RISKS OF ADVERSE MATERNAL AND PERINATAL OUTCOMES IN LOW AND MIDDLE-INCOME COUNTRIES (LMIC): SYSTEMATIC REVIEWS AND META-ANALYSES OF EVIDENCE

Dr. Soha Sobhy

A thesis submitted in partial fulfillment to the Barts and the London School of Medicine and Dentistry at Queen Mary University of London for the Degree of Doctor of Medicine (Research)

Women's Health research unit

Barts and the London School of Medicine and Dentistry

Queen Mary University of London

January 2017

Statement of originality

I, Soha Sobhy, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

Signature: 

Date: 27/01/1

PUBLICATIONS IN PEER REVIEWED JOURNALS FROM THE THESIS

1. Sobhy S, Zamora J, Dharmarajah K, Arroyo-Manzano, et al. Anaesthesia-related maternal mortality in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet Global Health. 2016;4(5):e320-e7.

2. Sobhy S, Babiker ZOE, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. BJOG 2016; DOI: 10.1111/1471-0528.14408.

3. Sobhy S, Rogazinska E, Khan KS, Accuracy of on-site tests to detect anaemia in antenatal care: a systematic review- submitted to IJGO

   Work included in new WHO Antenatal care Guidelines:
   WHO recommendations on antenatal care for a positive pregnancy experience, World Health Organization, Nov 2016, P. 41-42

Poster presentation and resulting peer reviewed abstract publications:

1. Sobhy S, Zamora J, Dharmarajah K, Arroyo-Manzano, et al. Anaesthesia-related maternal mortality in low- and middle-income countries (LMIC): A systematic review and meta-analysis, (2016), Global Health (EP6). BJOG: Int J Obstet Gy, 123: 121–129. doi:10.1111/1471-0528.14103

2. Sobhy S, Dharmarajah K, Zamora J et al. (2016) . Risks associated with anaesthesia in women with pre-eclampsia in low- and middle-income countries. Systematic review and mata-analysis. Poster Global Health. BJOG: An International Journal of Obstetrics & Gynaecology. 2016;123:107-16. DOI: 10.1111/1471-0528.13990

3. Sobhy S, Babiker ZOE, Zamora J, Khan KS, Kunst H Maternal and fetal outcomes of tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis, Poster Global Health. BJOG 2016;123:107-16. DOI: 10.1111/1471-0528.13990

Contributions to each paper and chapter are stated in appendix 1.

ABSTRACT

Background

Maternal death affects 303,000 women every year, with 99% of these occurring in low and middle-income countries (LMIC). Three in four direct maternal deaths are due to ,–haemorrhage, followed by hypertension in pregnancy. The major causes of indirect deaths are pre-existing tuberculosis and anaemia. My thesis is focussed on quantifying the burden of maternal death and perinatal outcomes from these conditions, identifying risk factors, and assessing role of tests to detect high-risk condition.

Methods

Systematic reviews of observational, comparative and diagnostic accuracy studies

Findings

Anaesthesia was the primary cause of death in 1.2 per 1000 undergoing surgery in pregnancy. General anaesthesia administration and non-physician anaesthetist practitioners were associated with poorer outcomes. In women with pre-eclampsia, there was a seven fold increase in maternal death in pre-eclamptic women undergoing caesarean section with general compared to regional anaesthesia. The rate of maternal mortality in women undergoing Caesarean section was 4.8 per 1000 procedures, mainly from postpartum haemorrhage. Emergency and second stage caesarean sections increased mortality and morbidity. The cadre or seniority of staff performing the caesarean section did not increase the risk of mortality.

Of the point of care tests identified to detect anaemia at a haemoglobin concentration of <110 g/l, Copper, Sahli's and HemoCue had high sensitivity and specificity. In

women with tuberculosis compared to those without, there was a significantly increased risk of poor fetal outcomes; perinatal death, preterm birth, low birth rate and birth asphyxia. Maternal outcomes were significantly worse.

Conclusion

Anaesthesia and caesarean sections contribute disproportionately to maternal deaths in LMIC. Copper, Sahli's and HemoCue were found to be accurate point of care tests for anaemia and should be more widely available to increase diagnosis. Tuberculosis leads to worse maternal and fetal outcomes.

TABLE OF CONTENTS **PAGE NUMBER**

CHAPTER 8: CONCLUSION

TABLE OF TABLES **PAGE NO.**

TABLE OF FIGURES **PAGE NO.**

DEDICATION

I dedicate this thesis to my family, for their unwavering support and especially my grandma for her constant encouragement and motivation.

I also dedicate it to all the women around the world who continue to suffer in the process of bringing new life to this world.

ACKNOWLEDGEMENTS

I am greatly indebted to my supervisors, Professor Shakila Thangaratinam and Professor Javier Zamora, who always had unlimited time, support and guidance to offer, and who gave me this opportunity and believed in me. I am also grateful to Professor Khalid Khan, for his guidance and support.

To my colleagues and fellow research students, Ewelina, Bassel and John, thank you for your friendship and your support.

I would like to thanks Mr. Ramesn Navaratnarajah who facilitated my job at royal London and the Portland, and who was always available to help if needed.

I would like to thank all co-reviewers featured in this thesis: Arri Coomarasamy, Heinke Kunst, Ramesan Navaratnarajah, David Arroyo Manzano, Nillani Murugesi, Kuhan Dharmarajah. I would like to thank the library team, for always finding my obscure international papers/ journal requests, especially Ewa.

Finally, I would like to thank all the members at Ammalife (especially Arri, Harry Gee and Maria) and Elly Appeal for their dedication to global maternal health and for providing funding to undertake this work.

List of abbreviations

BEmOC: Basic Emergency Obstetric Care Centre

CEmOC: Comprehensive Emergency Obstetric Care Services

CI: Confidence Interval

CPD: Cephalopelvic Disproportion

C/S: Caesarean Section

GA: General anaesthesia

HB: Haemoglobin

HCS: Heamoglobin colour scale

HIV: Human Immunodeficiency Virus

ITU: Intensive care unit

LMIC: Low- and middle income counties

MDG: Millennium Development Goal

MMR: Maternal Mortality Rate

NICU: Neonatal intensive care unit

OR: Odds Ratio

PET: Pre-eclampsia

PPH: Post partum Haemorrhage

RA: regional anaesthesia

SDG: Sustainable development goals

TB: Tuberculosis

UN: United Nations

WHO: World Health Organisation

Chapter 1: Introduction

1.1 Maternal mortality and morbidity in low and middle-income countries (LMIC)

Burden of maternal death:

Maternal death, defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, is a major global health issue.[1] About 99% of maternal deaths occur in low and middle-income countries (LMIC), with large disparities between, and within regions and countries. About half of these deaths occur in Sub-Saharan Africa, and a third in South Asia; these two regions together account for 85% of maternal mortality in the world (Fig1).

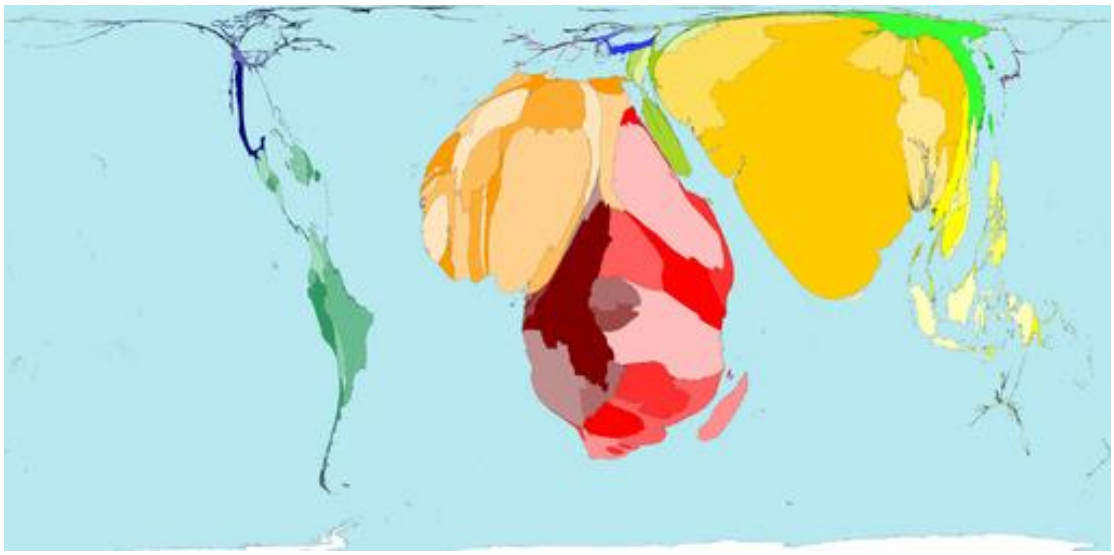


Figure1: Maternal death by burden. http:// worldmapper.org

Three in four maternal deaths are due to direct obstetric causes mainly haemorrhage, infection, pre-eclampsia, complication from delivery and unsafe abortion;[2] a quarter are from indirect causes and pre-existing medical conditions, such as human immunodeficiency virus (HIV), Malaria and tuberculosis (TB) .[2]

Global efforts to tackle maternal mortality:

Improvement of maternal health, with reduction in maternal mortality has long been a global health priority. This was emphasised in the UN Millennium Development Goals (MDG) framework, especially MDG4 the reduction by two-thirds the under-five mortality rate, and MDG5 the reduction of the maternal mortality ratio by three-quarters by 2015 (Fig 2).[3] The MDGs have now come to a close.

Fig2: Millennium Development Goals, UN 2015

Looking back, much progress has been made, but many countries did not reach this target.[4] Between 1990 and 2015, 10·7 million women worldwide died from maternal causes.[5] The global maternal mortality ratio (MMR), decreased by 43·9% (with the target being reduction by three quarters). The progress made and present levels of maternal mortality differ greatly between regions with the highest regional rate of decline for 1990–2015 occurring in eastern Asia (annual continuous rate of reduction 5·0%) and the lowest in the Caribbean (1·8%). Regional MMRs for 2015 ranged from 12 deaths per 100 000 live births for developed regions and 239 per 100 000 live births in developing countries with 546 per 100 000 for sub-Saharan Africa. [5]

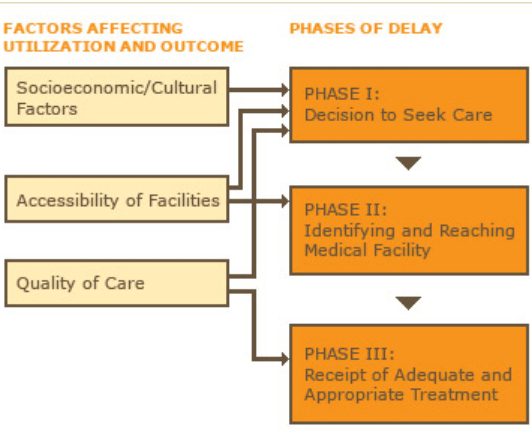
The yearly number of global maternal deaths decreased from 532,000 in 1990, to 303,000 in 2015. The largest proportion of deaths in 2015 occurred in sub-Saharan Africa (201,000 deaths) with the following countries having the top 5 highest MMR; South Sudan, Chad, Somalia, Central African Republic and Sierra Leone, mainly fragile and humanitarian settings.[5] The sustainable development agenda (SDG) has now taken over the MDGs with a target to reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030; and no country to have a maternal mortality rate of more than twice the global average.[6]

Contributors of maternal death in LMIC:

The majority of maternal deaths are preventable. To truly address this problem the underlying causes need to be understood and targeted. The three delays model is often used to explain the problem in LMIC (Fig3).[7]

Figure 3: Three delays model –Ref: UNFPA 2014

The three delays model describes the three different types of delay in care access; *Delay 1*: A delay in making the decision to seek care; this may due to a lack of awareness of the need to seek care, often due to lack of education or low social status of women. *Delay 2:* A delay in reaching appropriate care; this may be due to poverty, not being able to afford the transport required to reach the facility, poor roads and infrastructure. *Delay 3:* A delay in receiving care. These are a result of failures in the health services delivery system management.[8]



I will use an example of a woman with obstructed labour requiring a caesarean section to illustrate these delays. Delay one: a laboring woman stays at home in a village for several days, not realizing that this is abnormal or can be harmful to her and her baby, she seeks the advice of the village birth assistant and she is given herbs to increase contractions and when this doesn't work she is advised to go to the health facility. Delay Two: The nearest health facility is five hours away; she is too poor to afford transportation and walks. When she arrives at the nearest health center they diagnose obstructed labour and find that her fetus is dead, she needs a caesarean section but they do not perform this procedure. An ambulance is called and it takes another 4 hours to reach a district hospital where the procedure can be performed due to poor roads and delay in transport. Delay 3: On arrival to the district hospital it is busy; there is only one doctor and one non-physician anaesthetist and several women requiring caesarean sections, they are very understaffed and under resourced, they do not have the equipment to do blood tests. She is weak, very dehydrated and septic. When she eventually has her caesarean section, she is given a general anaesthetic, it is a difficult procedure and she suffers from severe hemorrhage from atony and trauma, she is not adequately resuscitated by the anaesthetist who lacked the training to deal with this emergency and the monitoring equipment to realise the severity of her condition. She dies on the operating table.

If there is any hope of achieving the SDG target, there needs to be a shift to a broader focus. Relying solely on maternal mortality to assess a country's status in the area of maternal health overlooks the importance of maternal morbidity, which at its most severe is a precursor to maternal mortality.[9] Maternal morbidity is defined as "any health condition attributed to and/or aggravated by pregnancy and childbirth that has a

negative impact on the woman's wellbeing." [10] Maternal death is only the tip of the iceberg, for every woman that dies there are 20-30 more that suffer an acute or chronic morbidity often leaving them with long term disability.[11] The true burden of maternal morbidity is unknown; the causes of maternal morbidity are many and complex, varying in severity and cover a broad range of conditions requiring a variety of interventions. [12]

Major causes of maternal death in LMIC addressed by the thesis:

Haemorrhage, which is related to delivery and surgical procedures such as caesarean section, is the leading cause of maternal death in LMIC. This is followed by hypertension in pregnancy, and other indirect causes of maternal deaths from pre-existing conditions such as tuberculosis, HIV and malaria.

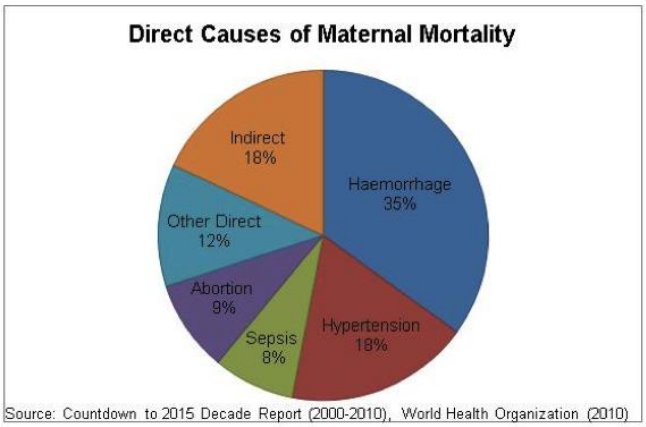


Figure 4: Causes of maternal mortality. WHO 2010 countdown to 2015.

My thesis will focus on three areas: anaesthetic and surgical related maternal mortality and morbidity, both are an essential components of comprehensive emergency obstetric care and have an impact on all other maternal deaths; indirect maternal deaths including infectious diseases in pregnancy as they are now contributing for up to a quarter of maternal deaths; and anaemia a major contributor of both direct and indirect maternal mortality and morbidity. All are directly and indirectly related to the top killers of mothers.

1.2 Obstetric anaesthesia and caesarean sections in LMIC

Anaesthesia and surgical interventions during pregnancy are an essential part of comprehensive emergency obstetric care (CEmOC). These interventions are often needed in an emergency to treat complications of pregnancy and delivery such as major hemorrhage, complications of abortion, obstruction and pre-eclampsia, without timely intervention the mother is sure to die and the newborn would suffer long term disability or death.[12] Unfortunately these procedures for safety, also contribute to the woman's death, at a disproportionate rate in LMIC.

Caesarean section is the commonest surgical procedure in Africa, with WHO recommending an optimal caesarean section rate of 10-15%.[13] Many countries in sub-Saharan Africa have an overall rate much lower than this and are below 1% for the poorest populations in 20 countries, most of them in sub- Saharan Africa.[14] About 18% of facilities did not perform the procedure due to lack of skills (53%), nonfunctioning equipment (43%), and lack of supplies/drugs (33%) including oxygen and blood.[15]

Surgery is only possible with the availability of anaesthesia; requiring skilled personnel, equipment and infrastructure. Most LMIC have a ratio of less than 1 physician or non-physician anaesthesia provider per 100,000 population.[16] Anaesthesia providers in LMICs include physicians, nurses, and technicians; the safety of non-physician anesthetics in not known. A large survey in 191 countries showed that 107 had nurse anaesthetists administering anaesthesia as part of the workforce. [17] These anaesthetic

personnel have varying degrees of education and training, and may or may not have credentials or be licensed.[18] In Uganda only 6% of centers giving an anaesthetic to pregnant women fulfilled the appropriate conditions to deliver safe anaesthesia.[19] A Lancet commission into global surgery found that if the number of physician anaesthetists was increased to 20 per 100,000, maternal mortality could be reduced by 13%.[20] The magnitude of maternal deaths and risk factors for these are not known.

1.3 Maternal complications from obstetric anaesthesia in women with pre-eclampsia

Hypertensive disorders are the second most common cause of maternal mortality, mainly from pre-eclampsia. In addition to the risks inherent to the condition, these mothers face additional risks from delivery, which is the treatment for the condition. In mothers with severe pre-eclampsia and eclampsia, and not in labour, caesarean section, necessitating anaesthesia is often the only option to minimise complications to mother and baby.

High-risk women cause a particular difficulty to healthcare workers and require extra skill and expertise when administrating an anaesthetic or carrying out surgery. Choosing the right type of anaesthesia, e.g. sedation, local, regional or general, the amount and type of drugs and fluids are crucial parts of care.[21] Skilled anaesthetists are particularly vital for these women, and can have a big impact on the clinical outcomes through resuscitative measure, understanding patient's pathophysiology and by recognising and addressing emergencies swiftly. The risk of maternal deaths from anaesthesia attributed causes, and risk factors are not known in women with pre-eclampsia undergoing a surgical procedure.

1.~~3~~4 Anaemia in pregnancy

The WHO Multicountry Survey on Maternal and Newborn Health has identified anaemia as the most common indirect cause of adverse maternal outcomes including maternal death.[22] Severe anaemia in mothers also increases the risk of perinatal mortality.[23] Anaemia has been linked to poor maternal and perinatal outcomes with a high incidence of low birth weight, small for gestational age and prematurity.[24] Pregnant women with anaemia have also been shown to have an increased risk of caesarean section,[25] anaemia also increases the morbidity associated with the procedure.[26]

The commonest cause of anaemia in pregnancy is iron deficiency and this is easily treated if identified. In LMIC most women are given prophylactic treatment for anaemia in the form of FeFol a combined ferrous sulphate and folic acid tablet. The gold standard method of diagnosis is a lab based test but this is often expensive, requires specialist skills and unavailable especially in more rural settings. Diagnosis is therefore mainly reliant on symptoms and physical signs such as pallor and bedside tests such as hemoCue and WHO colour scale, however the accuracy of these tests especially as a diagnostic tool is unknown, and without accurate early detection of disease, treatment which will improve maternal outcomes will not be initiated.

1.5 Infectious diseases in pregnancy: Tuberculosis (TB)

Indirect maternal deaths are increasing in number and now account for a quarter of maternal deaths; these include infectious diseases such as TB, HIV, and malaria, as well as pre-existing or new onset medical disorders.

According to the World Health Organization, Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. [27]

The majority of TB related deaths occur in LMIC; TB is among the top five causes of death in women of reproductive age, and is a significant contributor to maternal mortality.[28] Ending the TB epidemic by 2030 is among the health targets of the newly adopted Sustainable Development Goals.[29]

The effects of TB on pregnancy may be influenced by many factors, including the severity of the disease, timing of diagnosis, the location of disease, HIV co-infection and the treatment instituted.[30] Although there is discrepancy in the literature, obstetric complications that have been reported in these women include a higher rate of spontaneous abortion, small for date uterus, preterm labour, low birth weight and increased neonatal mortality.[31] There is also the risk of congenital tuberculosis, a rare complication of in utero tuberculosis infection, which is associated with a high neonatal mortality.[32] While other infectious diseases are either prophylactically treated in pregnancy (malaria) or routinely screened for (HIV, Syphilis) TB is not, despite it being treatable if identified.

1.6. Aims and objectives

My overall aim is to quantify the burden of maternal and perinatal mortality and morbidity in LMIC, and risk factors for complications from exposure to surgical and anaesthetic procedures, pre-existing conditions such as pre-eclampsia and tuberculosis, which are major contributors of maternal deaths. My additional aim is to assess the accuracy of simple tests to diagnose conditions such as anaemia, which could easily be treated to improve pregnancy outcomes.

Research overview

The specific research questions that I have attempted to answer in this thesis are given below, and summarised in a structured format in Table 1.1

Obstetric anaesthesia related maternal mortality and morbidity in all women

- What are the rates of anaesthesia-attributable maternal deaths as a proportion of all maternal deaths, and of all deliveries, in low and middle-income countries?
- What are the rates of anaesthesia-attributable maternal deaths in pregnant women undergoing surgical procedures in low and middle-income countries?
- What are the risk factors for anaesthesia-related maternal deaths, specifically setting, type of anaesthesia and anaesthetic practitioner?

Anaesthesia related maternal mortality and morbidity in women with pre-eclampsia

- In women with pre-eclampsia, what are risks of complications with general and regional anaesthesia?

Caesarean section related maternal mortality and morbidity in all women

- What are the rates of caesarean section related maternal death and caesarean section case fatality rates in low and middle-income countries?
- What are the main causes of caesarean section deaths?
- What are the risk factors for caesarean section -related maternal deaths in LMIC?

Anaemia:

- What methods are used to diagnose anaemia in pregnancy and which is the most accurate?

Infectious diseases: TB

- Are the risks of maternal and fetal complications increased in women with TB in pregnancy, compared to those without the disease?

Table 1. Structured questions for each chapter of this thesis

Chapter number	Population	Intervention or test	Outcome	Research design
3	Pregnant women in LMIC undergoing surgical procedure	Anaesthetic interventions	-Rate of anaesthesia attributable maternal deaths. -Rates of anaesthesia attributable deaths in women undergoing a surgical procedure.	Meta-analysis of observational studies
3	Pregnant women in LMIC undergoing anaesthesia for surgical procedure	Setting (urban/ rural) Practitioner (Physician / non physician) Type of anaesthesia (general/ regional)	Odds of Maternal death, admission to ITU and PPH. Fetal: Perinatal death, low Apgar scores.	Meta-analysis of comparative studies

4	Pregnant women with pre-eclampsia in LMIC undergoing anaesthesia for surgical procedure	Type of anaesthesia (general/ regional)	Odds of Maternal: Death, admission to ITU and PPH. Fetal: Perinatal death, low Apgar scores	Meta-analysis of comparative studies
5	Pregnant women in LMIC	Cesarean section	Rates of maternal and perinatal mortality and morbidity in women having a caesarean section	Systematic review and meta-analysis
5	Pregnant women in LMIC undergoing caesarean section	Type of caesarean section (emergency / elective & second / first stage) Type and grade of operating surgeon/ practitioner	Odds of Maternal death, admission to ITU, PPH, post partum infections, and surgical complications. Fetal: Perinatal death, low Apgar scores.	Meta-analysis of comparative studies
6	Pregnant women in LMIC with suspected anaemia	Tests used to diagnose anaemia: -WHO colour scale - HemoCue -Copper sulphate, -NBM 80, -Sahli's test -Clinical assessment	Sensitivity and specificity of tests to diagnose anaemia.	Meta-analysis of diagnostic test accuracy studies
7	Pregnant women in LMIC	Tuberculosis	Maternal death, maternal morbidity, anaemia, and caesarean delivery. Perinatal mortality, low Apgar score, low birth weight and preterm birth.	Systematic review and meta-analysis of controlled studies.

