number of contacts with health system was influenced by the following factors:

1. evidence supporting improving safety during pregnancy through increased frequency of maternal and fetal assessment to detect problems (149, 150, 244);

2. evidence supporting improving health system communication and support around pregnancy for women and families (153, 154);

3. evidence from HIC studies indicating no important differences in maternal and perinatal health (150)

4. outcomes between ANC models that included at least eight contacts and ANC models that included more (11–15) contacts (149, 150, 244);

5. evidence indicating that more contact between pregnant women and knowledgeable, supportive and respectful health-care practitioners is more likely to lead to a positive pregnancy experience (150, 294)

The work in Chapter 7 falls under point four above. The largest drivers for the revision of the schedule as cited by the GDG were the increased perinatal deaths seen in the reduced ANC model as compared to the 8-visit model, as well as greater maternal satisfaction with increased antenatal care contacts.
The timing of the contacts was increased with additional contacts at 34 to 38 weeks, as these time points will facilitate assessment of fetal well-being when stillbirth risk is highest, especially for SGA pregnancies as shown in Chapter 4 and 5. This is also a time during pregnancy when interventions can be implemented to prevent adverse obstetric outcome if problems are identified. One of the findings from Chapter 7 was that stillbirths due to complications of hypertension represented a significant proportion of deaths at 32 and 38 weeks. Research from South Africa has shown that the average time between the last antenatal care visit and a maternal near miss event due to hypertension is 2.6 weeks (279), thus the increased number of contacts should allow sufficient time for intervention to reduce deaths due to hypertension.

The increase in antenatal contacts does not necessarily translate into high quality care and implementation of the new guidelines must be comprehensive, taking into account all recommendations. Recommendation E.7 should also be implemented alongside other quality-improvement activities and Recommendations A.1 to E.6. Implementation of this guideline will include a practical implementation manual for health care practitioners, incorporating ANC recommendations and good clinical practice.

The evidence from Chapter 7 in favour of increasing the number of antenatal care contacts was presented to the South African Medical Council and the Minister of Health resulting in a change in antenatal care scheduling policy as of April 2017. The relevance of the study within the South African clinical context which used data from three South African provinces (Chapter 7) as well as the fact that the study used real-world data, formed the basis for the decision to increase the number of recommended in ANC contacts. South Africa was the first country to formally increase the number of antenatal care contacts in response to the emerging evidence.
9.4.3 Future research directions

Perinatal mortality and hypertension

As South Africa is one of the first countries to adopt the new WHO guidelines on 1st April 2017, the implementation of the guidelines is being heavily evaluated. The upscaling of ANC to the new 8-visit model (BANC Plus) is expected to take at least 12 months. The first preliminary analysis evaluating the progress implementation and perinatal mortality outcomes was conducted in December 2017 (295). This analysis used data from four circumscribed catchment areas (1 urban, 2 pre-urban and 1 rural sub-districts) across South Africa. There was an overall increase in the number of contacts between March 2017 (n=4.5) and November 2017 (n=5.4; 53% of women had > 8 contacts). There was also an increase in the detection of antenatal hypertension with 10.3% diagnosed in March compared to 16.5% in November (60% increase). The stillbirth rate was unchanged at 27.6/1000. This is likely due to the implementation being in the early stages therefore the impact on stillbirth not yet being realised. A small sample size also led to low power to test this outcome. Implementation evaluation should continue to examine the impact of the new ANC schedule on hypertension and stillbirth rates.

To investigate the impact of increasing the number of ANC contacts from four to eight, future studies should consider using PPIP data and the fetuses-at-risk approach as employed in Chapter 7. It would be possible to compare stillbirth risk across pregnancy in Mpumalanga and Limpopo provinces before and after implementation to examine if the peak in stillbirth risk is still observed at 38 weeks gestation. It would also be possible to compare the proportion of deaths due to hypertension before and after implementation.

Health system factors for implementation

One of the potential barriers to implementation of an 8-visit ANC model in LMICs is the increase in resources and financial input required. In many LMICs, national and sub-national level health budgets are limited. In countries that are still targeting interventions to reduce intrapartum and neonatal deaths such as access to skilled birth attendants, the provision of ANC to reduce stillbirths is a low
priority. This is reflected in data showing that many countries are currently struggling to establish quality antenatal care with the previous four visit model (155). With regards to the new 8-visit model, programme reports from Ghana and Kenya indicate that inadequate equipment, supplies, infrastructure and training may impede implementation (151, 152).

In addition women have expressed concern about the indirect costs of the increased number of contacts (151, 152). The evaluation conducted in South Africa found an increase in workload at both the primary health care clinics as well as the referral hospitals when increasing the number of ANC contacts to eight. This increase in workload will need to be met by additional staff and resources, at a cost to already strained healthcare systems. The implications of the increased workload on the health system will also need to be carefully evaluated in the future. Although there is an increased input required, the expected outcomes may be cost saving in terms of hospital admissions, decrease in maternal deaths (particularly due to hypertension) and lives saved in terms of stillbirth.