Chapter 2: Methods

What methods are needed to answer these questions?

When considering the hierarchy of evidence in medicine and public health, systematic reviews and meta-analyses are at the top of the pyramid (Fig5), for this reason, these are the main methods employed in my research.

Fig 5: hierarchy of evidence in medical research

Systematic reviews and meta-analyses

A systematic review involves five key steps in the identification, appraisal and application of the evidence, which consist of the following:

- *Step 1: Framing questions for a review*

  The problems to be addressed by the review ~~is~~ are specified in a clear, unambiguous and structured question~~s~~ at the beginning of the work. The question is formed and defined using the PICO format: population, intervention,

control/ comparison and outcome with clear inclusion and exclusion criteria for every aspect. It is also best practise to register the review at this stage.

- *Step 2: Identifying relevant work*

  An extensive search is done using multiple resources and databases (both computerized and printed) without language restrictions. Reference lists and the grey literature is searched to ensure all relevant studies are included. The study selection criteria will flow directly from the review questions and be specified *a priori*. Reasons for inclusion and exclusion are recorded. Identifying relevant studies is done by two people independently to reduce selection bias.

- *Step 3: Assessing the quality of studies*

This step appraises the aspects of the study design, conduct and analysis, and is relevant to every step of the review. The quality of a study can be defined as the degree to which it aims to minimise bias and error. There are standardised quality tools that are used depending on study design e.g. Newcastle Ottawa scale for cohort or case control studies, Cochrane for randomised controlled trials, QUADAS for studies of test accuracy. Quality assessment is carried out by two people independently to reduce bias. In this thesis the main methods used to assess quality have been a modified prevalence scale, Newcastle Ottawa scale and QUADAS, theses will be described in more detail in the relevant chapters.

- *Step 4: Summarising the evidence*

Data extraction and data analysis consists of tabulation of study characteristics, quality and effects as well as use of statistical methods for exploring differences and significance of results and combining their effects if suitable (meta-analysis). Exploration of heterogeneity should be planned as well as identifying potential sources. If an overall meta-analysis cannot be done, subgroup meta-analysis may be possible. Data extraction is again carried out by two people independently to ensure data accuracy, detailed information regarding data extraction and analysis is included in every chapter.

- *Step 5: Interpreting the findings*

Taking into account issues discussed in the previous steps such as study quality and heterogeneity as well as exploring the risk of publication bias and related biases will help to determine whether the overall summary can be trusted or not. Any recommendations should be graded by reference to the strengths and weaknesses of the evidence. [33]

By collating all the available evidence, reviews often highlight gaps in research and the paucity in quality and number of existing studies and provide justification for new well-defined studies, as well as providing recommendations for guidelines and policy. Details of such recommendations have been detailed in the upcoming chapters.

Role of the funding source

Ammalife and Elly Appeal (Bart's Charity), Charities with a focus on maternal health research in developing countries funded my work. The Charities had no influence on the development, conduct or reporting of this work.

Chapter 3: Anaesthesia-attributed maternal mortality in LMIC countries: A

systematic review

3.1 Abstract:

Background

The safety of anaesthesia administered to pregnant women in low- and middle-income countries (LMIC), where there is a paucity of physician anaesthetists and resources, needs quantification. We undertook a systematic review to estimate the rate of anaesthesia-related deaths in pregnant women having obstetric surgical procedures in LMIC, and the proportion of all maternal deaths attributed to anaesthesia.

Methods

We searched major electronic databases until 1st October 2015, without language restrictions, for studies including pregnant women in LMIC, which reported maternal deaths and complications in women exposed to anaesthesia. Two independent reviewers undertook quality assessment and data extraction. A random effects model was used to synthesise the rate data. Odds ratio was the measure of association between outcomes and anaesthesia-related risk factors.

Findings

We included 140 studies. Anaesthesia was the primary cause of death in 1.2 per 1000 (95% CI 0.8 to 1.7, I^2 =83%) pregnancies undergoing an obstetric surgical procedure (44 studies; 632,556 pregnancies). Anaesthesia accounted for 2.8% (95% CI 2.4 to 3.4, I^2=75%) of all maternal deaths (95 studies; 32,149,636 pregnancies, 36,144 maternal deaths), 3.5% (95% CI 2.9 to 4.3, I^2=79%) of direct maternal deaths, and 13.8% (95% CI 9.0 to 20.7, I^2=84%) of deaths during or after caesarean section.

Exposure to general anaesthesia increased the odds of maternal (OR 3.3, 95% CI 1.2 to 9.0, I^2=58%), and perinatal deaths (OR 2.3, 95% CI 1.2 to 4.1, I^2=73%) compared with regional anaesthesia (25 studies; 414,069 pregnancies). The rates of any maternal death were higher when anaesthesia was administered by non-physician (9.8/1000, 95% CI 5.2 to 15.7, I^2 =92%) than physician anaesthetists (5.2/1000, 95% CI 0.9 to 12.6, I^2=95%).

Conclusion:

Anaesthesia contributes to a disproportionately large number of maternal deaths in women undergoing surgery in low- and middle-income countries. The current international priority on strengthening health systems should address the factors identified in our review for improving anaesthetic care.

Key words: anaesthesia, maternal, mortality, low- and middle-income countries

Publication arising from this Chapter

Sobhy S, Zamora J, Dharmarajah K, Arroyo-Manzano D, Wilson M, Navaratnarajah R, Coomarasamy A, Khan KS, Thangaratinam S, Anaesthesia-related maternal mortality in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet Global Health. 2016; 4(5): e320-e7.

Poster presentation at Royal College Obstetrics and Gynaecology Congress 2016 and associated abstract in BJOG:

Sobhy S; Zamora J, Dharmarajah K, Thangaratinam, S Anaesthesia-related maternal mortality in low- and middle-income countries (LMIC): A systematic review and meta-analysis, BJOG 2016, Vol 123, 121–129 DOI: 10.1111/1471-0528.14103

3.2 Introduction

A quarter of million mothers die every year during or after pregnancy and childbirth, and 99% of these are from low- and middle-income countries (LMIC).[34] Anaesthetic interventions are an integral part of emergency obstetric care.[35] However, there is a paucity of physician anaesthetists in many of the poorest countries, with an estimated ratio of one physician anaesthetist per million women.[20] There is also a lack of infrastructure, drugs and equipment.

The need for safe and affordable surgery and anaesthesia in LMIC is recognised, with peri-operative death as a global safety indicator.[36] Anaesthetic complications as a cause or contributor to maternal mortality in LMIC have been neglected and there are no robust estimates of maternal deaths from obstetric anaesthesia, or of overall maternal mortality attributable to anaesthesia. Complications of anaesthesia remain one of the most clearly avoidable deaths. Factors that contribute to maternal and perinatal mortality in mothers exposed to anaesthesia in these regions also need identification.

Individual studies have provided varied and imprecise results, with up to a fifth of all direct maternal deaths attributed to anaesthesia-related procedures.[37] Systematic reviews report estimates of complications in all individuals exposed to anaesthesia, not specifically in pregnant women.[38] We undertook a systematic review to obtain precise estimates of anaesthesia-attributed deaths in pregnant women undergoing obstetric surgical procedures in LMIC, and the rates of overall anaesthesia-attributed maternal mortality. We also identified the factors linked to adverse outcomes in pregnant women exposed to anaesthesia.

3.3 Methods

We undertook the systematic review using a prospective protocol (PROSPERO No. CRD42015015805) [39] in line with current recommendations, and reported as per the PRISMA guidelines.[40]

Literature search

I searched Medline, Embase, Scopus, CINAHL, Web of Science and WHO Library and Medicus until 1st October 2015 and used MeSH headings, text words and word variants for "pregnancy" and combined them with terms for low resource countries like "low-income " or "middle-income" or "developing country". These were combined with terms related to anaesthesia and surgery such as “an(a)esthesia” or “an(a)esthetist” or “nurse an(a)esthetist” or “c(a)esarean section” (Appendix 1). There were no language restrictions. Additionally, I searched the reference lists of the included studies and relevant reviews for eligible studies.

Study selection

Studies were selected in two stages. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second, we examined the full texts of the retrieved papers. Two independent reviewers (SS, KD) selected the papers against pre-specified inclusion criteria. Discrepancies were resolved after discussion with a third reviewer (ST). Studies were included if they assessed maternal and perinatal outcomes in pregnant women exposed to anaesthesia in countries categorised as LMIC by the World Bank.[41] Exclusions included studies in high-income countries, those involving non-pregnant women, case reports, and studies published before 1990 to ensure that the estimates reflect the current burden of the condition. Anaesthesia-attributed complications were defined as those that occurred directly as a result of anaesthesia (as determined by the primary study authors), e.g. failed

intubations or a high spinal; anaesthesia-related outcomes as those that were directly or indirectly associated with anaesthesia. Maternal mortality included death of a mother during pregnancy, and at any time until 42 days after delivery, irrespective of the duration and site of the pregnancy as defined by the WHO. This included deaths from any cause related to or aggravated by pregnancy and its management, but not from accidental or incidental causes.[1] Direct maternal deaths were those that resulted from obstetric complications; indirect maternal deaths from conditions aggravated by physiological effects of pregnancy, by pre-existing disease, or by diseases that developed during pregnancy.[1] We grouped direct and indirect maternal deaths together as overall maternal death.

Perinatal death included any fetal death that occurred after 28 completed weeks of gestation, stillbirth and early neonatal death until one week after birth.[42] Apgar score is a measure of physical condition of a newborn, taking into account and assigning points (0,1or 2 for each domain for a total of 10) for heart rate, respiratory effort, reflexes, muscle tone and skin coloration, and is assessed at 1, 5 and 10 minutes.[43] Apgar scores were classed as low if they were less than or equal to 7 at one and five minutes. We accepted the primary study authors' definitions for maternal and fetal complications such as postpartum hemorrhage, cardiac arrest and admission to the intensive care unit.

Study quality assessment and data extraction

Two independent reviewers (SS and KD) undertook study quality assessment and data extraction, and discrepancies were resolved with input from the third reviewer (ST). For studies on rates of anaesthesia-attributed maternal death, we assessed the following criteria: representativeness of the population, sample selection, outcome assessment,

adequacy of sample size and ascertainment of the cause of maternal death to anaesthesia.[44, 45] A study was considered to be adequate for representativeness if it included institutions from multiple settings such as rural and urban hospitals in a region or country, and to be inadequate if it included only a single hospital or unit. Sample selection was classed as adequate if all deliveries or maternal deaths were included, and as inadequate if a particular group of women were excluded. We considered outcome assessment to be adequate when a confidential enquiry, verbal autopsy or professional panel determined the cause of death; a lack of special effort or use of registry data from only one source was considered to be inadequate. An adequate sample size included data on at least 10,000 births. Studies that accounted for the cause of death in at least 95% of maternal deaths were deemed to be adequate for ascertainment of cause of death. A study was classed as high quality if three of the above five criteria were met.[44]

For comparative studies, we used the Newcastle-Ottawa scale to evaluate the risk of bias in selection, comparability of cohorts and outcome assessment.[46] Studies that scored four stars for selection, two stars for comparability and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains was deemed to have a high risk of bias.[46]

Data were extracted on the number of events (anaesthesia-attributed maternal deaths), number of women exposed to anaesthesia, total and direct maternal deaths, and deaths during or after caesarean section, to compute corresponding proportions for individual studies. We extracted data on the number of events (anaesthesia-related maternal death

and pregnancy complications) in women exposed and un-exposed to risk factors such as type of anaesthesia (regional, general), setting (urban, rural) and practitioner (physician, non-physician).

Data analysis

Summary rates of deaths from anaesthesia were estimated in all pregnant women undergoing surgical procedures, and the proportion of all maternal deaths (direct and indirect) attributed to anaesthesia. Sub-group analysis and meta-regression were performed for the following factors that were specified *a priori*: geographical location (World Bank classification), country income (low-, low-middle, upper-middle) and year of publication (before and after 2000). We assessed the effects of study quality (low, high) and design (prospective, retrospective) on the maternal mortality rates. We used multilevel random effects logistic models, and included the above factors. The meta-regressions were run as separate univariate analyses. Sensitivity analysis was performed by limiting our findings to only direct maternal deaths. We also assessed the proportion of all maternal deaths during or after caesarean section attributed to anaesthesia.

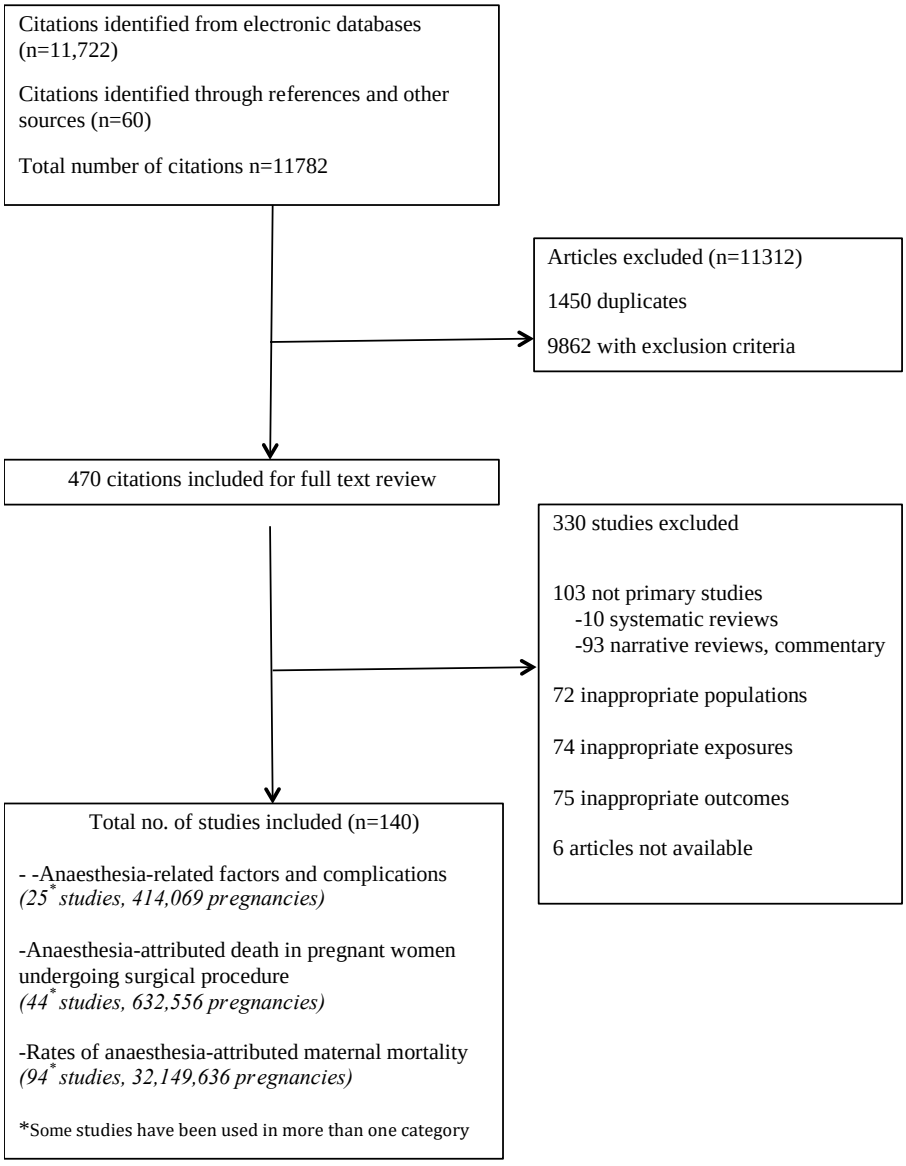
We computed odds ratios for various risk factors and anaesthesia-related complications in individual studies, and pooled them using a random effects model. Peto Odds Ratio was used when the numbers of events were too scarce.[47] Heterogeneity was evaluated using I^2 statistic. When comparative data were not available, we reported the proportion of complications for each risk factor separately, and provided summary estimates.

~~We assessed publication bias and small study effect using funnel plots and begg's and egger's tests.~~ All analyses were performed using Stata 13.[48]

3.4 Results

From 11,782 citations, we included 140 studies. 44 studies (632,556 pregnancies) reported deaths from anaesthesia in women exposed to surgical procedures; 95 studies (32,149,636 pregnancies, 36,144 deaths) computed anaesthesia-attributed maternal mortality; and 25 studies (414,069 pregnancies) assessed the association of various risk factors and complications in pregnant women undergoing anaesthesia (Fig 6).

Figure 6. Study selection process in the systematic review of anaesthesia-related maternal mortality in low- and middle-income countries (LMIC)



Characteristics of the included studies

44 studies (632,556 pregnancies) reported deaths from anaesthesia in women exposed to surgical procedures. These studies were from 15 countries, which were grouped into the following World Bank regions: Sub-Saharan Africa (n=38 studies), South Asia (n=4), East Asia and the Pacific (n=2). The majority of studies were facility based (42/44, 95%) and in nearly three-quarter (31/44, 71%) of studies, the women were managed in an urban setting. Both high and low risk women were evaluated, and caesarean section was the most commonly performed surgical procedure. Studies ascertained the cause of maternal deaths and exposure to anaesthesia from theatre records, patient notes, facility and countrywide maternal death reviews, and verbal autopsies.

Of the 95 studies (31 countries) that reported on anaesthesia-attributed maternal deaths as a proportion of all maternal deaths, 55% (52/95) provided facility-based data, and 30% (29/95) provided countrywide data. In half (45/95, 47%) of the studies, women were managed in an urban setting.

Studies compared the odds of adverse maternal and fetal outcomes for risk factors such as the type of anaesthesia (25 studies, 414,069 pregnancies), setting (1 study, 8070 pregnancies) and anaesthesia provider (1 study, 8070 pregnancies). Rates of any maternal death in anaesthesia administered by a non-physician were assessed in 8 studies (27,714 pregnancies), and by a physician anaesthetist in 6 studies (20,313 pregnancies).

The characteristics of the individual studies included in the systematic review are provided in Appendix 3.

Quality of the studies

Around two-thirds (65/95, 68%) of the included studies on anaesthesia-attributed maternal mortality had low risk of bias. About half had high risk of bias (46/95, 48%) for representativeness of the population and setting, 90% had adequate sample selection (85/95), a quarter had high risk of bias for outcomes reporting (23/95, 24%). Three quarters of all studies had adequate sample size (74/95, 77%) and about two-thirds adequately accounted for maternal deaths (59/95, 62%) (Appendix 4a). Four fifth (21/25, 84%) of studies on risk factors for complications in women exposed to obstetric anaesthesia had high risk of bias (Appendix 4b).

3.41: Mortality rates from anaesthesia in women undergoing obstetric surgical procedures

The risk of deaths from anaesthesia in women undergoing surgical procedures in pregnancy was 1.2 per 1000 women (95% CI 0.82 to1.7, I^2 = 83%), with the highest rates in sub-Saharan Africa (1.5 per 1000 women, 95% CI 1.1 to 2.2, I^2=85%) (Table 2). Appendix 5a provides estimates for individual countries.

Subgroup analysis and meta-regression showed a statistically significant difference between regions (p=0.004). The risks of death from anaesthesia were higher in rural than urban setting (p=0.02), and in low- and low-middle income than upper middle-income countries (p=0.003). There were no differences for year of publication (p=0.74) (Table 2).

Table 2: Mortality rates from anaesthesia in women undergoing obstetric surgical procedures in low- and middle-income countries

Factors	No. of studies	No. of deaths n	No. of women undergoing surgical procedures N	Maternal deaths / 1000 women undergoing surgery n/N	95% CI	I^2	Meta-regression p-value
World Bank Regions							
South Asia	4	16	37,132	0.34	(0.13-0.90)	71%	**0.004**
Sub-Saharan Africa	38	237	567,431	1.5	(1.1-2.2)	85%	
East Asia and Pacific	2	11	27,993	0.40	(0.22-0.71)	-	
Year							
<2000	17	55	49,232	1.2	(0.76-1.7)	50%	0.74
≥2000	27	209	583,324	1.2	(0.74-2.1)	86%	
Setting							
Urban	31	85	72,203	1.5	(1.0-2.3)	67%	**0.02**
Rural	1	1	69	14.5	(0.00-42.7)	-	
Both	12	178	560,284	0.67	(0.37-1.2)	89%	
Country income							
Low	13	53	33,431	1.5	(0.84-2.8)	63%	
Lower Middle	27	90	80,295	1.4	(0.92-2.2)	72%	**0.003**
Upper Middle	4	121	518,830	0.23	(0.20-0.28)	24%	
OVERALL	**44**	**264**	**632,556**	**1.2**	**(0.82-1.7)**	**83%**	

3.42 Anaesthesia-attributed maternal mortality rates

Anaesthesia was the cause of 2.8% (95% CI 2.4 to 3.4, I^2=75%) of all maternal deaths (direct and indirect), with the highest rates in Middle East and North Africa (6.2%, 95% CI 3.9 to 9.7, I^2 =86%), and the lowest in East Asia and Pacific (1.5%, 95% CI 0.9 to 2.3, I^2=63%).

Meta regression demonstrated a significant difference in the overall anaesthesia-attributed mortality rates by geographical region (p = 0.004) and year of publication (p=0.002). There were no significant differences by setting (p=0.29), study design (p=0.68), income level (p=0.57) or study quality (p=0.12). (Table 3)

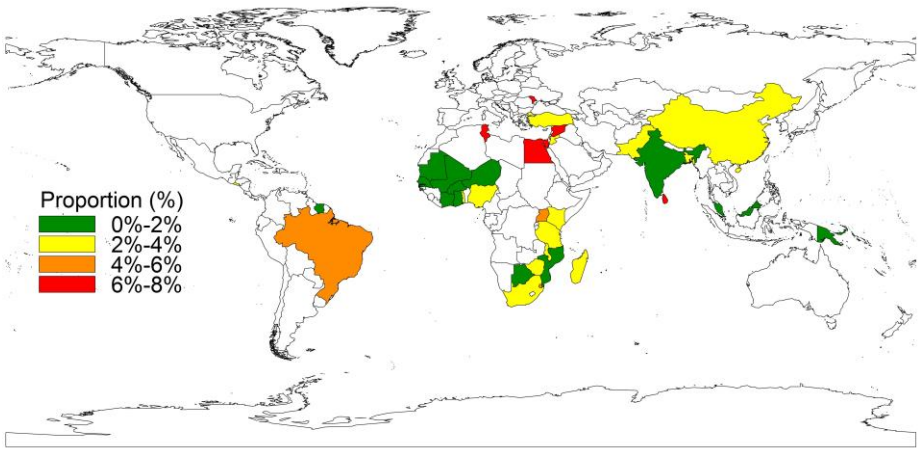
The global burden of anaesthesia-attributed overall maternal mortality is depicted in Table 3, and estimates from individual countries are provided in Appendix 5b and shown as a world map in figure 7.

Table 3. Anaesthesia-attributed maternal mortality in low- and middle-income countries

Factors	No. of studies	No. of deaths from anaesthesia (n)	Total no. of maternal deaths (N)	Anaesthesia attributed mortality (%)	95% CI	I^2	Meta-regression p-Value

World Bank Regions*							
Sub-Saharan Africa	50	675	24,873	2.9	(2.3-3.6)	61%	**0.004**
South Asia	18	89	4,317	2.4	(1.5-3.8)	79%	
Middle East and North Africa	10	136	2,555	6.2	(3.9-9.7)	86%	
East Asia and Pacific	9	49	3,276	1.5	(0.9-2.3)	63%	
Europe and Central Asia	4	14	455	3.0	(1.3-6.7)	64%	
Latin America and The Caribbean	4	24	668	3.6	(2.4-5.3)	0%	
Year							
<2000	28	250	6,589	4.1	(3.0-5.5)	77%	
>2000	67	737	29,555	2.4	(1.9-2.9)	72%	
Setting							**0.002**
Rural	8	14	894	1.9	(0.9-3.8)	38%	
Urban	45	245	7,987	3.3	(2.5-4.2)	72%	
Both	42	728	27,263	2.5	(1.9-3.4)	80%	0.29
Study design							
Prospective	9	35	1,819	2.5	(1.1-5.6)	77%	
Retrospective	86	952	34,325	2.9	(2.4-3.4)	75%	
Country income							0.68
Low	17	89	3,171	2.6	(1.9-3.6)	35%	
Lower Middle	38	199	8,130	2.6	(1.9-3.6)	78%	
Upper Middle	40	699	24,843	3.1	(2.4-4.1)	78%	0.57
Study quality							
High	65	859	32,099	2.6	(2.1-3.2)	79%	
Low	30	128	4,045	3.6	(2.6-4.8)	59%	
							0.12
OVERALL	**95**	**987**	**36,144**	**2.8**	**(2.4-3.4)**	**75%**	

Figure 7: World map depicting the burden of anaesthesia-attributed maternal mortality in low- and middle-income countries



Anaesthesia was responsible for 3.5 % (95% CI 2.9 to 4.3, I^2=79%) of the 20,780 direct maternal deaths (76 studies, 26,750,727 pregnancies) (Table 4), and for 13.8% (95% CI 9.0 to 20.7, I^2 =84%) of all maternal deaths that occurred during or after caesarean section (31 studies, 1028 deaths) (Table 5).

Table 4: Anaesthesia-attributed deaths as a proportion of all direct maternal deaths in low- and middle-income countries

Factors	No. of Studies	No. of anaesthesia attributed deaths (n)	No. of direct maternal deaths (N)	Rate(%)	95% CI	I^2
World Bank Regions						
Latin America and The Caribbean	4	24	487	4.9	(3.3-7.3)	0%
East Asia and Pacific	8	47	2,756	1.7	(1.0-2.8)	72%
Europe and Central Asia	4	14	356	3.8	(1.6-8.6)	66%
Middle East and North Africa	6	84	1,431	6.0	(4.5-7.9)	45%
South Asia	12	56	2,066	3.3	(1.7-6.1)	85%
Sub-Saharan Africa	42	641	13,684	3.9	(3.1-4.9)	72%
Year						
<2000	23	194	5,473	3.7	(2.6-5.1)	81%
>2000	53	672	15,307	3.5	(2.8-4.4)	79%
Setting						
Rural	6	9	353	3.1	(1.3-7.3)	58%
Urban	35	218	5,567	3.9	(2.9-5.2)	75%
Both	35	639	14,860	3.3	(2.5-4.3)	85%
Design						
Prospective	9	17	1,134	1.9	(0.9-3.9)	44%
Retrospective	67	849	19,646	3.7	(3.1-4.6)	80%
Income						
Low-Income	15	94	2,351	3.6	(2.3-5.6)	73%
Lower-Middle Income	27	105	4,167	3.1	(2.1-4.5)	75%
Upper-Middle Income	34	667	14,262	3.9	(3.0-5.0)	79%
Quality						
High	56	768	18,340	3.3	(2.6-4.2)	83%
Low	20	98	2,440	4.5	(3.2-6.3)	61.%
OVERALL	**76**	**866**	**20,780**	**3.5**	**(2.9-4.3)**	**79%**

Table 5: Anaesthesia-attributed maternal deaths as a proportion of caesarean section deaths in low- and middle-income countries

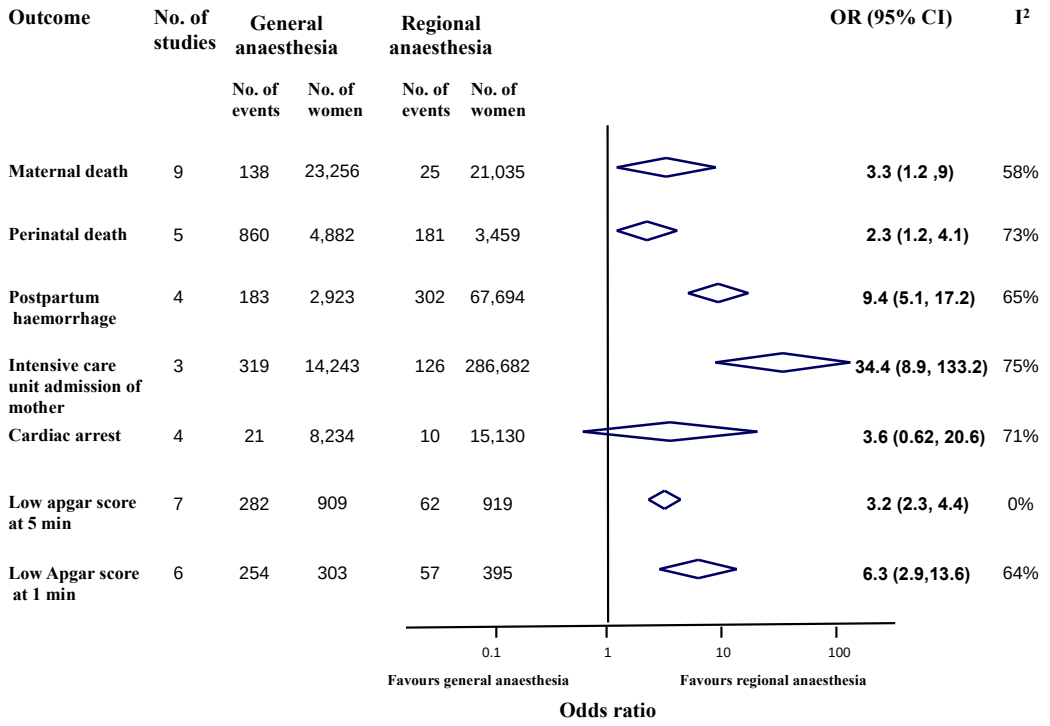
Factor	No. of Studies	No. of anaesthesia attributed deaths (n)	No. of caesarean section deaths (N)	Rate (%)	95% CI	I^2	Meta-regression P-Value
World Bank Regions							
South Asia	3	13	122	8.5	(3.0-22.0)	70%	
Sub-Saharan Africa	25	110	606	16.1	(9.8-25.4)	84%	0.34
East Asia and Pacific	3	22	300	8.0	(4.2-14.7)	66%	
Year							
<2000	14	83	601	14.5	(6.9-28.0)	91%	0.80
>2000	17	62	427	13.5	(8.3-21.3)	64%	
Setting							
Rural	1	1	5	20.0	(0.00-55.1)	-	
Urban	18	63	396	14.5	(6.7-28.0)	88%	0.90
Both	12	81	627	13.1	(8.9-18.8)	70%	
Income							
Low Income	8	44	192	21.3	(14.0-31.0)	33%	
Lower Middle Income	19	76	509	13.5	(6.8-24.9)	87%	0.51
Upper Middle	4	25	327	7.3	(3.5-11.2)	55%	
OVERALL	**31**	**145**	**1028**	**13.8**	**(9.0-20.7)**	**84%**	

3.43: Factors linked to adverse outcomes in pregnant women exposed to anaesthesia

Administration of general anaesthesia tripled the odds of maternal (OR 3.3, 95% CI 1.2 to 9.0, I^2=58%), and doubled the perinatal death odds (OR 2.3, 95% CI 1.2 to 4.1, I^2=73%) when compared to regional anaesthesia. There was an increase in other

complications such as postpartum haemorrhage (OR 9.4, 95% CI 5.1 to 17.2, I^2=65%), low Apgar score at 1 minute (OR 6.3, 95% CI 2.9 to 13.6, I^2=64%) and at 5 minutes (OR 3.2, 95% CI 2.3 to 4.4, I^2=0%) with general compared to regional anaesthesia (Fig 8). There were no differences in cardiac arrest (OR 3.6, 95% CI 0.6 to 20.6, I^2=71%) between the two groups.

Figure 8. Maternal and fetal complications in women exposed to general vs. regional anaesthesia in low- and middle-income countries (LMIC)



Management in a rural setting was associated with an increase in the odds of maternal death (OR 2.1, 95% CI 1.2 to 3.7) compared with an urban setting.[49]

No comparative data were available for physician versus non-physician providers. One study reported an increase in the odds of maternal deaths (OR 2.7, 95% CI 1.6 to 4.6) when managed by non-physician anaesthetists without formal structured training

compared to those with training.[49] The overall risk of any maternal death (6 studies, 27,515 women) when care was provided by non-physicians was 9.8/1000 (95% CI 5.2 to 15.7, I^2 =92%); rate of anaesthesia-attributed maternal deaths (5 studies, 24,613 women) was 1.8/1000 (95% CI 0.25 to 4.3, I^2 =85%). The corresponding estimates for physician anesthetists were 5.2/1000 (95% CI 0.9 to12.6, I^2= 95%) for any maternal death (8 studies, 20,253 women), and 1.3/1000 (95% CI 0.16 to 3.1, I^2 =79%) for anaesthesia-attributed maternal deaths (7 studies, 20,464 women) respectively (Table 6)

Table 6: Type of anaesthetic provider and rates of maternal deaths in low- and middle-income countries.

Outcome	Anaesthesia provider	No. of studies	No. of events	No. of women	Rate / 1000 women	95% CI	I^2
Any maternal death	Non-physician	6	199	27,515	9.8	5.2-15.7	92%
	Physician	8	60	20,253	5.2	0.9-12.6	95%
Anaesthesia attributed maternal death	Non-physician	5	42	24,613	1.8	0.3-4.3	85%
	Physician	7	21	20,464	1.3	0.2-3.1	79%

3.44: Causes of anaesthesia attributed maternal mortality

The underlying causes were reported for 124 maternal deaths (24 studies). Half (56/124, 45%) of all deaths resulted from airway complications such as difficult or failed intubation, esophageal intubation, bronchospasm, ventilation difficulties and hypoxia; a third (38/124, 31%) from pulmonary aspiration; a quarter (34/124, 27%) from issues related to staff competency, poor pre-assessment, intraoperative monitoring and

equipment failure. Other causes included cardiac arrest at induction or during the procedure (7/124, 6%), 'high' spinal anaesthesia (8/124, 6%), and drug overdose or adverse reactions (7/124, 6%).

3.5: Discussion

Anaesthesia contributes disproportionately to maternal mortality in LMIC. Exposure to general anaesthesia, and administration of anaesthesia by non-physicians, particularly those with no formal training, were major risk factors for maternal deaths from anaesthesia. We have mapped the safety of obstetric anaesthesia across various economic regions and individual countries. Most studies were from Sub-Saharan African region, which also had the highest risk of deaths from anaesthesia in women undergoing surgery. One in seven deaths during or after caesarean section was due to anaesthesia, an exceedingly high mortality rate compared to developed countries.[50]

Ours is the first review, to our knowledge, to comprehensively evaluate the risk of maternal deaths from anaesthesia in LMIC. We assessed the extent of the problem in detail by assessing rates of death in women exposed to surgery, and as a proportion of any, direct, and caesarean section related maternal deaths. The effects of study quality on mortality estimates were reported. We looked for variations in anaesthesia-attributed maternal mortality rates according to economic regions, individual countries, setting, year and anaesthesia provider, and identified the anaesthesia related risk factors for various maternal and fetal complications in women undergoing surgery.

Our findings were limited by the differences in quality and reporting of outcomes in the studies. Fewer studies were published in low-income countries that were outside

Sub Saharan Africa. It is likely that the actual rates of anaesthesia-attributed deaths are higher than current estimates due to paucity of data from the lowest income countries with high rates of maternal mortality and poor healthcare resources. We found significant heterogeneity in our findings despite adjusting for various factors. The antenatal risk status of the mother was not known. Few studies provided detailed reports on the underlying cause of death from anaesthesia. Studies mainly focused on evaluating the risks associated with type of anaesthesia, and less on other factors. This limited our synthesis, and we could only provide rates for these risk factors separately.

Administration of anaesthesia in pregnancy requires specific training, which takes into account maternal physiological changes, particularly in the third trimester. The rates of complications such as failed intubation are ten-fold higher in pregnant women than in general population.[51] In Cochrane review including high- and high-middle income countries, general anaesthesia in pregnant women was also associated with increased blood loss compared with regional anaesthesia, but studies do not have sufficient sample size to assess maternal deaths.[52] The increased mortality and morbidity that we identified in our review with general anaesthesia could be due to the following reasons: inadequate training and resources, poor general condition of the mother at baseline necessitating general anaesthesia, or concomitant complications such as postpartum haemorrhage worsening the outcome. The low Apgar scores at one and five minutes associated with general anaesthesia exposure are also indicators of absence of good maternal and neonatal care, and the lack of newer volatile agents which limit the risk if fetal respiratory depression.

In high-income countries such as the US, there are no differences in anaesthetic complications between physician and non-physician anaesthetists. [53-55] Although

comparative rates were not available for LMIC setting, the reported estimates of maternal mortality were higher for anaesthesia administered by non-physician anaesthetists than their physician counterparts; the risks were also high for non-physicians without adequate training.[49] However, compared to the rigorous additional training provided to non-physician anaesthetists in the US, their counterparts in LMIC have very little training, and the training received is very variable amongst countries. Many of the reported causes of anaesthesia-attributed deaths such as airway complications and pulmonary aspiration with general anaesthesia, and hypotension and high spinal with regional anaesthesia are preventable with appropriate training and resources.[56]

The global definition and classification of anaesthesia-attributed deaths require standardisation to identify the real burden of exposure to anaesthesia. Anaesthetists should be part of the panel analysing the causes of maternal deaths, and the level of contribution of anaesthesia to the death should be reported clearly.[57]

Strategies to reduce maternal mortality should include increasing the number of anaesthetists, resources, and the level of training in LMIC. Implementation of simple measures, such as the WHO 'Safer Surgery' checklist before and during surgery would minimise the adverse outcomes.[58] The adoption of these measures among anaesthesia providers in the developed world has reduced maternal death from anaesthetic complications to very low levels. Governmental and non-governmental organisations should prioritise investment in obstetric anaesthesia, to implement the World Health Assembly's resolution to include emergency and essential surgical care and anaesthesia as a component of universal health coverage.[59]

3.6: Conclusion

Anaesthesia is a major contributor to maternal deaths in pregnant women undergoing surgery in low- and middle-income countries. Targeted efforts are needed to provide safe obstetric anaesthesia by improving training, infrastructure and resources.

Chapter 4. Association of type of obstetric anaesthesia and maternal mortality and morbidity in women with pre-eclampsia in LMIC: a systematic review

4.1 Abstract:

Background:

Pre-eclampsia contributes significantly to the global burden of maternal and fetal mortality and morbidity, and delivery is often expedited with caesarean section to prevent or treat complications. The safety of various types of anaesthesia administered to mothers with pre-eclampsia has been long debated.

Methods:

We searched major electronic databases until June 2016, without language restrictions, and included studies comparing general with regional anaesthesia in women with pre-eclampsia. Two independent reviewers undertook quality assessment and data extraction. We reported the measure of association between outcomes and type of anaesthesia as odds ratio (OR) ~~and~~ with 95% confidence intervals (CI), using a random effects model. We assessed risk of bias of included studies using the Newcastle Ottawa scale.

Findings:

From 11,782 citations, 14 studies (10,411) were included; 37% (3899/10,411) had mild pre-eclampsia, 61% (6304/10,411) had severe pre-eclampsia and 2% (208/10,411) had eclampsia; 16% (1701/10,411) of caesarean sections were performed under general anaesthesia and 84% (8710/10,411) under regional anaesthesia. There was a seven-fold increase (OR 7.70, 95% CI 1.9 to 31.0 I^2=58%) in maternal death in pre-eclamptic women undergoing caesarean section with general anaesthesia compared to regional

anaesthesia, and an increase in pulmonary oedema (OR 5.16, 95% CI 2.5 to 10.4, I^2=0%) and maternal intensive care unit admissions (OR 16.25, 95% CI 9.0 to29.5, I^2=65%). Exposure to general anaesthesia increased the odds of perinatal death (OR 3.01, 95% CI 1.4 to 6.5, I^2=56%), low Apgar score at 1 minute (OR 2.5, 95% CI 1.3-4.6, I^2=49.9%) and at 5 minutes (OR4.73, 95% CI 2.4-9.5, I^2=40%), when compared to regional anaesthesia.

Conclusion:

Regional anaesthesia is safer in women with pre-eclampsia, and should be considered where there are no contraindications.

Key words: pre-eclampsia, anaesthesia, maternal mortality

Publications arising from this chapter:

Poster presentation at British Maternal and fetal medicine society conference 2016 and associated publication in BJOG

Sobhy S, Dharmarajah K, Zamora J, Thangaratinam S, (2016), Risks associated with anaesthesia in women with pre-eclampsia in low- and middle-income countries. Systematic review and meta-analysis. *BJOG-an international journal of obstetrics and gynaecology* vol. 123, 112-113.

4.2: Introduction:

Pre-eclampsia is defined as de-novo hypertension present after 20 weeks of gestation combined with proteinuria (>300 mg/day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction. [60, 61] Pre-eclampsia contributes significantly to the global burden of maternal mortality and maternal morbidity; with it being one of the biggest causes of intensive care unit admissions, as well as leading to poor perinatal outcomes. [34, 62, 63]

There is a higher risk of needing an operative delivery in women with pre-eclampsia,[64] and anaesthetic management of these patients remains a challenge. There has been long standing concern regarding the safest type of anaesthesia for use in patients with pre-eclampsia, especially in those with severe disease or eclampsia.[65] It is now generally accepted that regional anaesthesia is considered safer where no contraindications exist in pregnant women.[66] However healthcare professionals in many LMIC vary in their preference for the type of anaesthesia, some favouring general anaesthesia over regional anaesthesia. Studies in LMIC on type of obstetric anaesthesia provide imprecise and varied estimates of risks.

I undertook a systematic review of studies that compared the rates of adverse maternal and perinatal complication in pregnant women who were administered general vs. regional anaesthesia in LMIC.

4.3: Methods

The systematic review was done using a prospective protocol in line with current recommendations, and reported as per the PRISMA guidelines.[40]

Literature search

We searched Medline, Embase, Scopus, CINAHL, Web of Science and WHO Library and Index Medicus from inception until April 2016. We used MeSH headings, text words and word variants for "pregnancy" and combined them with terms for low resource countries like "low- income " or "middle income" or " developing country". These were then combined with an(a)esthesia and surgery related terms such as " an(a)esthesia" or " an(a)esthetist" or " nurse an(a)esthetist" or 'c(a)esarean section" (Appendix 2). There were no language restrictions. Additionally, we searched the reference lists of the included studies, and relevant reviews and articles for eligible papers. A subset of the all studies that included women with pre-eclampsia were included in this review,

Study selection

Studies were selected in a two-stage process. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second stage, we did a detailed examination of the full texts of the retrieved papers. Two independent reviewers (SS, KD) selected the papers against pre-specified inclusion criteria. Any discrepancies were resolved after discussion with a third reviewer (ST). Studies were included if they were comparative cohort studies, and assessed maternal and perinatal outcomes in pre-eclamptic women exposed to general or regional anaesthesia in LMIC as defined by the World Bank.[41] We excluded studies in high-income countries, those involving women without pre-eclampsia and studies published before 1990.

Maternal death was defined as the death of a woman while pregnant or within 42 days (or 1 year for late maternal deaths) of birth or termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.[1]

Perinatal death included any fetal death that occurred after 28 completed weeks of gestation, stillbirth and early neonatal death until one week after birth.[42] Apgar scores were classed as low if they were less than or equal to 7 at one and five minutes. We accepted the authors' definitions for other maternal and fetal complications such as postpartum hemorrhage, cardiac arrest and admission to the intensive care unit.

The definitions for mild, moderate, severe pre-eclampsia and eclampsia were taken as defined by the study authors and included in Appendix 6.

Quality assessment of the included studies

We used the Newcastle-Ottawa scale to evaluate the risk of bias in the selection, and comparability of subjects and cohorts and of the outcome.[46] Studies that scored four stars for selection; two stars for comparability and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains was deemed to have a high risk of bias.[46]

Data extraction and analysis

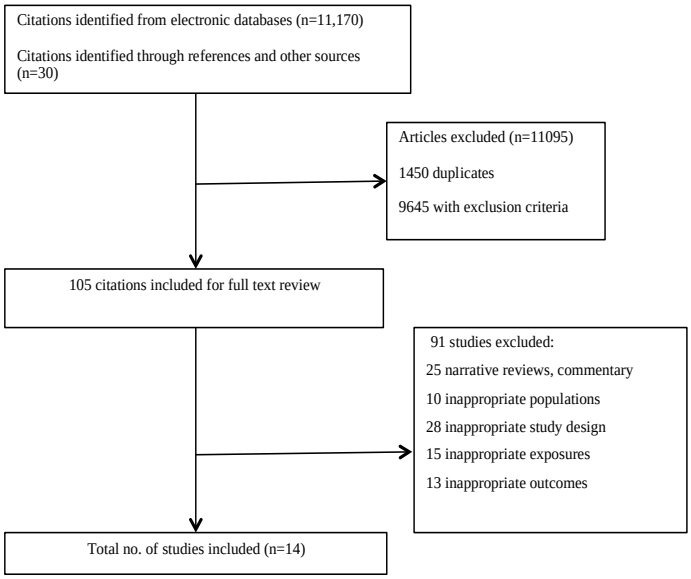
Data were extracted by two independent reviewers (SS and KD). We obtained

information on study design, setting, population characteristics, type of anaesthesia, year of publication and maternal and fetal outcomes. We extracted data on the number of events observed amongst women exposed to the different types of anaesthesia, mainly general and regional anaesthesia. We computed individual study odds ratios and pooled them using a random effects model. Heterogeneity was evaluated using I^2 statistic. All analyses were performed using Stata 12.[48]

4.4: Results

From 11,200 citations, we included 14 studies that evaluated the association between type of anaesthesia and pregnancy complications in women diagnosed with pre-eclampsia. (Figure 9)

Figure 9: Study selection process in the systematic review of maternal and fetal outcomes related to type of anaesthesia in women with pre-eclampsia in low- and middle-income countries



Characteristics of the included studies

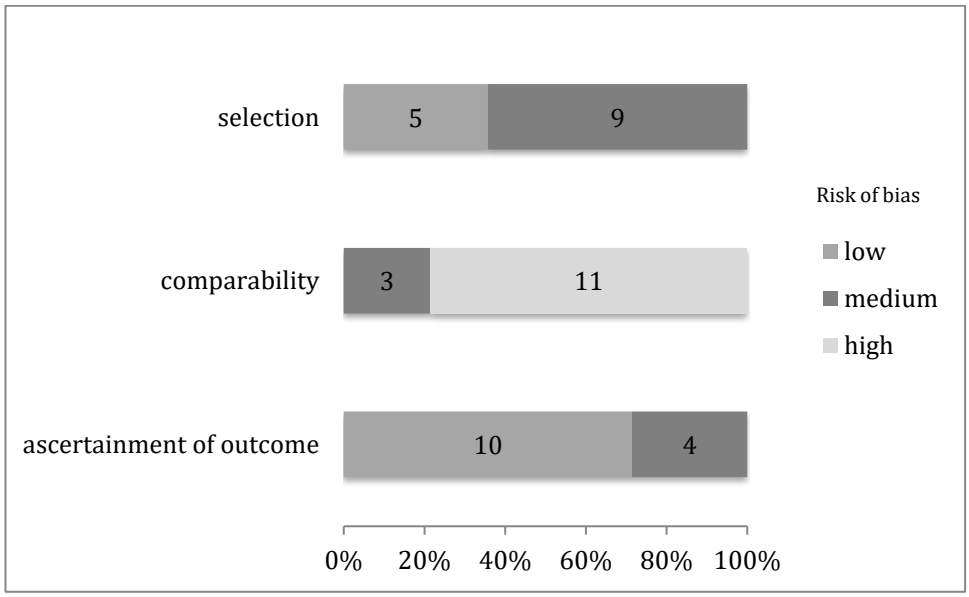
Fourteen studies included 10,411 pregnant women undergoing caesarean section with varying severity of pre-eclampsia. Of these, 37% (3899/10,411) had mild pre-eclampsia, 61% (6304/10,411) had severe pre-eclampsia and 2% (208/10,411) had eclampsia; 16% (1701/10,411) of caesarean sections were performed under general anaesthesia and 84% (8710/10,411) under regional anaesthesia. The studies included women from Nigeria (n=5), South Africa (n=3), India (n=2) and 1 study from each of the following countries: Iran, Pakistan, Thailand and Taiwan. All women were delivered in tertiary centers. Ten were retrospective observational studies, one was a prospective study and three were randomised studies.