Indicators to measure outcomes of ANC

The WHO is currently in the process of developing new and relevant indicators to assess the coverage and quality of antenatal care. This is paramount to the next stages of evaluation to assess the implementation of the new ANC model. To date there is no wide consensus on the indicators for quality of ANC. Possible indicators may include coverage of 8 ANC contacts as well as the number of contacts in each trimester. These indicators are relevant due to the recent findings around the importance of temporal considerations, the coverage of essential interventions delivered through ANC, and the gap between those attending and those receiving key interventions.
CHAPTER 9 OVERVIEW OF KEY FINDINGS, DISCUSSION AND CONCLUSIONS

9.5 New developments in classification of perinatal deaths

9.5.1 Key findings

During the period of this doctorate, the new ICD-PM classification system was published. The ICD-PM had not been systematically reviewed or applied to any existing perinatal mortality dataset. This provided the unique opportunity for the application of ICD-PM to PPIP. One of the strengths of this study was the fact it utilised a database from a LMIC where the mortality burden is high. Testing the functionality of a classification system in settings with limited resources and where the majority of perinatal deaths occur is crucial. The application of ICD-PM in HICs would not be generalisable to resource-restricted settings and thus this analysis was an essential step in evaluating the development of ICD-PM.

One of the most important findings was that the majority of perinatal deaths occur in the antepartum period, further highlighting the importance of optimising antenatal care and detecting methods for pregnancies at risk of stillbirth. Previously, stillbirths had been classified as macerated or fresh making the distinction between antepartum and intrapartum period more difficult to untangle. One major difference between the classification systems was that ICD-PM classified more deaths as having a maternal complication. This was due to intrapartum asphyxia been classified as a maternal condition.

9.5.2 Implications for policy and practice

The Chapter 8 study was used as a framework for translation of ICD-PM into other countries using PPIP or similar data collection systems. A workshop was developed based on the learnings from Chapter 8 for the 'UNICEF Workshop for Quality of Care for Newborns in Middle East and North Africa' (Beirut, Lebanon, September 2017). This was presented to clinicians (neonatologists, paediatricians, obstetricians), Department of Health representatives as well as UNICEF country officials from Syria, Iraq, Iran, Sudan, and The Gambia. The settings represented were largely from teaching hospitals with established death review meetings using ICD-10 codes.
9.5.3 Future research directions

WHO is currently reviewing the ICD-PM to further improve the coding system in consultation with a working group, consisting of experts in the field. The International Stillbirth Alliance also holds annual working group discussions around ICD-PM in data-rich settings however the focus of this work is predominantly around the experience in HICs.

One area for future discussion is the increased number of deaths classified with a maternal complication in ICD-PM. Using ICD-PM it appears more deaths have maternal complications, however, it is by classifying abnormal labour as a maternal condition. The question arises if all women with intrapartum asphyxia should by definition have had abnormal labour and hence considered ‘unhealthy’. Whether this is an accurate approach in classifying and comparing deaths between countries needs to be explored further.

9.6 Study limitations

There are several limitations to the studies in this doctorate. The first challenge was the lack of sociodemographic data which limited the ability to account for important confounders such as economic status or rural location. Although the study findings are generalisable at a population level, they may not be generalisable across difference socioeconomic or geographical strata. The inability to adjust for such confounders means the effect of these factors on outcomes is unknown.

The second challenge was that most data were aggregated at the facility level. The third challenge was the lack of consistency between definitions such as stillbirth between previous studies in HICs compared with South Africa, limiting comparability between settings.
9.7 Study strengths

All of the analyses in this thesis included a large number of women across South Africa, across all levels of care. This allowed for sufficient statistical power, improving the ability to explore a range of outcomes and increasing internal validity. In addition to this, the high rate of adverse obstetric outcomes occurring in LMICs, allowed for robust analyses with a large number of events. As events are rarer in HICs, alternative study approaches need to be employed such as pooled intercountry data or data sets collected over long periods of time (10 years plus). These methods have their own limitations, such as temporal changes in care and birth weights that need to be adjusted for.

The majority of evidence across the areas examined in this thesis has previously been produced from studies in HICs. The studies conducted in South Africa allow for a greater degree of generalisability to similar LMICs. This is particularly the case for neighbouring countries such as Zimbabwe, Botswana, and Namibia, who have similar culture and maternal/perinatal challenges, but where quality data is not readily available. In addition, quality improvement data from LMICs is often from the most highly-resourced and well-functioning health facilities, precluding the generalisability of findings at a national level. This doctorate was able to overcome this limitation by using mandatory reporting data from all facilities across South Africa.