The studies reported the following outcomes: maternal death (n=8), perinatal death (n=7), low Apgar score at 1 minute (n=6), low Apgar score at 5 minutes (n=5), postpartum hemorrhage (n=3), intensive care unit admission (n=6), seizures (n=6), pulmonary oedema (n=4), postpartum haemorrhage (n=4), and one reported on the following outcomes, admission to neonatal intensive care unit (NICU), post operative ventilation, blood transfusion and cerebral vascular accidents (CVA). Appendix 6 shows characteristics of included studies.

Quality of the studies

Quality assessment by the Newcastle Ottawa Scale for comparative studies on type of anaesthesia in women with pre-eclampsia showed that a fifth (3/14, 21%) had high risk of overall bias. None of the studies had a high risk of bias for selection or outcome assessment domains, and three quarters (11/14) had high risk of bias for comparability. The risks of bias for individual domains are provided in Fig 10.

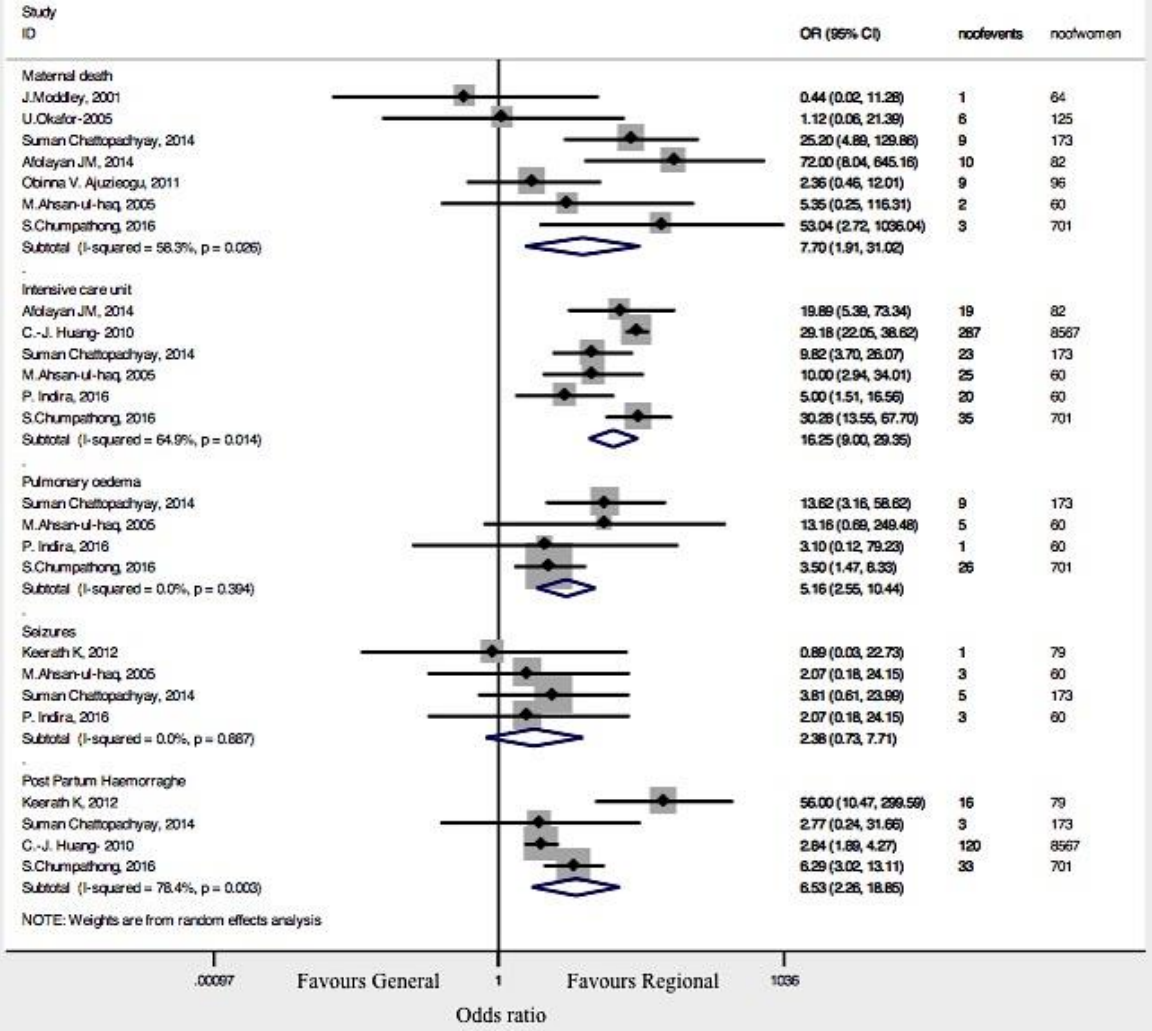
Figure10: Newcastle Ottawa quality scale for studies evaluating type of anaesthesia in women with pre-eclampsia



4.41: Effects of types of anaesthesia on maternal outcomes

Administration of general anaesthesia increased the odds of maternal death (OR 7.70, 95% CI 1.9-31.0, I^2=58%) by seven fold in women with pre-eclampsia compared with regional anaesthesia. There was a significant increase in the odds of maternal admission to intensive care unit (OR 16.25, 95% CI 9.0 to 29.5, I^2=65%), need for post operative ventilation (OR 45.0, 95% CI 8.16 to 248.12), pulmonary oedema (OR 5.16, 95% CI 2.5 to 10.4, I^2=0%) and post partum haemorrhage (OR 6.53, 95% CI 2.3 to 18.9, I^2=78%). There was no significant difference in the risk of seizures. (Fig 11).

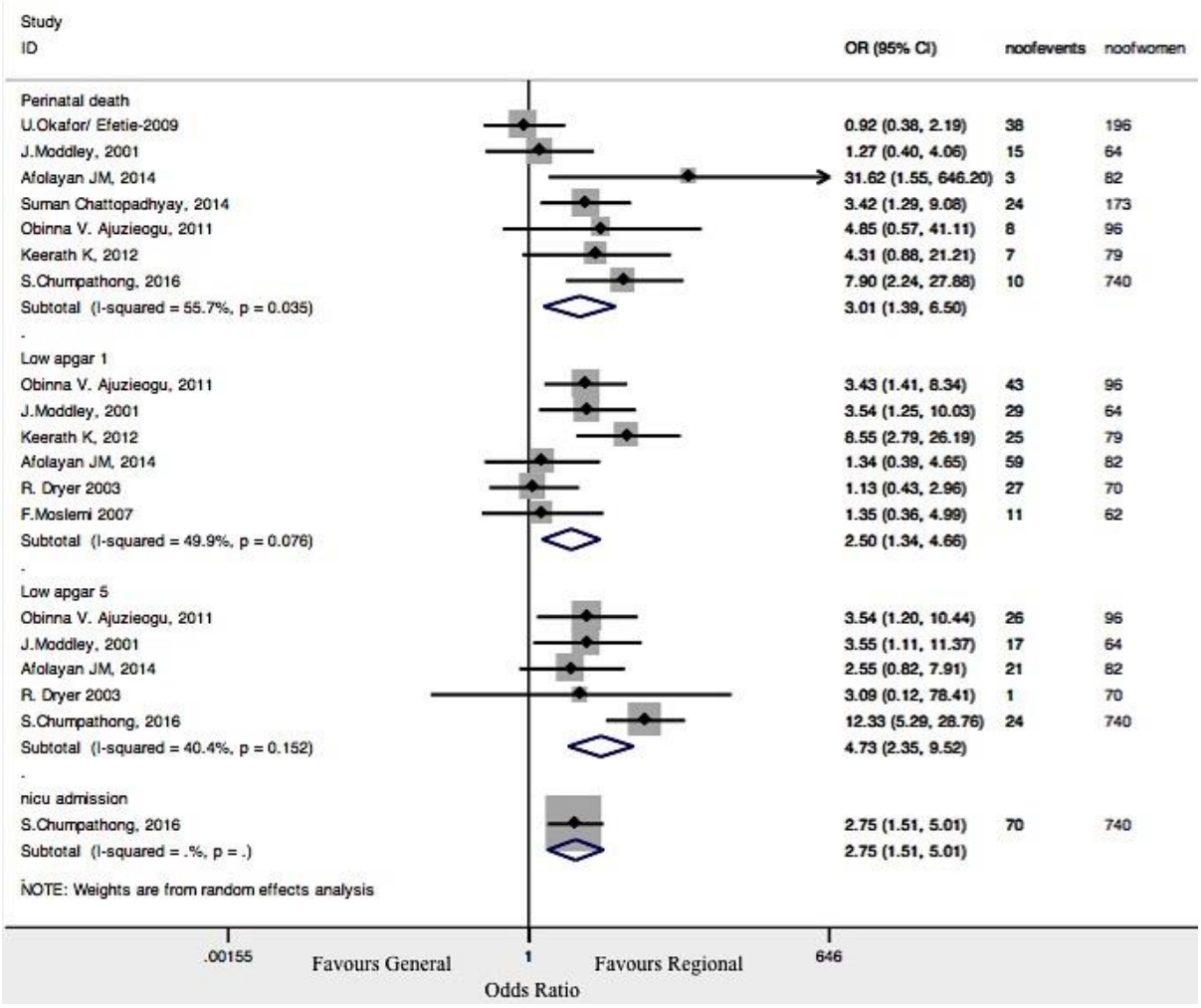
Figure 11: Maternal outcomes in women with pre-eclampsia exposed to general vs. regional anaesthesia in low- and middle-income countries (LMIC)



4.42: Effects of types of anaesthesia on perinatal outcomes

The odds of perinatal death ~~was~~ were increased by three fold (OR 3.01, 95% CI 1.4 to 6.5, I^2=56%) when general anaesthesia was administered to women with pre-eclampsia rather than regional anaesthesia. There was a significant association between general anaesthesia administration and low Apgar score at 1 minute (OR 2.50, 95% CI 1.3 to 4.6, I^2=50%), at 5 minutes (OR 4.73, 95% CI 2.4 to 9.5, I^2=40%), and admission to NICU (OR2.75, 95% CI 1.5 to 5.0) than regional anaesthesia (Fig 12).

Figure 12: perinatal outcomes in women with pre-eclampsia exposed to general vs. regional anaesthesia in LMIC

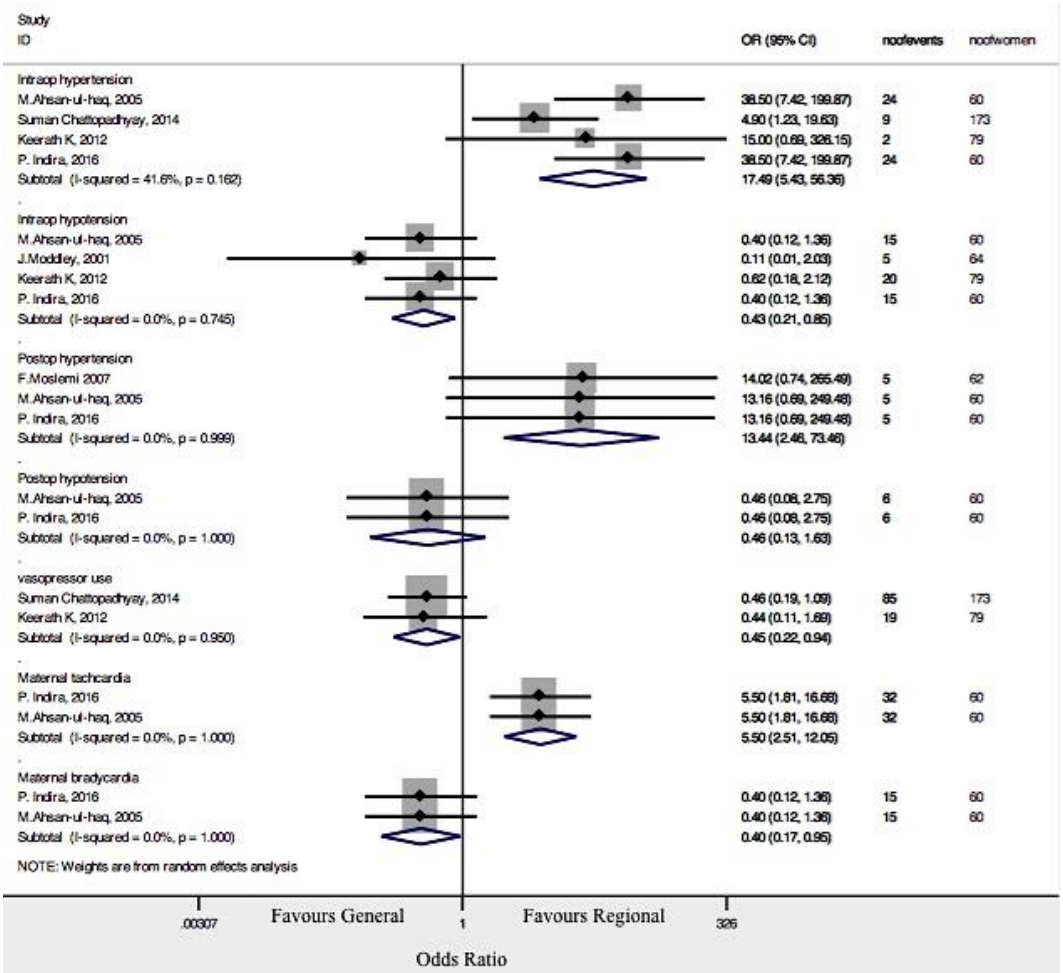


4.43:Effects of types of anaesthesia on maternal heamodynamic state

General anaesthesia was significantly associated with intraoperative hypertension (OR 17.49, 95% CI 5.43-56.36, I^2=41%), postoperative hypertension (OR 13.4, 95% CI 2.46-73.46, I^2=0%), and maternal tachycardia (defined as rise of 25% from baseline) in this group (OR 5.50, 95% CI 2.51-12.05, I^2=0%). (Figure 13)

We observed a protective effect of general anaesthesia on intraoperative hypotension (OR 0.43, 95% CI 0.21-0.85, I^2=0%), vasopressor use (OR 0.45, 95% CI 0.22-0.94, I^2=0%), and maternal bradycardia (defined as fall of 25% from baseline) (OR 0.40, 95% CI 0.17-0.95, I^2=0%) than regional anaesthesia. There were no differences in postoperative hypotension (OR 0.46, 95% CI 0.13-1.63, I^2=0%) (Figure 13).

Figure 13: Heamodynamic status of women with pre-eclampsia exposed to general vs. regional anaesthesia in LMIC



4.5: Discussion

General anaesthesia is associated with increase in maternal and perinatal death, and other complications such as maternal intensive care admission, pulmonary oedema and low Apgar scores at one and five minutes. There was also a higher association of intraoperative and postoperative hypertension following general anaesthesia.

The review was carried out using a prospective protocol, and rigorous methodology. The studies included women across the spectrum of disease, and the findings are generalisable. We were able to perform analysis of comparative data for general and regional anaesthesia, for key clinical outcomes. We were limited by the heterogeneity in definitions of population, intervention and outcome. Individual studies did not provide data on outcomes according to the severity of the disease, and we were unable to look for a differential effect according to disease severity. The methods and drugs used to carry out the regional and general anaesthesia were not the same across the studies, or were not documented.[67, 68] The majority of the studies were limited to only tertiary centers, with the possibility of worse outcomes in district and rural settings. We were unable to undertake meta-regression to assess the effects of setting, practitioners, study quality and year of publication on outcomes due to paucity of data, and the small numbers of studies.

Existing systematic reviews in pregnant women in LMIC has shown tripling of odds of maternal death with caesarean section[69]; this was however doubled with seven fold increase of maternal death in women with pre-eclampsia. Women with pre-eclampsia are at higher risk from general anaesthesia, and the associated airway oedema makes intubations difficult, furthermore more than half of the women in the review had severe pre-eclampsia. The adverse effect on perinatal deaths with general anaesthesia in these women with pre-eclampsia was similar to that of general population in LMIC. [69]

We found an increase in intraoperative and post-operative hypertension (rise in 20-25% from baseline) in the general anaesthesia group. This is similar to the findings observed in other studies[70], and is hypothesised to be due to sympathetic response during intubation. Such a phenomenon could be very serious in women who have severe pre-eclampsia and are already severely hypertensive. UK confidential enquiries have found that in deaths the largest number of deaths following pre-eclampsia are secondary to intracranial haemorrhage, a known complication of severe hypertension.[50]

The fear of spinal anaesthesia in patients with severe pre-eclampsia is the perceived risk of severe hypotension and low cardiac output resulting in placental hypo perfusion and poor perinatal outcomes, as well as the risk of iatrogenic pulmonary oedema while correcting the hypotension.[65, 71] However studies have shown that patients with severe preeclampsia have less frequent and less severe hypotension in response to spinal anaesthesia than normotensive parturients. [72] Our findings have shown intraoperative hypotension (fall in 20-25% from baseline) in the spinal group, but this was reported to be easily treated and to have responded well to vasopressors.

In high-income countries it is now generally accepted that regional anaesthesia is considered safer where no contraindications exist in pregnant women, and in women with pre-eclampsia epidural anaesthesia is generally recommended. However in LMIC, these recommendations do not always filter through and are sometimes unclear or not always easy to follow. Anaesthetic care providers in LMIC are restricted in their ability to perform regional anaesthesia due to the high cost and unavailability of epidural and spinal sets, lack of personnel with the skills to administer regional anaesthesia, and moribund condition of the presenting patients, and little time and resources to optimise the condition prior to anaesthesia. Our systematic review has highlighted the potential harm with routinely using general anaesthesia in this group of very high-risk women. The haemodynamic effects and feto-maternal consequences of spinal anaesthesia need to be also compared with epidural anaesthesia, which is considered the current benchmark technique.

There is a need for well conducted large studies evaluating the risks of general and regional anaesthesia in LMIC, and compare the effects of administering anaesthesia between physician anaesthetists, and non-physician cadre of trained anaesthetic providers. Health policy makers need to prioritise improvements in the ability of maternity units in LMIC to provide safe anaesthesia and promote good practice guidelines in the management of high-risk patients. On going efforts such as those of LifeBox, which promote safe anaesthesia during surgery[58], needs to be extended to include high risk women undergoing caesarean section.

4.6: Conclusion:

Regional anaesthesia should be considered as the first choice of anaesthesia in women with pre-eclampsia in LMIC necessitating caesarean section if there are no specific contraindications. Further training is required in the management of these high-risk women especially when dealing with airway complications.

Chapter 5: Maternal and fetal complications related to caesarean section in LMIC

5.1: Abstract:

Background

Caesarean section is a life saving procedure for both mother and fetus. It ~~is~~ also poses a small but significant risk to mother and child, which are disproportionately high in LMIC.

Methods:

We searched major electronic databases until June 2016, for studies reporting risks of maternal death from caesarean section in LMIC. Two independent reviewers undertook quality assessment and data extraction. We also included unpublished studies without any language restrictions. We computed proportions of caesarean section deaths and complications and odds ratios for risk factors, and pooled the data using a random effects model.

Findings:

From 11822 citations, we included 192 studies. 69 studies (30868 maternal deaths, > 12 million deliveries, 50 countries) reported on caesarean section deaths as a proportion of all maternal deaths. 138 studies/ 205 cohorts (2601330 caesarean sections, > 11 million deliveries, 63 countries) reported on caesarean section deaths as a proportion of all caesarean sections. 47 studies (285655 caesarean sections) assessed the association of various risk factors and complications in pregnant women undergoing caesarean section

Of all maternal deaths 24% (95% CI 21.7 to 27, I^2=93.7%) had undergone a caesarean section with the highest rates in Latin America and the Caribbean (58%, 95% CI 42.7 to 73.5, I^2 =38%), and the lowest in East Asia and Pacific (17%, 95% CI 13.7 to 20.7, I^2=64.9%). The overall rate of death in women undergoing a caesarean section was 4.8 per 1000 (95% CI 4.23 to 5.6, I^2 = 97%) procedures,

with the highest rates in sub-Saharan Africa (10.0 per 1000 caesarean -sections, 95% CI 8.7 to 11.5, I^2=98%).

The overall rate of stillbirth in women undergoing a caesarean section was 44 per 1000 procedures (95% CI 35.0 to 54.9, I^2 = 99%), with the highest rates in sub-Saharan Africa (79 per 1000 caesarean sections, 95% CI 64.5t o 95.3, I^2=98%). The overall risk of perinatal death in women undergoing a caesarean section was 74 per 1000 caesarean sections (95% CI 60 to 88, I^2 = 99%), with the highest rates in Middle East and North Africa (116 per 1000 caesarean sections, 95% CI 0 to 478, I^2=99%).

The odds of maternal death was doubled (OR 2.14, 95% CI 1.20 to 3.82, I^2=62%), and perinatal death was quadrupled (OR 4.24, 95% CI 2.56 to 7.10, I^2=83%) with emergency than elective caesarean section. Caesarean section that was performed in the second stage of labour increased the odds of maternal death by 12 fold (OR 12.27, 95% CI 2.87 to 52.49, I^2=0%), and increased perinatal death (OR 9.23, 95% CI 4.24 to 20.10) compared to those performed before full dilatation. There was no significant difference in mortality with different cadres or seniority of staff performing the procedure.

Conclusion: Caesarean sections carry a high maternal mortality rate in low- and middle-income countries. Interventions should be used to reduce the rate of unnecessary caesarean sections and improve the safety of this procedure.

Publications arising from this chapter:

Accepted for poster presentation for Royal College of Obstetricians and Gynaecologist Congress 2017

5.2: Introduction:

Caesarean sections are a part of comprehensive emergency care (*CEmOC*) and is essential in the management of several obstetric emergencies. When used appropriately caesarean section is a life saving procedure for both mother and fetus. There is a lack of equity in the accessibility to caesarean sections with the lowest income countries having a caesarean section rate of 2%,[73] this leads to care being administered 'too little and too late' resulting in maternal and fetal complications. [74]

Although caesarean sections save lives, the surgery is potentially dangerous. This can be a result of ~~f~~from surg~~e~~rical ~~y~~ and anaesthesia related mortality and morbidity in the current pregnancy, and from uterine rupture during subsequent pregnancies. This risk is further heightened by lack of surgical skill, lack of equipment and lack of blood.[15] There are no robust estimates of maternal deaths from caesarean sections. The causes and factors that contribute to maternal mortality in mothers undergoing caesarean section are varied and multifactorial but need further clarification.

We undertook a systematic review to identify the factors linked to adverse outcomes in pregnant women undergoing a caesarean section in LMIC, and to obtain precise estimates of poor outcomes including death and associated factors.

5.3: Methods:

We undertook the systematic review using a prospective protocol (PROSPERO No. CRD42015029191) in line with current recommendations, and reported as per the PRISMA guidelines.[40]

Literature search

We searched Medline, Embase, Scopus, CINAHL, Web of Science and WHO Library and Index Medicus until 1st June 2016. We used MeSH headings, text words and word variants for "pregnancy" and combined them with terms for low resource countries like "low- income " or "middle-income" or "developing country". These were combined with terms related to caesarean sections and surgery such as “c(a)esarean section” or “an(a)esthesia” (Appendix 2). There were no language restrictions. Additionally, we searched the reference lists of the included studies and relevant reviews for eligible studies. We also obtained primary data from WHO Multi-country and Global surveys and re-analysed for factors of interest.

Study selection

Studies were selected in two stages. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second, we examined the full texts of the retrieved papers. Two independent reviewers (SS, NM) selected the papers against pre-specified inclusion criteria. Any discrepancies were resolved after discussion with a third reviewer (ST). Studies were included if they assessed maternal and perinatal outcomes in pregnant women undergoing a caesarean section in countries categorized as LMIC by the World Bank.[41] We excluded studies in high-income countries, those involving non-pregnant women, case reports, and studies published before 1990 to ensure that the estimates reflect the current burden of the condition.

Caesarean section was defined as the delivery of the fetus through an abdominal and uterine incision. Elective caesarean section are planned in advance and happen before labour often for conditions that make normal delivery dangerous for either mother or fetus. Emergency caesarean sections are often carried out because of concerns to the mother or fetus that develops before or after labour has started. First stage caesarean sections are defined as a caesarean section done before the cervix is fully dilated; second stage caesarean sections are defined as a caesarean section done after the cervix is fully dilated. We accepted the primary study authors’ definitions for elective and emergency caesarean

sections. Maternal mortality was defined as death of mother during pregnancy, and at any time until 42 days after delivery, irrespective of the duration and site of the pregnancy as defined by the World Health Organization (WHO). This included deaths from any cause related to or aggravated by pregnancy and its management, but not from accidental or incidental causes.[1] Perinatal death included any fetal death that occurred after 28 completed weeks of gestation, stillbirth and early neonatal death until one week after birth.[42] Apgar scores were classed as low if they were less than or equal to 7 at one and five minutes. We accepted the primary study authors' definitions for maternal and fetal complications such as postpartum haemorrhage, cardiac arrest and admission to the intensive care unit.

Study quality assessment and data extraction

Two independent reviewers (SS and NM) undertook study quality assessment and data extraction, and any discrepancies were resolved with input from the third reviewer (ST).

For studies assessing caesarean section case fatality rates, a study was considered to be adequate for representativeness unless the hospitals involved were private hospitals or funded by an NGO or were part of large multicounty trial where interventions were initiated. Sample selection was classed as adequate if all caesarean sections were included, and as inadequate if a particular group of women were excluded, e.g. only those undergoing an elective procedure. We considered outcome assessment to be adequate if registry data e.g. from theatre books or patient notes were used and inadequate if verbal reports were the source of information. Studies that accounted for the cause of caesarean deaths to mother of fetus in at least 95% of cases were deemed to be adequate for ascertainment of cause of death. A study was classed as high quality if three of the above four criteria were met.[44]

Data were extracted on the number of events (caesarean section maternal death and complications) in women exposed and un-exposed to risk factors such as type of caesarean (elective/ emergency, first stage/ second stage) and type of practitioner (physician, non-physician) as well as grade. We

obtained information on the number of women undergoing caesarean section, total number of maternal deaths, and deaths during or after caesarean section, to compute corresponding proportions for individual studies.

Data analysis

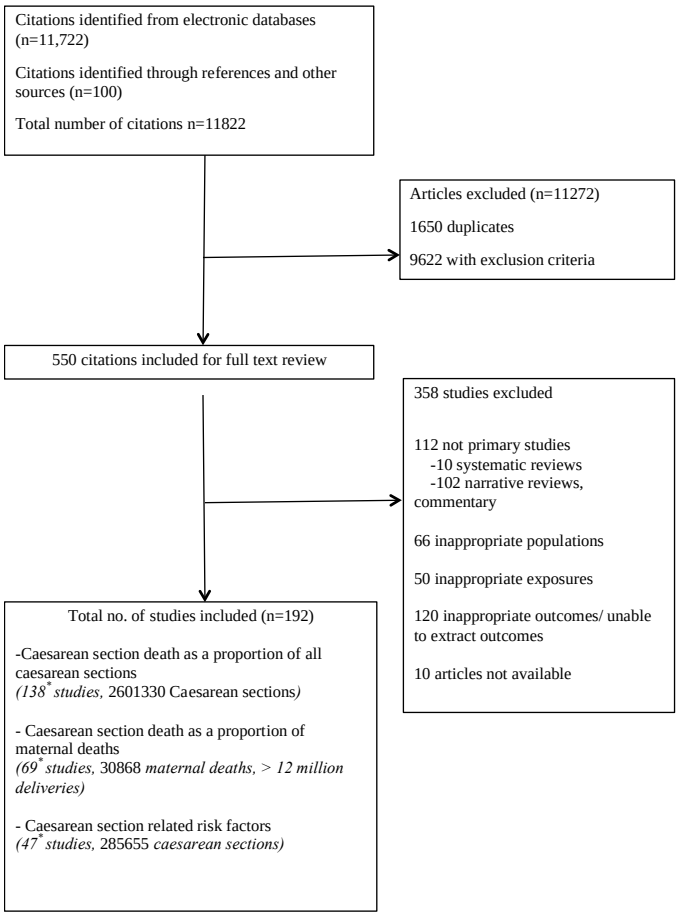
Summary rates of deaths following caesarean sections were estimated as a proportion of total maternal deaths and a proportion of total caesarean sections. Sub-group analysis and meta-regression were performed for the following factors that were specified *a priori*: geographical location (World Bank classification), country income (low-, low-middle, upper-middle), type of hospital, and year of publication (before and after 2000). We also assessed the effects of study quality (low, high) and study design (prospective, retrospective). We used multilevel random effects logistic models, and included the above factors. The meta-regressions were run as separate univariate analyses. We performed sensitivity analysis by excluding studies that included only subsets of the pregnant population, e.g. only elective caesarean sections. We did a further sensitivity analysis by carrying out caesarean section mortality rate as a proportion of postpartum maternal deaths rather than all maternal deaths. Proportions of causes of caesarean section mortality and morbidity were also calculated.

For comparative data, we computed odds ratios for various risk factors such as type (emergency V elective), timing of caesarean section (second V first stage) and type and grade of operating surgeon (junior V senior/ non-physician V physician) and pooled them using a random effects model. Heterogeneity was evaluated using I^2 statistic. All analyses were performed using Stata 13.[48]

5.4 Results:

From 11822 citations, we included 192 studies. (Figure 14).

Figure 14. Study selection process in the systematic review of caesarean section related mortality in low- and middle-income countries (LMIC)



69 studies / 119 cohorts (30,868 maternal deaths, > 12 million deliveries, 50 countries) reported on caesarean section deaths as a proportion of all maternal deaths. 138 studies/ 205 cohorts (260,1330 caesarean sections, > 11 million deliveries, 63 countries) reported on caesarean section deaths as a proportion of all caesarean sections. 47 studies (285655 caesarean sections) assessed the association of various risk factors and complications in pregnant women undergoing caesarean section; type of caesarean section (elective V emergency- 30 studies, 257073 caesarean section, second V first stage- 8 studies, 8988 caesarean sections,) and type of practitioner (11 studies, 59629 caesarean sections) were the analysed risk factors. Data was available from all World Bank regions. 114 studies provided caesarean section rates, these ranged from 2-60%, with and average of 21%.

Indications for caesarean sections

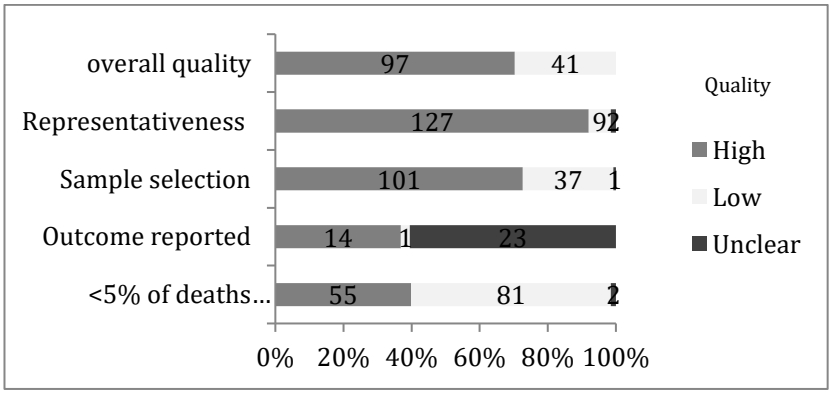
Indications for caesarean section were reported ~~on~~ by 89 studies and 345,688 caesarean sections. 22% (78,737/345,688) were done for failure to progress, cephalo-pelvic disproportion or obstruction, 17% (61,868, 345,688) were carried out due to previous cesarean section, 11% (41,181/345,688) were done for fetal distress, 7% (25,491/345,688) were done for hypertensive disorders, 3% (10,540, 345,688) were done for Antepartum haemorraghe, and 28 % (99,139, 345,688) were due to other cause such as multiple pregnancies, malpresentation or ruptured uterus

See appendix 7 for table of study characteristics.

Quality of the studies

Three quarters (97/138, 70%) of the included studies on mortality rates following caesarean section caesarean section were deemed high quality. Nearly all studies were deemed high quality (127/138, 92%) for representativeness of the population and setting, three quarters of studies (101/138, 73%) had adequate sample selection, four fifth were assessed as good quality for outcomes reporting (114/138, 82%) and two-fifth adequately accounted for <95% of maternal deaths (55/138, 40%) (Fig 15).

Figure 15: Quality assessment for studies providing rates of mortality following caesarean section.



5.41: Caesarean section related maternal mortality rates

Of all maternal deaths 24.3% (95% CI 21.7 to 27.9, I^2=93%) had undergone a caesarean section with the highest rates in Latin America and the Caribbean (58.4%, 95% CI 42.7 to 73.5, I^2 =38%), and the lowest in East Asia and Pacific (17%, 95% CI 13.7 to 20.7, I^2=65%). There was a statistically significant difference between the regions (p<0.001), and between different study designs (p<0.001) with higher estimates from prospective studies. (Table 7).

Of all maternal deaths who had delivered 36.7% (95% CI 31.7 to 41.7, I^2=94%) had delivered by caesarean section with the highest rates in Latin America and the Caribbean (73.5%, 95% CI 56.3 to 88.4, I^2 =38%). There was a statistically significant difference between the regions (p<0.001). Sensitivity analysis in appendix 8

Table 7: Rates of caesarean section deaths as a proportion of total maternal deaths.

Factors		Studies/Cohorts	n	N	Prevalence (%)	Heterogeneity I^2	Subgroup P Value
Region	East Asia and Pacific	18	624	3,372	17.1 (13.7; 20.7)	64.9%	<0.001
	Europe and Central Asia	1	50	174	28.7 (22.5; 35.9)	-	
	Latin America and the Caribbean	16	239	523	58.4 (42.7; 73.5)	37.5%	
	Middle-East and North Africa	13	364	2,029	35.0 (20.3; 51.1)	97.2%	
	South Asia	20	430	2,610	24.5 (17.6; 31.9)	91.6%	
	Sub-Saharan Africa	44	5,703	22,159	22.9 (20.2; 25.6)	93.1%	
Year of study	<2000	28	1,325	6,162	23.5 (18.7; 28.7)	95.0%	0.203
	>2000	84	6,085	24,705	25.0 (21.9; 28.3)	93.1%	
Study design	Prospective	53	562	1,813	33.8 (28.0; 39.9)	71.5%	<0.001
	Retrospective	59	6,848	29,054	22.2 (19.5; 25.0)	96.2%	
Income setting	Low	21	757	2,462	27.9 (20.2; 36.3)	93.9%	0.461
	Lower-Middle	49	1,074	6,178	22.0 (17.1; 27.1)	93.6%	
	Upper-Middle	41	5,567	22,172	24.0 (20.8; 27.3)	89.8%	
Quality	Low	9	213	844	20.4 (11.4; 31.0)	91.8%	0.239
	High	103	7,197	30,023	24.8 (22.0; 27.7)	93.9%	
Overall		**112**	**7,410**	**30,867**	**24.3 (21.7; 27.0)**	**93.7%**	

5.42: Risk of maternal death in women undergoing caesareans section

Caesarean section mortality rates were 4.8 (95% CI 4.2 to 5.6, I^2 = 97%) per 1000 procedures. Subgroup analysis and meta-regression showed a statistically significant difference between regions (p<0.001). The highest rates of deaths following caesarean sections was in Sub- Saharan Africa, with 10 per 1000 procedures, (95% CI 8.7 to 11.5, I^2=98%) and the lowest rates were in Europe and Central Asia with 0.3 per 1000, (95% CI 8.7 to 11.5, I^2=98%), (Table 8). Appendix 9 and figure 16 provides estimates for individual countries.

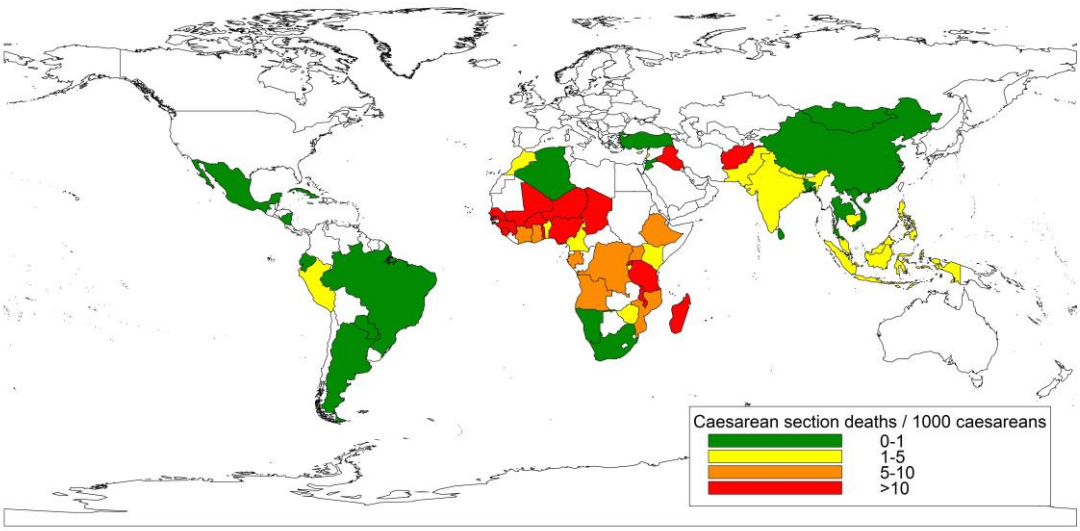
There was also a significant difference between year of study, with those published after year 2000 4.2 per 1000, (95% CI 3.5 to 4.9, I^2=96%) having almost half the rate of death as those published before year 2000, 7.6 per 1000, (95% CI 6.6 to 8.8, I^2=97%), (p<0.001). There was ~~also~~ a difference in income setting with low income countries having the highest rates of mortality of 11.0 per 1000, (95% CI 8.3 to 14.2, I^2=95%), (p<0.001). The quality of studies also affected the rates, (p<0.001). A sensitivity analysis excluding studies that included only specific groups of women did not show a significant difference in deaths rates. (Appendix 10)

Table 8: Rates of deaths in women undergoing caesarean section / 1000 caesarean sections.

Factor	Studies/ Cohorts	n	N	Prevalence (/1,000 C/S)	Heterogeneity I^2	Subgroup P Value

Region	East Asia and Pacific	16	143	151,361	0.6 (0.2; 1.1)	74.9%	<0.001
	Europe and Central Asia	2	51	130,596	0.3 (0.2; 0.5)	98.3%	
	Latin America and the Caribbean	17	202	215,982	0.6 (0.4; 0.8)	33.4%	
	Middle-East and North Africa	7	24	9,217	1.9 (0.0; 5.8)	84.8%	
	South Asia	24	289	91,287	1.6 (0.8; 2.7)	82.1%	
	Sub-Saharan Africa	99	5,848	1,894,908	10.0 (8.7; 11.5)	97.6%	
Year of study	<2000	30	947	302,637	7.6 (4.8; 10.9)	98.3%	0.035
	>2000	136	5,650	2,193,655	4.2 (3.5; 4.9)	96.3%	
Study design	Prospective	97	1,647	290,461	3.5 (2.3; 4.9)	95.9%	<0.001
	Retrospective	69	4,950	2,205,831	7.7 (6.6; 8.8)	97.5%	
Income setting	Low	56	1,809	134,763	11.1 (8.3; 14.2)	95.1%	<0.001
	Lower-Middle	44	559	153,747	1.7 (0.9; 2.7)	88.4%	
	Upper-Middle	65	4,189	2,204,841	2.8 (2.3; 3.4)	95.9%	
Quality	Low	32	1,397	137,403	8.9 (6.1; 12.1)	95.3%	<0.001
	High	133	5,194	2,356,829	4.0 (3.4; 4.6)	96.0%	
Type of Hospital	District hospital	22	171	20,093	6.8 (4.4; 9.7)	68.3%	0.004
	Mixed	19	4,724	2,033,216	6.2 (4.6; 7.9)	99.2%	
	Private hospital	2	3	1,470	1.5 (0.0; 4.6)	100.0%	
	Teaching hospital	48	1,127	243,966	9.1 (5.9; 12.8)	97.9%	
	Tertiary hospital	26	304	41,692	8.9 (5.9; 12.6)	89.7%	
Overall		**166**	**6,597**	**2,496,292**	**4.8 (4.23; 5.6)**	**97.0%**	

Figure 16: world map showing individual countries rates of mortality following caesarean section.



5.43: Risk of stillbirth and perinatal mortality in women undergoing caesarean section

Stillbirth

The overall rate of stillbirth in women undergoing a caesarean section was 44 per 1000 procedures (95% CI 35 to 55, I^2 = 99%), with the highest rates in sub-Saharan Africa (79.2 per 1000 C-sections, 95% CI 64 to 95.3, I^2=97%) (Table 9). Subgroup analysis and meta-regression showed a statistically significant difference between regions (p=0.001), between income groups (p=0.001), with the lowest income countries having the highest rates of stillbirths (76 per 1000 caesarean sections, 95% CI 54 to 103, I^2=98%), between type of hospitals (p=0.001), between study design (p=0.001) and by year (p=0.003) with rates after year 2000 being almost half of that before 2000. (Table 9).

Table 9: Still birth rates following caesarean sections

Analysis		**Studies/ Cohorts**	**n**	**N**	**Prevalence /1,000 CS**	**Heterogeneity**	**Subgroup P Value**
						I^2	
Region	East Asia and Pacific	10	586	17,264	13.8 (0.2; 45)	99.3%	<0.001
	Europe and Central Asia	0	-	-	-	-	
	Latin America and the Caribbean	9	2,418	187,084	9.0 (6.4; 12.1)	93.4%	
	Middle-East and North Africa	2	65	2,782	22.4 (17.2; 28.3)	99.2%	
	South Asia	11	423	21,107	18.7 (9.6; 30.5)	95.3%	
	Sub-Saharan Africa	41	5,440	68,780	79.2 (64.5; 95.3)	97.9%	
Year of study	<2000	17	4,152	48,713	75.2 (49.0; 106.4)	99.1%	0.003
	>2000	56	4,780	248,304	35.9 (28.8; 43.7)	98.3%	
Study design	Prospective	45	2,114	89,196	29.3 (21.2; 38.6)	98.2%	<0.001
	Retrospective	28	6,818	207,821	74.5 (50.9; 102.2)	99.6%	
Income setting	Low	23	2,131	25,489	76.4 (53.6; 102.8)	98.1%	0.001
	Lower-Middle	22	3,076	63,021	23.3 (10.7; 40.3)	99.2%	
	Upper-Middle	28	3,725	208,507	40.2 (29.3; 52.7)	98.8%	
Quality	Low	13	2,220	29,151	74.4 (52.9; 99.1)	95.1%	0.003
	High	59	6,687	265,806	39.8 (30.5; 50.4)	99.1%	
Type of Hospital	District hospital	5	560	7,298	77.4 (29.6; 144.8)	98.6%	<0.001
	Mixed	5	2,214	154,146	49.6 (16.8; 97.8)	97.7%	
	Private hospital	2	34	1,937	16.6 (11.3; 22.9)	99.4%	
	Teaching hospital	21	4,129	48,934	67.6 (44.5; 94.9)	98.9%	
	Tertiary hospital	19	834	16,978	47.9 (31.1; 68.1)	96.4%	
Overall		**73**	**8,932**	**297,017**	**44.4 (35.0; 54.9)**	**99.1%**	

Perinatal death

The overall risk of perinatal death in women undergoing a caesarean section was 74 per 1000 caesarean sections (95% CI 60 to 88, I^2 = 99%), with the highest rates in Middle East and North

Africa (116 per 1000 caesarean sections, 95% CI 0 to 478, I^2=99%) and lowest in Europe and Central Asia (1.8 per 1000 caesarean sections, 95% CI 0.9 to 3.8). Subgroup analysis and meta-regression showed a statistically significant difference between regions (p=0.001), between income groups (p=0.002), with the lowest income countries having the highest rates of perinatal mortality (107 per 1000 caesarean sections, 95% CI 83 to 133, I^2=99%), between type of hospitals (p=0.001), between study design (p=0.011) and by year (p=0.007), with rates after year 2000 being almost half of that before 2000. (Table 10).