Another advantage was the ability to conduct analyses that use real-world, whole population data. Thus offering a true reflection of what occurred and removing the challenges associated with experimental methods. Using real-world data has the advantage of including all relevant subjects, and reduces selection bias which can be present in RCTs and experimental study designs.

9.8 Summary

In summary, there are many issues contributing to the high still birth rate in South Africa, and significant challenges in detecting pregnancies at risk of stillbirth remain. The public health strategies to reduce stillbirths, including increased number of antenatal care contacts in the third trimester and
the introduction of a new classification system, appear to be promising strategies for understanding
the causes of perinatal death and reducing the rate of stillbirth. The ability of a global fetal growth
chart to increase the detection of SGA pregnancies appears less promising and more research in this
area is needed. As South Africa is one of the few LMICs with data to conduct such analyses, this thesis
has produced findings generalisable to surrounding countries which could potentially have a public
health impact in improving antenatal care and reducing the perinatal mortality burden in the region.
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REFERENCES


REFERENCES

REFERENCES

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APPENDIX A

AUTHORSHIP DECLARATION: CO-AUTHORED PUBLICATIONS

This thesis contains work that has been [published and/or accepted for publication].

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<td><strong>Lavin T, Pattinson RC, Nedkoff L, Gebhardt S, DB Preen.</strong> Stillbirth risk across pregnancy by size-for-gestational-age: application of the fetuses-at-risk approach using South African perinatal audit data. <em>Accepted with minor revisions</em></td>
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Details of the work:
Location in thesis:
Chapter 7

Student contribution to work:
85% - conceptualised study with senior author, conducted analysis, drafted and revised paper.

Co-author signatures and dates:

Details of the work:
Lavin T, Allanson E, Nedkoff I, Preen D & Pattinson RC. Applying the international classification of diseases to perinatal mortality data, South Africa. *Bulletin of the World Health Organization, in press*

Location in thesis:
Chapter 8

Student contribution to work:
85% - conceptualised study with senior author, conducted analysis, drafted and revised paper.

Co-author signatures and dates:

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Our Ref: RA/4/1/7955 20 November 2015

Professor David Preen
School of Population Health
MBDP: M431

Dear Professor Preen

HUMAN RESEARCH ETHICS OFFICE – EXEMPTION FROM ETHICS REVIEW

Increasing neonatal survival in low-resource settings: evidence from South Africa's Perinatal Problem Identification Program

Student(s):

Based on the information you have provided to the Human Ethics office in relation to the above project, the described activity has been assessed as exempt from ethics review at the University of Western Australia.

However, should there be any significant changes to the protocol, you must contact the HREO to determine whether your exempt status remains valid or whether you will be required to submit an application for ethics approval.

If you have any queries please contact the Human Ethics office at humanethics@uwa.edu.au.

Please ensure that you quote the file reference – RA/4/1/7955 – and the associated project title in all future correspondence.

Yours sincerely

Dr Caixia Li
Manager, Human Ethics
Stillbirth risk across pregnancy by size-for-gestational-age in Western Cape, South Africa: application of the fetuses-at-risk approach using perinatal audit data
South African Medical Journal

Dear Ms Lavin,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript.

For your guidance, reviewers' comments are appended below.

If you are prepared to undertake the work required, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by Dec 11, 2018. Please let us know if you require additional time.

To submit a revision, go to https://samj.editorialmanager.com/ and log in as an Author. You will see a menu item called Submission Needing Revision.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal
APPENDIX D

Date: Aug 14, 2018
To: "Tina Lavin" tina.lavin@uwa.edu.au
    "Lee Nedkoff" lee.nedkoff@uwa.edu.au, "David Preen"
cc: david.preen@uwa.edu.au, "Gerhard Theron" gbth@sun.ac.za, "Robert Pattinson" robert.pattinson@up.ac.za
From: "SAMJ" submissions@hmpg.co.za
Subject: Your Submission

Attachment(s): SAMJ 2017 page fees form -13485.pdf

Ref.: SAMJ13485
INTERGROWTH-21st vs local South African standards (Theron-Thompson) for identification of small-for-gestational-age in stillbirths: a closer look at variation across pregnancy
South African Medical Journal

Dear Ms Lavin,

We are pleased to tell you that your work has now been accepted for publication in South African Medical Journal.

Before we send to the production team however, please could you attend to the following technical issues:
1. Please provide figures in pdf
2. References should be in superscript in square brackets, and entered manually without referencing software.
3. Reference list should include year, issue, volume and page numbers, as well as DOIs where possible.

Please send your amended manuscript to claudian@hmpg.co.za

Also note that as per the author guidelines, page-fee charges have been implemented since March 2017 for all research articles. Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@hmpg.co.za

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Best wishes

Bridget Farham, PhD
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