Table 10: Perinatal death rates following caesarean sections

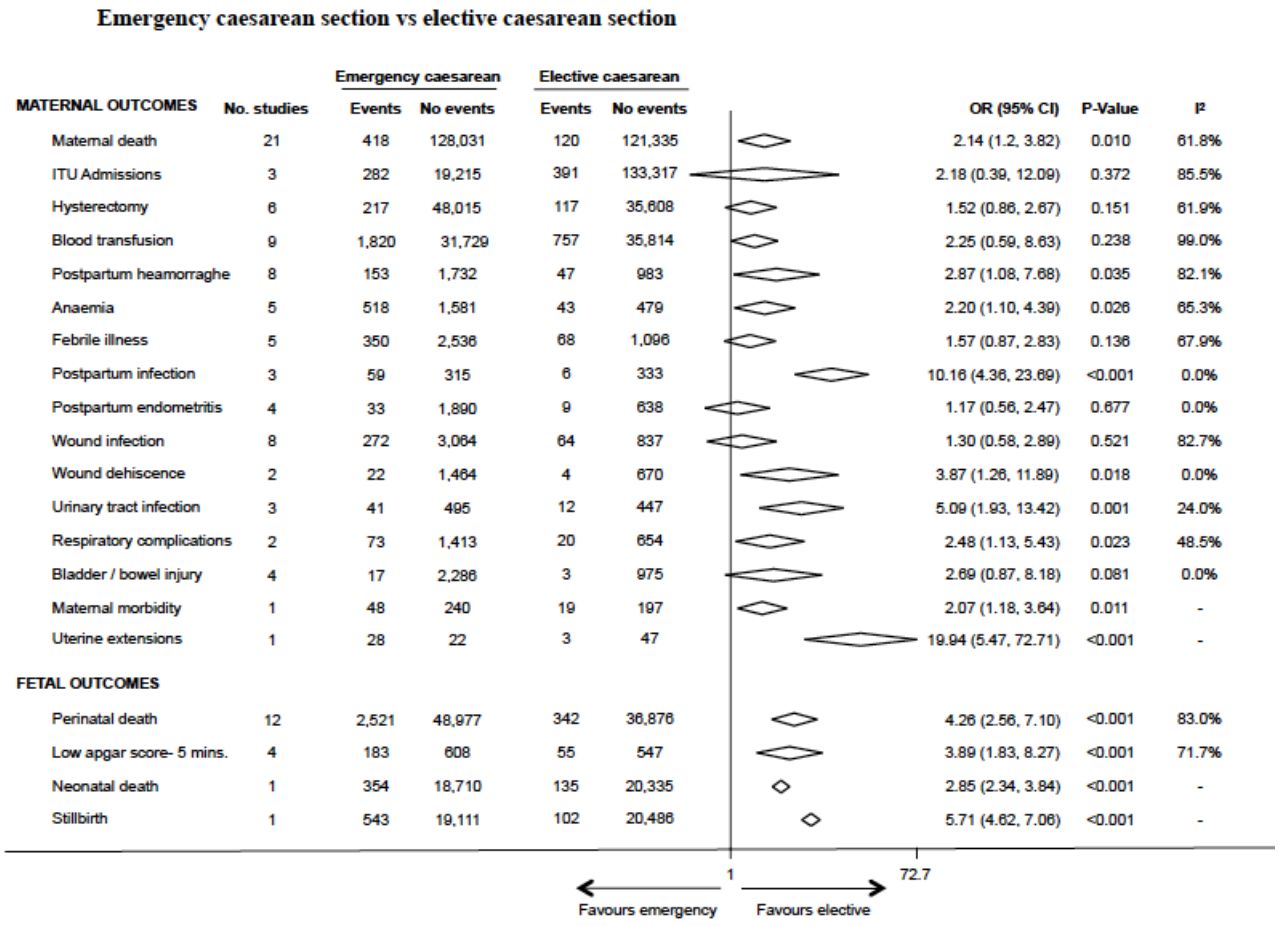
Analysis		**Studies/Cohorts**	**n**	**N**	**Prevalence / 1000 C/S**	**Heterogeneity I^2**	**Subgroup P Value**
Region	East Asia and Pacific	12	1,039	19,719	25.0 (2.7; 67.8)	99.5%	<0.001
	Europe and Central Asia	1	7	3,817	1.8 (0.9; 3.8)	-	
	Latin America and the Caribbean	8	607	34,974	17.5 (14.3; 21.0)	-	
	Middle-East and North Africa	3	1,549	6,013	116.3 (0.0; 477.9)	99.9%	
	South Asia	13	883	23,491	43.9 (26.9; 64.7)	97.5%	
	Sub-Saharan Africa	72	10,461	111,982	99.3 (83.8; 115.9)	98.7%	
Year of study	<2000	24	6,828	55,906	119.0 (78.4; 166.5)	99.5%	0.007
	>2000	85	7,718	144,090	62.1 (50.2; 75.2)	98.9%	
Study design	Prospective	64	6,308	121,778	57.7 (45.2; 71.6)	99.0%	0.011
	Retrospective	45	8,238	78,218	97.9 (70.1; 129.7)	99.5%	
Income setting	Low	39	6,362	63,277	107.0 (83.0; 133.6)	99.0%	0.002
	Lower-Middle	32	5,665	70,798	57.1 (33.2; 86.6)	99.5%	
	Upper-Middle	38	2,519	65,921	57.3 (41.8; 75.1)	98.8%	
Quality	Low	28	4,326	47,397	93.2 (75.2; 113.0)	97.1%	0.047
	High	80	10,151	150,539	68.0 (51.8; 86.1)	99.4%	
Type of Hospital	District hospital	18	1,103	14,092	78.5 (42.9; 123.3)	98.6%	<0.001
	Mixed	10	3,230	27,030	129.4 (94.8; 168.4)	98.4%	
	Private hospital	2	73	1,937	37.7 (29.6; 46.7)	99.8%	
	Teaching hospital	34	6,660	63,568	89.1 (57.3; 127.1)	99.5%	
	Tertiary hospital	24	1,498	25,645	71.1 (47.5; 98.8)	98.3%	
Overall		**109**	**14,546**	**199,996**	**73.6 (60.0; 88.4)**	**99.4%**	

5.44: Risk factors for adverse outcomes in pregnant women undergoing caesarean section

Emergency vs. elective caesarean section

The odds of maternal death ~~was~~ were doubled (OR 2.14, 95% CI 1.20 to 3.82, I^2=62%), and perinatal death was quadrupled (OR 4.26, 95% CI 22.56to 7.10, I^2=83%) with emergency rather than elective caesarean section. There was a significant increase in other complications such as postpartum haemorrhage (OR 2.87, 95% CI 1.08 to 7.68, I^2=82%), postpartum infection (OR 10.16, 95% CI 4.36 to 23.69, I^2=0%), wound dehiscence (OR 3.87, 95% CI 1.26 to 11.89, I^2=0%) and respiratory complications (OR 2.48, 95% CI 1.13 to 5.43, I^2=48.5%). (Figure 17) Appendix 11 includes table of results.

Figure 17: Maternal and fetal outcomes following emergency and elective caesarean sections.



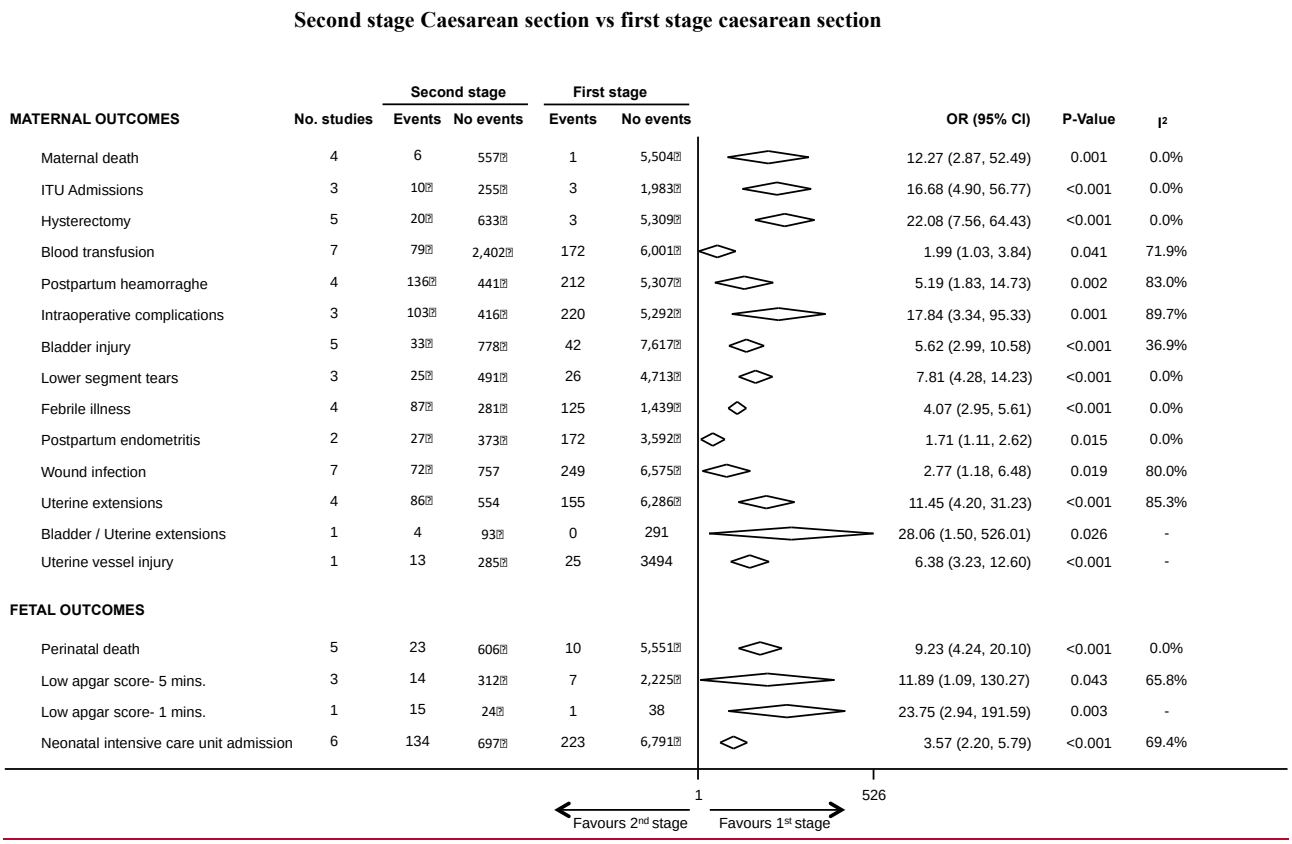
Second vs. first stage of labour caesarean section

Caesarean section that was performed in the second stage of labour increased the odds of maternal death by 12 fold (OR 12.27, 95% CI 2.87 to 52.49, I^2=0%) compared to those performed before full dilatation. There was also an increase in maternal ITU admissions (OR 16.68, 95% CI 4.90 to 56.77, I^2=0%), hysterectomy (OR 22.08, 95% CI 7.56 to 64.43, I^2=0%), postpartum hemorrhage (OR 5.17, 95% CI 1.78 to 15.03, I^2=83.3%) and the need for a blood transfusion (OR 1.99, 95% CI 1.03 to 3.84, I^2=71.9%).

There was a significant increase in intraoperative complications such as bladder injuries (OR 5.62, 95% CI 2.99 to 10.58, I^2=36.9%), lower segment tears (OR 7.1, 95% CI 4.28 to 14.23, I^2=0%) and extension of tears of uterine incisions (OR 11.45, 95% CI 4.20 to 31.23, I^2=85.3%). There was also an increase in infective complications such as postpartum endometritis (OR 1.71, 95% CI 1.11 to 2.64, I^2=83%), wound infections (OR 2.77, 95% CI 1.18 to 6.49, I^2=84%), and febrile illness (OR 4.07, 95% CI 2.95 to 5.61, I^2=0%).

The odds of complications in the offspring were increased when caesarean section was performed at full dilatation for perinatal death (OR 9.23, 95% CI 4.24 to 20.10, I^2=0%), low Apgar score at one (OR 23.75, 95% CI 2.94 to 191.6, I^2=0%) and 5 minutes (OR 11.89, 95% CI 1.09 to 130.3, I^2=0%), and admissions to neonatal intensive care unit (OR 3.57, 95% CI 2.20 to 5.79, I^2=69%), (Figure 18). Appendix 11 includes table of results.

Figure 18: Maternal and fetal outcomes following second and first stage caesarean sections.



Type of practitioner and caesarean section complications.

There was no significant difference in outcomes between a senior registrar and consultant, nor between a registrar and consultant. Comparison between a junior and senior registrar found that the odds of post partum hemorrhage (OR 4.87, 95% CI 2.25 to 10.55, I^2=0%) and wound dehiscence (OR 22.0, 95% CI 2.81 to 172.1, I^2=0%) were increased if a junior doctor was operating compared to a senior doctor. Comparison of non-physician and physician operators found that the odds of perinatal death (OR 1.54, 95% C1.1.07 to 2.24, I^2=95%) and wound dehiscence (OR 2.00, 95% CI 1.36 to 2.95, I^2=0%) were increased if a non-physician was operating in comparison to a physician. Hysterectomy (OR 0.15, 95% C1. 0.11 to 0.20, I^2=0%) and blood transfusion (OR 0.31, 95% C1.0.26 to 0.33, I^2=0%) were increased when the procedure was carried out by a physician.

(Table 11)

Table 11: Type of practitioner and associated maternal / perinatal outcomes.

	Outcome	No. of studies	Exposed		No exposed		Estimate				
			Events	No events	Events	No events	OR	Lower CI (95%)	Upper CI (95%)	P-Value	I^2
Registrar vs consultant	Anaemia	1	104	69	35	23	0.99	0.54	1.82	0.975	-
	Hypovolemic shock	1	19	154	6	52	1.07	0.41	2.82	0.892	-
	Maternal mortality	3	20	568	0	97	1.42	0.26	7.88	0.688	0%
	Postpartum haemorrhage	1	23	126	6	72	2.19	0.85	5.63	0.104	-
	Sepsis	1	35	138	12	46	0.97	0.47	2.03	0.940	-
	Fresh still birth	1	11	204	4	31	0.42	0.13	1.40	0.156	-
Senior registrar vs consultant	Anaemia	1	71	47	35	23	0.99	0.52	1.89	0.982	-
	Hypovolemic shock	1	13	195	6	52	0.58	0.21	1.59	0.289	-
	Maternal mortality	2	4	216	0	62	4.60	0.24	86.86	0.309	-
	Postpartum haemorrhage	1	10	267	6	72	0.45	0.16	1.28	0.134	-
	Sepsis	1	23	95	12	46	0.93	0.43	2.03	0.852	-
Junior registrar vs senior Registrar	Anaemia	2	110	212	72	323	2.71	0.26	28.68	0.408	79%
	Hypovolemic shock	1	19	154	13	195	1.85	0.89	3.87	0.101	-
	Maternal mortality	2	18	355	4	216	2.62	0.39	17.48	0.319	43%
	Postpartum endometritis	1	6	214	13	504	1.09	0.41	2.90	0.868	-
	Postpartum haemorrhage	1	23	126	10	267	4.87	2.25	10.55	<0.001	-
	Sepsis	2	36	286	25	370	1.04	0.59	1.84	0.891	0%
	Wound dehiscence	1	11	138	1	276	22.00	2.81	172.14	0.003	-
	Wound infection	1	12	208	27	490	1.05	0.52	2.11	0.898	-
Non-physician vs physician	Postpartum heamorrhage	1	1	732	4	1,568	0.54	0.06	4.80	0.577	-
	Fever	1	388	1,487	56	200	0.93	0.68	1.28	0.662	-
	Maternal morbidity	1	33	912	6	137	0.83	0.34	2.01	0.674	-
	Maternal mortality	7	323	141,497	258	148,012	1.27	0.79	2.04	0.326	7%
	Wound dehiscence	3	98	3,468	43	2,898	2.00	1.36	2.95	<0.001	0%
	Wound infection	2	157	2,451	47	1,781	1.34	0.90	1.99	0.156	0%
	Blood transfusion	1	1,052	129,679	3,599	137,552	0.31	0.29	0.33	<0.001	-
	Hysterectomy	1	41	130,726	304	140,703	0.15	0.11	0.20	<0.001	-
	Perinatal death	7	5,010	137,803	5,109	143,916	1.54	1.07	2.24	0.022	96%
	Stillbirth	1	2,749	127,994	3,019	138,414	0.99	0.94	1.04	0.563	-

5.45 Causes of maternal deaths in women undergoing caesarean section

The underlying causes of death were reported in 56 studies, with data on 4387 deaths following caesarean section. A Third (1207/4387, 38%) of all deaths resulted from postpartum hemorrhage, 15% (658/4387) related to pre-eclampsia, 14% (591/4387) from sepsis, 7.5% (330/4387) due to anaesthesia, and a quarter due to other causes such as pulmonary embolus and other respiratory complications, anaemia or pre-existing medical conditions.

Morbidity in women undergoing caesarean section

Morbidity following caesarean section (24 studies) was 27 % (95% CI 22to 31, I^2 = 99%), these included post partum haemorrhage, blood transfusions, hysterectomy, post partum sepsis, wound infections, and itu admissions.

5.5: Discussion

The rates of maternal mortality in women undergoing caesarean sections in LMIC is 10-fold higher than what is observed in high-income countries,[(75)] with the risks increased further in Sub Saharan Africa. Deaths in women undergoing caesarean section contributed to a quarter of all maternal deaths. The outcomes were even worse for the fetus following caesarean section with stillbirths diagnosed in 1 in 22, and perinatal deaths about 1 in 13 women undergoing caesarean section. Emergency caesarean sections and those performed in the second stage of labour significantly increased maternal and perinatal mortality and morbidity. The rates of most maternal and fetal complications were not affected by the cadre or seniority of staff performing the caesarean section, however the odds~~ff~~ of hysterectomy was higher when a physician was operating in comparison to a non-physician, this maybe due to the fact that physicians may encounter the sickest, more complicated cases.

Ours review comprehensively and systematically evaluated the risk of maternal perinatal deaths, and other relevant outcomes in women undergoing caesarean section. We restricted our meta-analysis to only primary and published data rather than modelled data with many assumptions.[76] In addition to quantification of the rates of complications in women undergoing caesarean section, we explored in detail the risk factors for these outcomes. We looked for variations in death rates according to economic regions, individual countries and type of hospital.

There are limitations in estimating fatality rates from caesarean section, due to lack of data on underlying risk factor resulting in caesarean section, and could have influenced the mortality and morbidity. Hence, we were only able to quantify the overall association of caesarean section with complications. We were limited by the differences in reporting of outcomes, and their definitions in individual studies. Few studies were published in low-income countries that are outside Sub Saharan Africa and Asia. A large proportion of studies were from teaching and/ or tertiary hospitals, ~~and~~ although they will tend to be referred the sickest cases, they will also be the best equipped and staffed, ~~so~~ therefore the rates of deaths maybe higher in small rural centers. It is likely that the actual burden of complications is higher than our estimates, which were predominantly from facility-based data. We found significant heterogeneity in our findings which may be related to various factors and reflecting the variation in population, risk factors, setting and outcome.

Second stage caesarean section pose particular risk and require more surgical skill. Our review found poorer maternal and fetal outcomes following second stage caesarean section, and this was supported in previous reviews.[77] If alternative methods of delivery are possible these should be considered as first line, e.g. instrumental delivery,

symphysiotomy for obstructed labour or destructive deliveries for fetal deaths in neglected labours. [78, 79] These measure are much needed in low- income countries to reduce mortality and morbidity, more training is required to make sure that these procedures are performed safely.[80, 81]

We found haemorrhage to be the highest cause of death following caesarean section; similar concerns have been raised in the recent South African confidential enquiries.[82] Risk factors for haemorrhage should be identified earlier and modified if possible. Places with limitation in management of haemorrhage such as access to uterotonics and poor availability of blood should escalate their management of intra-partum and postpartum haemorrhage (PPH) earlier. Interventions such as balloon tamponade, B-lynch suture and early hysterectomy should be considered. PPH and the need for blood transfusion were also contributed to morbidity following the procedure. This is followed by wound infection and postoperative pyrexia. Better morbidity definitions and data is needed to fully assess the rates of morbidity associated with caesarean sections.

The most frequent indication reason for caesarean section was failure to progress and cephalo-pelvic disproportion, this is possibly being over diagnosed and safe active management of labour should be encouraged, we do not have the figures of how many of these labours were augmented. The second most frequent cause was a previous caesarean section, as the caesarean section rises and with hospitals in LMIC reluctant to undertake a trial of vaginal birth after caesarean section (VBAC) this will only further increase the caesarean section rate and exacerbate the long term problem with associated such as ruptured uterus, placenta praevia and accrete in future pregnancies. Audits need to be done not just for caesarean outcomes, and but also audits of the

appropriateness of cesarean section are essential. Studies in the literature where this has been done found that suboptimal management occurred in large numbers of cases and that there was a lack of awareness and use of evidence-based guidelines, leading to unnecessary procedures.[83, 84] Robsons criteria for caesarean section may be helpful in monitoring caesarean sections in the future and follow trends so interventions can be better targeted. [85]

Caesarean section are commonly done either to save the mother or the fetus. However the very high rate of observed stillbirths and perinatal deaths in our review indicate the possibility of inappropriate indication for the procedure e.g. for a dead fetus or the procedure being done far too late, putting the mother at risk without the benefit of having a live baby. Current guidelines have moved away from recommending a set caesarean section rate, but recommend that every woman who needs a cesarean section should receive one in a timely manner. Ecological studies found that once the caesarean section rate reached 10-15% at a population level the mortality curve had no significant impact on maternal and infant mortality rates [86, 87], and the recent rise in caesarean section rate has been a cause for concern. With the global increase in caesarean sections, there is a need to ensure that only truly medically indicated caesarean sections take place and that they are done in a timely manner to reduce poor outcomes.

Caesarean section rates should be monitored and only necessary caesarean sections should be done. Improving access and infrastructure is essential but not without improving quality and safety. Strategies to reduce maternal mortality should include increasing the number of anaesthetists and obstetricians- or increase the numbers of people able to do caesarean sections by task shifting. Non-physician cadres should be adequately trained and supervised to ensure safe care. Implementation of simple

measures, such as the WHO ‘Safer Surgery’ checklist before and during surgery would minimise adverse outcomes.[58] Governmental and non-governmental organisations should prioritise investment in obstetric surgery, to implement the World Health Assembly’s resolution to include emergency and essential surgical care and anaesthesia as a component of universal health coverage.[59]

5.6: Conclusion

Caesarean section death rates are disproportionately high in LMIC. More needs to be done to increase access to caesarean section where they are needed, but also reduce the caesarean section rate where they are overused through targeted intervention. Efforts are needed to provide safe obstetric surgery by improving training, infrastructure and resources.

Chapter 6: Accuracy of on-site tests to detect anaemia in antenatal care: a systematic review

6.1:Abstract

Background:

Anaemia is a significant contributor to poor maternal and perinatal outcomes. Its prevalence in pregnancy varies but is estimated to be 42% in low- and middle-income countries. Testing for anaemia is poorly done in these countries especially in rural settings, where diagnosis is often based on symptoms and physical examination. Onsite tests are available but their accuracy is unclear. We carried out a systematic review to determine the accuracy of on-site tests used to detect anaemia in pregnancy.

Methods:

Medline, Embase, Scopus, CINAHL and Web of Science were searched from inception till February 2016. Background information was extracted as well as true positive, true negative, false positive and false negative rates. QUADAS-2 tool was used to assess study quality. Sensitivity, specificity, likelihood ratios and post-test probabilities were calculated for each test.

Findings:

Ten studies (4023 pregnant women) were included. Half of the studies had a low risk of bias for study design and all had a low risk of bias for applicability. Of the tests identified to detect anaemia at a haemoglobin concentration of <110 g/l, Copper sulphate had a sensitivity 97% (95% CI 88-100) and a specificity 71% (95% CI 55-85), Sahli's method had a sensitivity 86% (95% CI 75-94) and a specificity 83.3% (95%

CI 68-93) and HemoCue had sensitivity of 85% (95% CI 79-90) and a specificity 80% (95% CI 76-83).

Conclusion:

There should be wider availability of onsite tests found to be accurate in this review, to help improve detection of anaemia in pregnant women.

Publication arising from this Chapter:

Included in new WHO Antenatal care Guidelines:

WHO recommendations on antenatal care for a positive pregnancy experience, World Health Organization, Nov 2016, P. 41-42

Sobhy s, Rogosinska E, Khan KS, Accuracy of on-site tests to detect anaemia in antenatal care: a systematic review, 2017 - Submitted to IJGO

6.2: Introduction

Maternal anaemia, measured as low haemoglobin concentration (Hb) in the blood remains a serious global health problem. It affects 42% of women in pregnancy, with Africa and Southeast Asia being the most affected.[88, 89] An estimated 56 million pregnant women are affected by anaemia, a condition that declined by only 5% since 1995.[88] Anaemia is considered the most common indirect cause of adverse maternal outcomes and maternal death, contributing to up to 50% of both.[22] The risks of macerated late fetal death, fresh stillbirth, and early neonatal death were also consistently increased in mothers with severe anaemia.[23] Studies have shown a link between anaemia and low birth weight, small for gestational age and preterm birth.[89, 90] Women with anaemia are less likely to withstand the adverse effects of excessive blood loss and are more susceptible to infection, fatigue, and depression.[91] Anaemia pre-operatively also increases risks of poor outcomes.

Testing for anaemia is poorly done in low and middle-income countries especially in rural settings. In this setting, diagnosis of anaemia is often based on symptoms and physical examination rather than on objective testing, and so anaemia goes undetected and untreated.[92] Although laboratory tests such as haemiglobincyanide by spectrometry is the gold standard, this is expensive and not widely available.[93] As a result, simple, safe, accurate and low-cost haemoglobin assessment tools are needed. [94] Tests currently available in use are HemoCue, WHO color scale, and copper sulphate, however, their accuracy is unclear.

Reviews exist on the accuracy of tests such as the WHO colour scale, HemoCue, and non-invasive methods, but these did not include studies conducted in antenatal care setting exclusively.[95, 96] Anaemia in pregnancy is diagnosed using a different threshold

compared to a non-pregnant population.[97] The use of a mixed population in previous reviews is a key deficiency because spectrum variation has an impact on accuracy.[98, 99] Reviews have also previously used HemoCue as a reference,[96] since this is more widely available in low-income countries, however studies have shown that Haemoglobin concentration measured by HemoCue has a lower precision than that of automated analysers, and its precision is also variable by sample type.[100-104]

This systematic review bridges highlighted gap assessing the accuracy of the on-site test in detecting anaemia in pregnant women.

6.3: Methods

We undertook the systematic review using a prospective protocol (PROSPERO No.CRD42015029172) in line with current recommendations and reported according to PRISMA guidelines.[40]

Literature search

We searched Medline, Embays, Scopus, CINAHL and Web of Science from inception until February 2016 and with no language restrictions. We used MeSH headings, text words and word variants for "pregnancy" and combined them with terms for "An(a)emia " and "H(a)emoglobin", with exclusion (NOT) for words relating to the fetus such as cord, neonatal and placenta, (Appendix 12). Additionally, we searched the reference lists of the included studies and relevant reviews for eligible studies.

Study selection

Studies were selected in two stages. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second, we examined the full texts of the retrieved papers. Two independent reviewers (SS, ER) selected the

papers against pre-specified inclusion criteria. Any discrepancies were resolved through a discussion with a third reviewer (KSK). Studies were included if they met the following criteria: recruited pregnant women attending antenatal care; evaluated tests assessing Hb compared with a laboratory-based reference test.

Study quality assessment and data extraction

Two independent reviewers (SS and ER) undertook study quality assessment and data extraction, and any discrepancies were resolved with input from the third reviewer (KK). Data were extracted using a standardised, pre-piloted form. Information on the type of test, the setting, the type of sample (venous or capillary) and the type of practitioner doing the tests was included. Data were extracted for different thresholds of Hb reported in the studies. The definition of anaemia in pregnancy, per the World Health Organisation standards, is Hb concentration below 110 g/l[97], at sea level with three grades of severity; mild (109-100 g/l), moderate (990-700 g/l) and severe (<700 g/l). True positive, true negative, false positive and false negative rates were extracted for the reference test and index test in a 2x2 table. Where the sensitivity, specificity, positive and negative predictive values were presented, the parameters needed to assess accuracy were re-calculated.

Study quality was assessed using the QUADAS-2 tool independently by two reviewers (SS and ER).[99] Four domains were evaluated: patient selection, use of the index test implementation of the reference standard, and flow of patients through the study and timing of the index test(s) and reference standard ("flow and timing"). Each domain is assessed in terms of the risk of bias and the first three are also assessed in terms of concerns regarding applicability of the findings. The risk of bias was assessed as low, high or unclear for each domain. We considered a study to be of high quality if the

patients were selected in a consecutive or randomised manner, specific inclusion and exclusion criteria were applied, the index and reference standard tests were recognised and performed with an appropriate delay between them, and all patients received a laboratory based reference test.

Data analysis

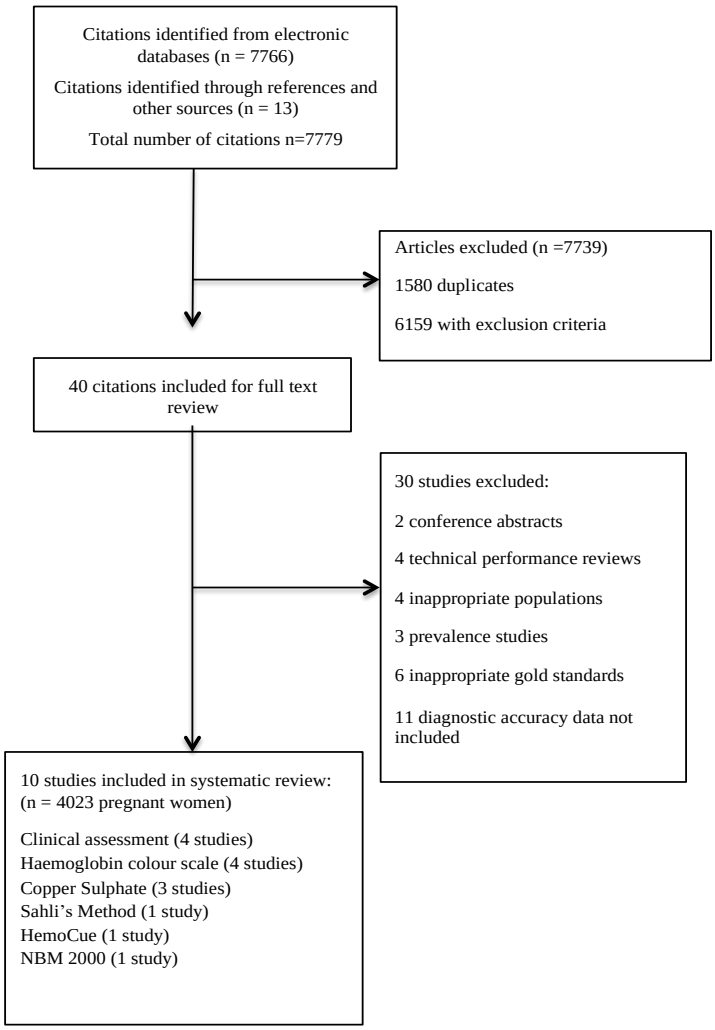
Numbers of true positive, false positive, true negative and false negative rates were obtained from the publication or, if necessary, calculated from the reported estimates. The study data was plotted in the receiving operating characteristic (ROC) space. Where we had a sufficient number of studies, we pooled the diagnostic accuracy parameters using a bivariate, hierarchical model (random effect).[105] If less than four studies reported accuracy of a given test, we pooled sensitivity and specificity, as well as likelihood ratios using univariate model.[106] We calculated 95% confidence intervals (CIs) for all estimates. The analyses were done using STATA software version 12.1.[48] Assuming a pre-test probability of 42% for Hb < 110g/l [89, 107] we calculated post test probabilities for a negative and positive test result using an online calculator.[108] We used a pre test probability of 8% for moderate anaemia and 1% for severe anaemia.[107] Due to limitations of available statistical methods we did not assess the publication bias.[109, 110]

6.4: Results

Out of 7776 citations, 10 studies were selected (Figure 19). These studies included 4023 pregnant women from seven low- and middle-income countries, South Africa (n=2), Malawi (n=1), Benin (n=1), Kenya (n=1), India (n=2), Pakistan (n=1) and Indonesia (n=2). Six tests were identified in the review and compared with a laboratory standard. Five studies reported data on clinical examination,[111-115] four on Haemoglobin Colour

Scale (HCS)[112-114, 116] and three reported on Copper sulphate test.[117-119] HemoCue[112], Sahli's haemoglobinometer[119]and NBM 2000[120]a non-invasive haemoglobin sensor, were reported on by one study each. The studies were all published between 1996 and 2016. The prevalence of anaemia (haemoglobin < 110 g/l)[97] across the studies varied from 23 - 77 % (appendix 13 details study characteristics).

Figure 19: Study selection for accuracy review for on-site tests to detect anaemia in pregnancy.



Quality assessment

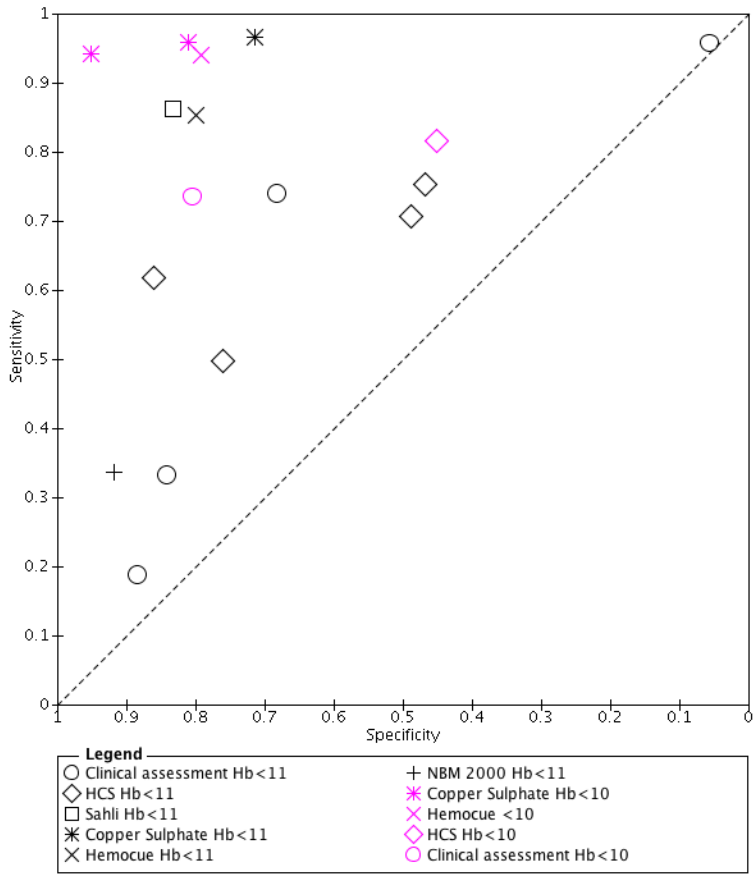
Half of all of studies (50%) had low risk of bias and low concern regarding applicability across all domains. Two studies (20%) had a high risk of bias regarding patient selection; and three studies (30%) had an unclear risk of bias as the recruitment process was not adequately described. One study had an unclear risk of bias regarding flow and timing. All studies had low risk of bias for applicability (Appendix 14).

6.41: Accuracy of the tests by disease severity

For mild anaemia (Hb <110 g/l) four tests provided diagnostic accuracy data: clinical assessment (4 studies, 1853 women), HCS (4 studies, 1051 women), HemoCue (1 study, 671women), Copper sulphate (1 study, 100 women), Sahli's method (1 study, 100 women) and NBM 2000 (1 study, 269 women) (Table 11).

In order of decreasing sensitivity values these were: Copper sulphate with sensitivity 97% (95% CI 88-100) and specificity 71% (95% CI 55-85), Sahli's method with sensitivity 86% (95% CI 75-94) and specificity 83% (95% CI 68-93), HemoCue with a sensitivity of 85% (95% CI 79-90) and specificity 80% (95% CI 76-83); HCS with a sensitivity of 67% (95% CI 56-76) and specificity of 67% (95% CI 48-82); clinical assessment with a sensitivity 56% (95% CI 19-92) and specificity 62% (95% CI 30-93), (appendix 4) and NBM 2000 with a sensitivity 34% (95% CI 27-41) and specificity 92% (95% CI 82-97) (Figure 20).

Figure 20: Overview of on-site test accuracy to detect mild anaemia (haemoglobin < 110 or < 100 g/l) among pregnant women in Receiver Operating Characteristic (ROC) Space



For moderate anaemia (Hb <80 g/l) one study provided diagnostic accuracy data for three tests: clinical assessment (644 women), HCS (641 women) and HemoCue (671women). Another study provided data for Copper sulphate (100 women) and Sahli's method (100 women) for a cut-off of Hb <88 g/l.

In order of decreasing sensitivity values these were: HemoCue had a sensitivity 97% (95% CI 85-99) and specificity 94% (95% CI 92-96%); Sahlis method had a sensitivity 83% (95% CI 85-98%) and specificity 93% (95% CI 85-98%); HCS, sensitivity 82% (95% CI 61-93%), and specificity 76% (95% CI 73- 79%), Copper sulphate with sensitivity 75% (95% CI 55-89%) and specificity 94% (95% CI 86-98) and clinical assessment with sensitivity 62% (95% CI 44-77) and specificity 76% (95% CI 72-78) (Table 12).

For severe anaemia, defined as Hb less than 60 g/l, one study provided diagnostic accuracy data for three tests: clinical assessment (644 women), HCS (641 women) and HemoCue (671 women) and another study provided data for Copper sulphate (100 women) and Sahli's method (100 women) for Hb less than 68 g/l.

In order of decreasing sensitivity values these were: HemoCue a sensitivity 83% (95% CI 44-97) and specificity 99% (95% CI 98-100), Sahli's method had a sensitivity of 75% (95% CI 35-97) and specificity 93% (95% CI 86-98), Copper sulphate had a sensitivity 83% (95% CI 24-91%) and specificity 99% (95% CI 86-98%), HCS with sensitivity 50% (95% CI 15-85%) and specificity 98% (95% CI 97-99%), and clinical assessment with sensitivity 50% (95% CI 15-85%) and specificity 75% (95% CI 71-78%) (Table 12).

Table 12: Accuracy of on-site tests used to diagnose anaemia in pregnancy

							Likelihood ratio (95% CI)		*Post test probability %	
Threshold	**Index test**	**No. of studies**	**Prevalence %(95%CI)**	**No. of women**	**Sensitivity %(95%CI)**	**Specificity %(95%CI)**	**+ve test result**	**-ve test result**	**+ve test result**	**-ve test result**
Mild Hb <110g/l	Clinical	4	47 (27-72)	1853	56 (19-92)	62 (30-93)	1·7 (1·0-2·9)	0·57 (0·33-1·03)	55	29
	*HCS	4	42 (17-67)	1051	67 (56-76)	67 (48-82)	2·0 (1·3-3·1)	0·50 (0·40- 0·62)	59	27
	*$CUSO_4$	1	58 (48-67)	100	97 (88-100)	71 (55-85)	3·4 (2·1-5·5)	0.05 (0·01-0·19)	71	3.5
	SAHLI method	1	58 (48-67)	100	86 (75-94)	83 (68-93)	5·2 (2·6-10·3)	0·17 (0·09-0·32)	79	11
	NBM 2000	1	77 (72-82)	269	34 (27-41)	92 (82-97)	4·1 (1·7-9·7)	0·72 (0·64- 0·82)	75	34
	HemoCue	1	23 (20-27)	671	85 (79-90)	80 (76-83)	4·3 (3·5-5·1)	0·18 (0·12- 0·27)	76	12
Mild Hb <100g/l	Clinical	1	52 (49-55)	644	73 (70-78)	80 (77-84)	3·8 (3·1-4·6)	0·33 (0·28-0·39)	73	19
	HCS	1	32 (28-35)	641	82 (76-86)	45 (41-50)	1·5 (1·3-1·7)	0·40 (0·30- 0·55)	52	23
	$CuSO_4$	2	13 (7-9)	549	96 (89-100)	89 (72-99)	9·3 (2·1-40·4)	0·06 (0·02-0·17)	87	4.2
	HemoCue	1	32 (29-36)	671	94 (90-97)	79 (75-83)	4·5 (3·7-5·4)	0·08 (0·05-0·13)	76	5.5
Moderate Hb <80g/l	Clinical	1	5 (3-6)	644	62 (44-77)	76 (72-78)	2·5 (1·9-3·5)	0·50 (0·31- 0·80)	22	5.3
	HCS	1	3 (2-5)	641	82 (61-93)	76 (73- 79)	3·4 (2·7- 4·4)	0·24 (0·10-0·58)	27	2.6
	HemoCue	1	5 (4-7)	671	97 (85-99)	94 (92-96)	16·7 (12·2-23·0)	0·03 (0·01- 0·22)	65	0.33
	$CuSO_4$ *(Threshold 88)	1	28 (20-37)	100	75 (55-89)	94 (86-98)	13·5 (5·1-35·8)	0·26 (0·14-0·50)	60	2.8
	Sahli *(Threshold 8.8)	1	28 (20-37)	100	83 (63-94)	93 (85-98)	11·8 (5·0-28·0)	0·10(0·09-0·43)	57	1.1
Severe Hb <70g/l	Clinical	2	7 (0-3)	1806	72 (47-97)	71 (34-97)	2·9 (1·1-8·2)	0.4(0·37-0·52)	20	3.4
	CUSO4	1	8 (4-15)	100	63%(24-91)	93 (86-98)	9·6 (3·7-24·6)	0.4(0·16-0·98)	46	3.4

	*(Threshold 6.8)									
	Sahli *(Threshold 6.8)	1	8 (4-15)	100	75%(35-97)	93 (86-98)	11·5 (4·8-27·5)	0·27(0·08-0·89)	50	2.3
Severe Hb<60g/l	Clinical	1	1 (0-2)	644	50% (15-85)	75 (71-78)	2·0 (0·74-5·3)	0·67(0·25-1·78)	**2.0**	**0.7**
	HCS	1	1 (0-2)	641	50 %(15-85)	98 (97-99)	31·9 (10·0-101·4)	0·51 (0·19-1·35)	**24**	**0.5**
	HemoCue	1	1 (0-2)	671	83(44-97)	99 (98-100)	138·5 (48·9-392·1)	0·17(0·03-1·00)	**58**	**0.2**

*HCS=Heamoglobin Colour scale, CUSO4= copper sulphate method

Pretest probability for Hb< 110g/l / Hb<100- 42%, Hb<80~~0~~- 10%, Hb,<70~~0~~- 8%, Hb<60~~0~~- 1%

6.5: Discussion

Copper sulphate, Sahli's method and HemoCue have the highest sensitivities (>85%) in detecting anaemia.

The review was conducted in a systematic manner, covered a wide range of tests and included women with a range of anaemia severity making the findings more generalizable across the spectrum of the disease. Included papers were predominantly of a high quality. The Cyanmethaemoglobin spectrophotometry method is the global reference standard for detecting haemoglobin concentration. One of the limitations of the review is that it included studies that used any laboratory tests as a reference standard, this included automated cell counters. Although these are calibrated against the reference standard this may have affected the accuracy of the test, however, this is unlikely to be significant.

In order to compare the accuracy of all identified tests, we used the univariate model to pool sensitivity and specificity estimates when fewer than four studies were available. This approach does not account for the correlation between both parameters as in bivariate model; however, the estimates obtained using both models are fairly similar.[121] There were not enough women in the studies with severe anaemia (Hb <60 g/l) therefore the accuracy of the data at this level may not be reliable.

Assuming a prevalence estimate for anaemia (Hb <110g/l) of 42%,[89] we calculated post-test probabilities for all evaluated tests. After the test, amongst test-negative women, using the Copper sulphate method the prevalence of women who do not have anaemia was reduced to 4%. Using Sahli's method this probability was reduced to 11% and for HemoCue, there was a reduction to 12%. The HCS performed only marginally better

(reduction to 27%), than clinical examination alone (reduction to 29%). Several reviews and studies have recommended the use of the HCS,[96] however, in our review this test had a high likelihood ratio for a negative test result suggesting it is not as clinically useful as advocated. More training would increase its accuracy as shown in studies, as it performs well under lab conditions.[122] NMB2000 the non-invasive haemoglobin probe had very poor sensitivity but high specificity, making this test better for ruling in the disease in the context of screening.

In LMIC where resources are limited, high cost, inadequate training and lack of facilities generally prevent the use of technologically advanced equipment, especially at a primary health care level.[123] Health workers, therefore, need a simple, cheap and robust device for measuring haemoglobin concentration[123], but this should not be at the expense of compromising accuracy. Deciding which is the 'best' test depends on many factors, such as cost, resources required, the setting in which it will be used, and the skills of the health care workers; therefore this may be better evaluated at the local level.

If screening for anaemia is used to decide who should be referred for further investigation and treatment than it is important that the screening test has a high sensitivity. This is imperative in the case of severe anaemia as it is important not to miss women with this condition, as this can have significant clinical implications to both mother and child.

Increasing a test's sensitivity usually results in a reduction in specificity.[124] Using tests with a high sensitivity but not very specific leads to unnecessary referrals for further investigation what adds to the cost of the health service and wastes valuable resources.[111]

However, cClinical implications of the test results also plays a big role, for anaemia the consequence of missing truly anaemic pregnant woman has more severe clinical implications than overtreatment. The majority of anaemia in these settings especially in pregnancy tends to be secondary to iron deficiency and therefore mild to moderate cases can be treated with iron tablets,[125] which tends to be well tolerated. For severe anaemia, the risk of treatment is greater as it may involve complex interventions including blood transfusions, the side effects of which can be serious including the spread of blood-borne disease.[126] Testing is also important to monitor the effects of any intervention or treatment given once the diagnosis is established.

More research needs to be done on this topic, as there were very few studies available. It will also be interesting to see how newer non-invasive tests, especially those using readily available technology such as mobile phones, will perform in the future.[127, 128] There are many studies assessing devices for the detection of anaemia, however these reported correlation coefficients which can be misleading and are less clinically useful as compared to sensitivity and specificity, studies reporting different parameters also limits the ability to perform meta-analysis of these studies, future studies should be encouraged to report these more useful accuracy parameters.

6.6: Conclusion

Tests found to be accurate in this review should be made more widely available, in order to help improve the detection of anaemia.

Chapter 7: Maternal and fetal outcomes of tuberculosis during pregnancy and the postpartum period: A systematic review and Meta-analysis

7.1: Abstract

Background: There is dearth of data on the epidemiology, clinical features, and outcomes of active tuberculosis (TB) in pregnancy.

Methods: We conducted a systematic review and meta-analysis assessing maternal and perinatal outcomes in pregnant women with and without active TB, searching Medline, Embase, Web of science and Scopus from inception to October 2015. Two independent reviewers selected studies, undertook quality assessment and data extraction. Information on study design, setting, population characteristics, TB diagnosis and treatment as well as obstetric outcomes were obtained. Risk of bias was assessed using the Newcastle-Ottawa scale. Data were pooled and Odds ratios using random effects modelling was calculated for maternal and perinatal outcomes. ~~Standard~~ Weighted mean differences were calculated for gestational age and birth weight.

Findings: We included 13 studies (3384 pregnancies associated with active TB, 112530 pregnant women without TB). Using Newcastle Ottawa scale, 7 studies had a low risk or medium risk of bias and 6 had a high risk of bias. There was a significantly increased risk of poor fetal outcomes; perinatal death (OR 4.2 95% CI 1.5-11.8 I2 57.2%) preterm birth (OR 1.7, 95% CI 1.2-2.4, $I^2$66..5%), low birth ~~rate~~ weight (OR1.7 95% CI 1.2 -2.4, I^2 53.7%) and birth asphyxia (OR 4.6 95%CI 2.4-8.6, I I^2 46.3), Maternal outcomes were also significantly worse; maternal morbidity (OR 2.8, 95%CI 1.7-4.6, I^2 60.3%), anaemia (OR

3.9, 95%CI 2.2-6.7, I^2 29.8%) and Caesarean delivery (OR 2.1, 95%CI 1.2-3.8, I^2 61.1%), compared to pregnant women without active TB.

Conclusion: TB in pregnancy results in poor maternal and fetal outcomes. Early diagnosis and treatment is important to help prevent poor outcomes.

Publication arising from this Chapter:

Sobhy S, Babiker ZOE, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. BJOG 2016*; DOI:* 10.1111/1471-0528.14408.

Poster presentation at British maternal and fetal medicine society (BMFMS) conference 2016 and associated abstract publication:

Sobhy S, Babiker ZOE, Zamora J, Khan KS, Kunst H Maternal and fetal outcomes of tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis, poster Poster Global Health. BJOG 2016;123:107-16. DOI: 10.1111/1471-0528.13990

7.2: Introduction

Tuberculosis (TB) is still one of the world's deadliest communicable diseases. Although the greatest burden of TB infection is in resource-limited countries, resource-rich countries have seen a resurgence of TB, largely as a result of an increase in migrant populations in these countries.[129] In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease.[130] Interestingly, South-east Asia, Western pacific and African regions, which have the highest TB disease burden, also have the highest maternal mortality rates. In women, TB is now among the three leading causes of death in reproductive age (15–45 years).[131] In 2013, an estimated 510 000 women died as a result of TB, more than one third of whom were HIV-positive.[130] It is, expected that the incidence of TB among pregnant women would be as high as, if not higher than in the general population.[132, 133] It is estimated that as many as 216500 (95% CI 192100-247000) pregnant women have active TB globally.[134]Indirect maternal deaths now account for 28% of total maternal deaths; these include TB infections.[34]

Studies of active TB in pregnancy have shown varied results and the relationship between TB and adverse pregnancy outcomes remains unclear. Quantitative data synthesis can overcome this deficiency and imprecision. Reviews exist on this topic, but none have been conducted in a systematic manner or included meta-analysis. To collate the evidence on maternal and perinatal outcomes of pregnancies associated with active TB we conducted a systematic review.

7.3: Method

Study selection

Major databases; Medline, Embase, Web of science and Scopus databases were searched using the subject keywords and MeSH terms for TB, pregnancy, maternal morbidity, mortality and perinatal morbidity, mortality. We also searched all references of review papers and relevant articles. The search was not restricted by language or date, and is up to date till October 2015 (Appendix 15). Additionally, we searched the reference lists of the included studies, and relevant reviews and articles for eligible papers. Two independent reviewers (S.S, H.K) identified all relevant abstracts using a pre-specified inclusion and exclusion criteria in a two- stage process. In the first stage, we screened the titles and abstracts of all citations for potentially relevant papers. In the second stage, we examined in detail the full texts of the retrieved papers. Any discrepancies were resolved after discussion with a third reviewer (KK). Studies were included if they had a cohort of pregnant women with TB and pregnant women without TB as a control group that had pregnancy outcome data included.

Quality assessment of the included studies

Quality assessment of included studies was carried out using the Newcastle-Ottawa scale to evaluate the risk of bias in the selection, and comparability of subjects and cohorts and of the outcome.[46] Two independent reviewers (SS and HK) allocated stars for adherence to a pre-specified criterion. Studies that scored four stars for selection, two stars for comparability and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. Any study with a

score of one for selection or outcome ascertainment, or zero for any of the three domains was deemed to have a high risk of bias.

Data extraction and analysis

Using a Piloted data extraction form, information on study design, setting, population characteristics, TB diagnosis and treatment as well as obstetric outcomes were obtained. Two independent reviewers (SS and HK) extracted data in 2x2 tables for comparative dichotomous outcomes.

The outcomes assessed were maternal mortality defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.[(1)] Deaths from active TB are classified as an indirect maternal death. Maternal morbidity was defined as any health condition attributed to and/or aggravated by pregnancy and childbirth that had a negative impact on the woman's wellbeing.

Perinatal death included intrauterine fetal deaths after 28 completed weeks of gestation, stillbirth and early neonatal death until one week after birth.[(135)] Apgar scores were classed as low if they were less than or equal to 7. Preterm birth was defined as babies born alive between 28- 37 weeks of completed pregnancy. We accepted the authors' definitions of other fetal complications such as small for gestational age.

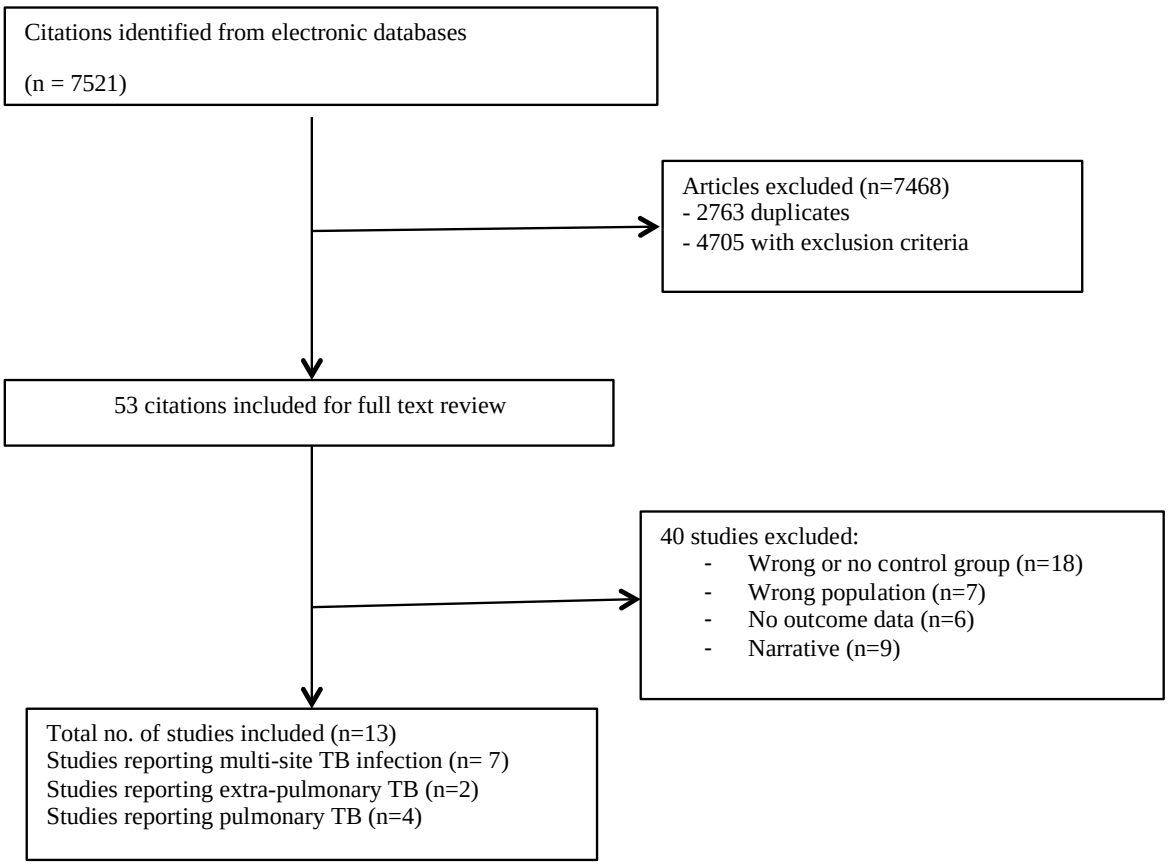
We calculated the odds ratios of adverse pregnancy outcomes in women with TB for individual studies and pooled the numbers for an overall estimate, using a random effects

model. For continuous data, after pooling the standard mean difference was calculated. We assessed for heterogeneity using the I^2 tests. All analyses were undertaken using Stata SE.12 statistical software.[48]

7.4: Results

Thirteen studies out of 7521 studies met the inclusion criteria (Figure 21).

Figure 21: Study selection process for the systematic review on pregnancy outcomes in women with Tuberculosis.

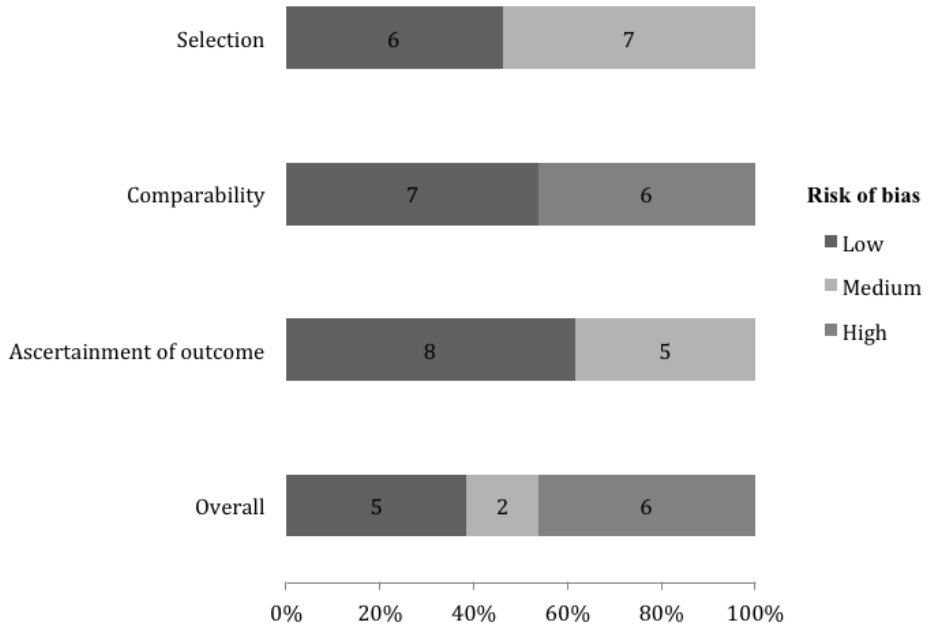


The studies included 3384 pregnant women with active TB and 119448 pregnant women without TB as controls. Ten studies reported on pre-term birth as an outcome, six studies

reported on low birth weight, seven on perinatal death, four on congenital anomalies, three on asphyxia and two reported on small for gestational age and acute fetal distress. Low Apgar score at one minute was reported on by one study. For maternal outcomes, five studies reported maternal death as an outcome, five on maternal morbidity, five reported on delivery by caesarean section, three reported on anaemia. Miscarriage and antenatal admission were reported on by one study each. Half the studies (6/13) were from low income and middle-income countries and 61% (8/13) studies were published after year 2000. Study characteristics are shown in appendix 16.

The quality of the studies is shown in figure 22. 100% of included studies had low or medium risk of bias for study selection, 53% had low risk of bias for comparability of cohorts. The risk of bias for outcome assessment was low or medium in 100%. Overall 53% of studies had low or medium risk of bias.

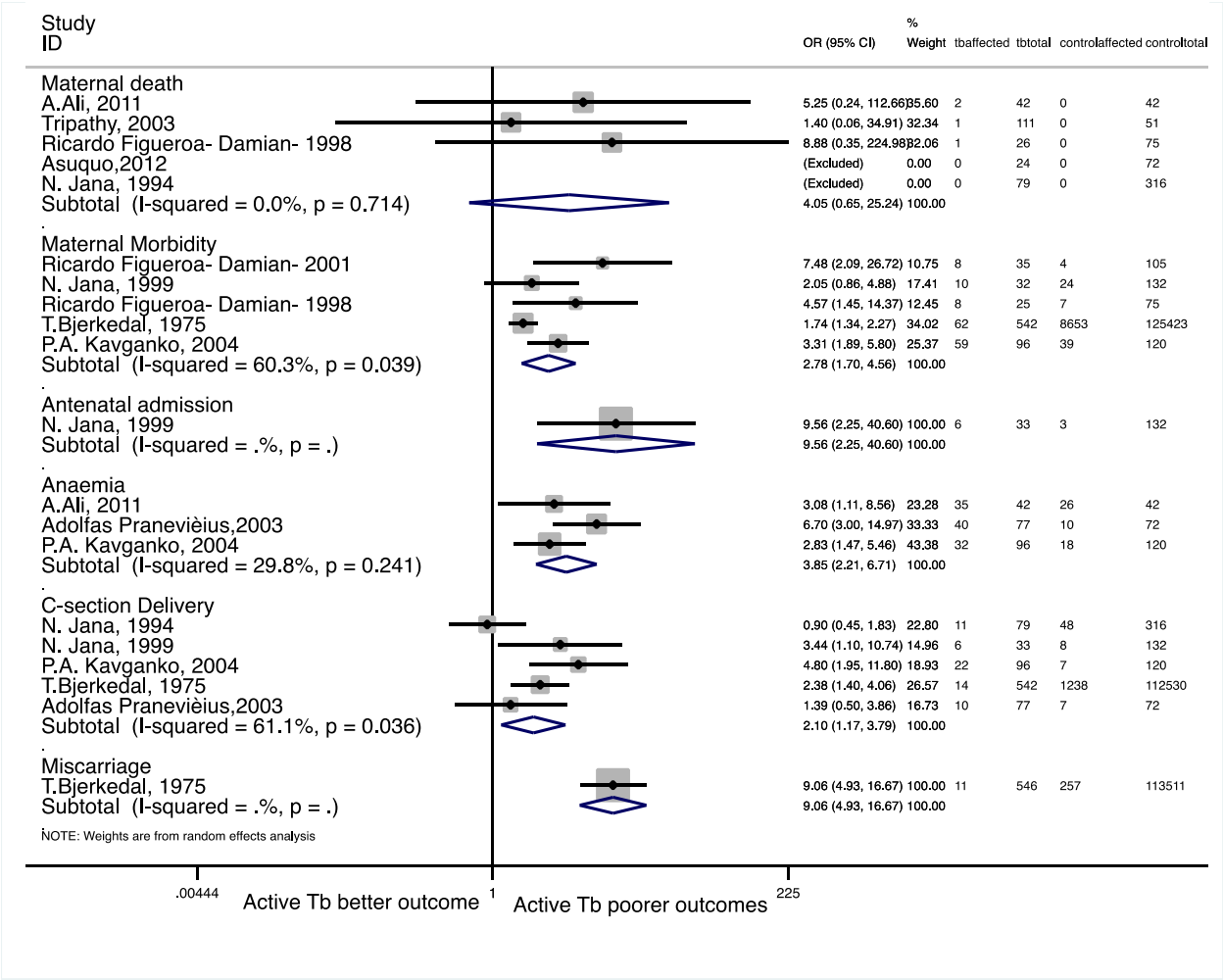
Figure 22: Quality assessment using the Newcastle-Ottawa Scale of studies included in a review on pregnancy outcomes in women with Tuberculosis



7.41: Maternal outcomes in women with TB

Maternal outcomes were poorer in pregnant women with TB compared to those without. Although not significant the trend towards more maternal deaths in women with TB was present (OR 4.1 95%CI 0.65-25.2, I^2 0%). Of the women who died 50% had HIV co-infection. Maternal morbidity was almost 3 times greater (OR 2.8, 95%CI 1.7-4.6, I^2 60.3%) compared to the control group. The odds of antenatal admission was 9 times greater (OR 9.6 95% CI 2.3-40.6). Anaemia was increased 4 times in the TB group (OR 3.85 95% CI 2.21-6.71 $I^2$29.8%). Caesarean section was performed twice as often in women with TB (OR 2.10 95% CI 1.17-3.79 I^2 61%). The odds of miscarriage were 9 times greater in women with TB (OR 9.06 95% CI 4.93-3.16.67). (Figure 23)

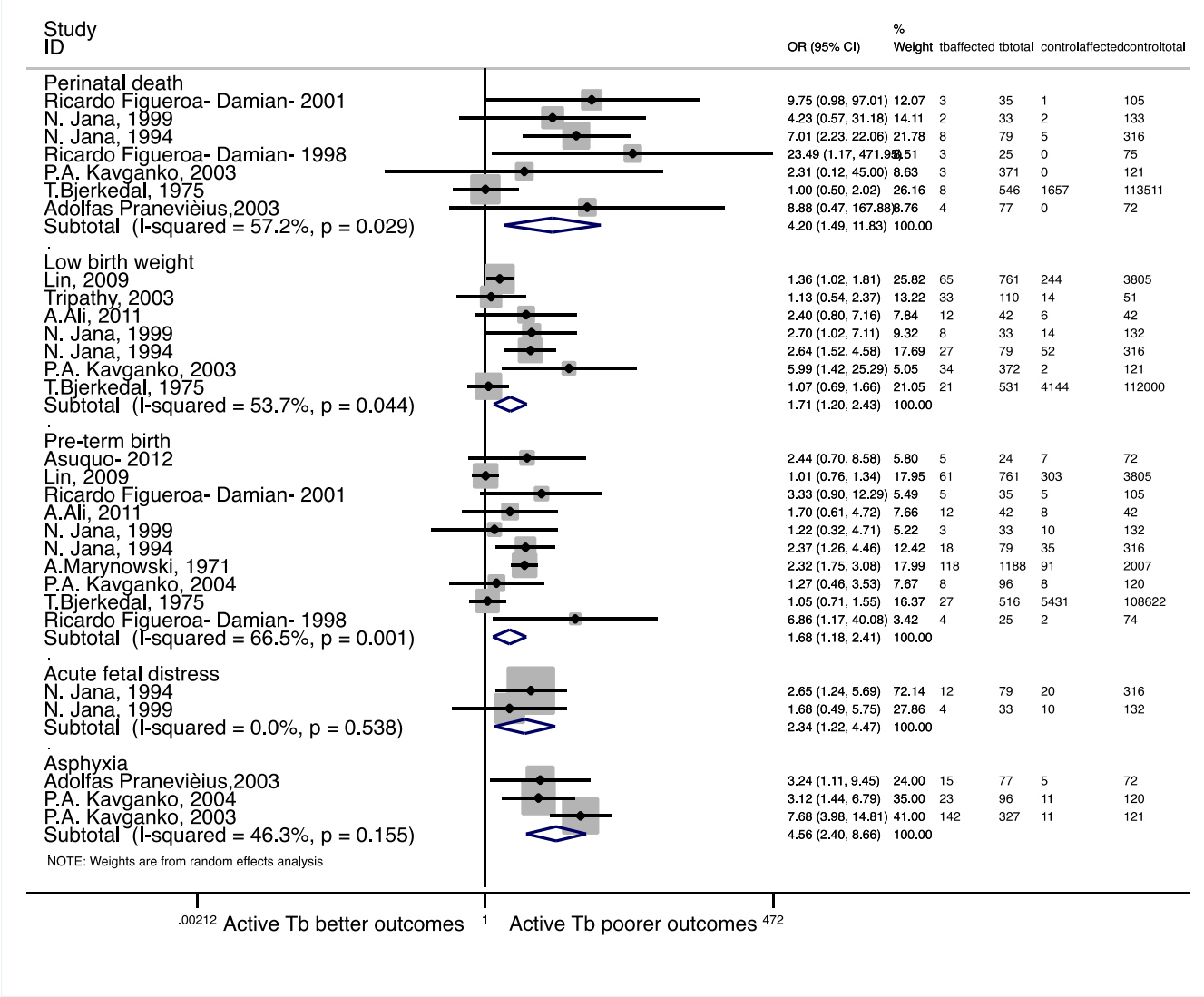
Figure 23: Maternal outcomes in women with Tuberculosis



7.42: Perinatal outcomes in women with TB

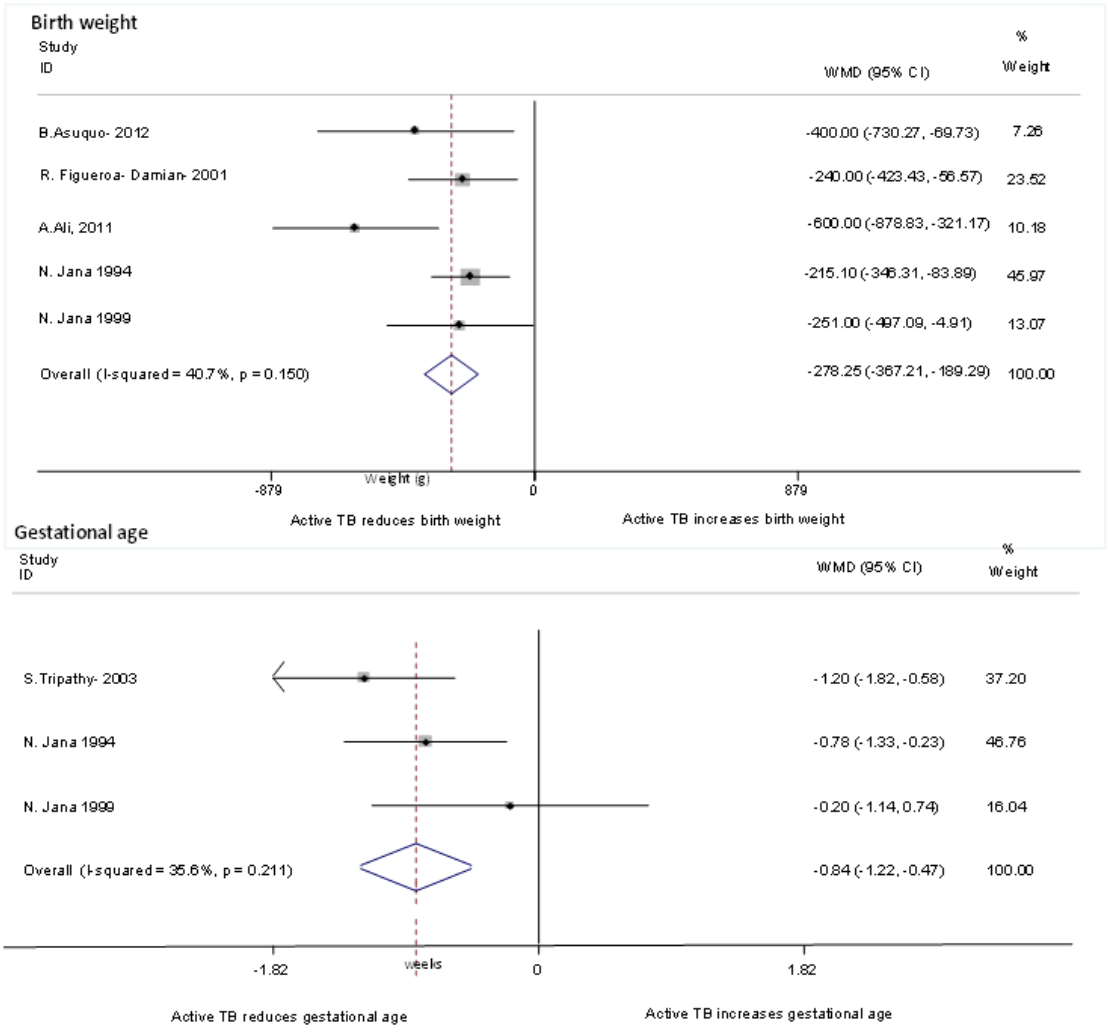
Of the perinatal outcomes, perinatal death was 4 times greater in patients with active TB (OR 4.2 95% CI 1.49 -11.83, $I^2$57.2%), preterm birth was 1. 6 times greater, (OR 1.7, 95% CI 1.2-2.4, $I^2$66.5%), low birth weight was 1.7 times greater (OR 1.7 95% CI 1.2 -2.4, I^2 83.1%). low Apgar score was 5 times greater (OR 5.71, 95% CI 1.4 -22.6) and acute fetal distress was 2.3 times greater (OR2.34, 95% CI 1.2 -4.5 I^2- 0%) compared to babies born in the control group. There was a non-significant difference for outcomes small for gestational age and congenital anomalies (Figure 24).

Figure 24: Perinatal outcomes in women with Tuberculosis



Babies born to mothers with TB had a lower mean birth weight (~~Standard~~ Weighted mean difference -0.54. (95% CI -0.71- -0.38), I^2 0%) and were born at an earlier gestation (Standard mean difference -0.43. (95% CI -0.61- -0.25), I^2 43.8%) compared to those without TB. (Figure 25)

Figure 25: Weighted mean difference for perinatal outcomes in women with Tuberculosis



7.43: Breakdown by disease location

Location of TB; pulmonary and extra-pulmonary were reported on by 4 and 2 studies. There was not a significant difference in the maternal and perinatal outcomes by location of disease. However in one study[136] among those with extrapulmonary TB those that had lymph node TB had no adverse outcomes, but TB at other extra-pulmonary sites did adversely affect pregnancy outcomes. (Table 13)

Table 13: Outcomes of pregnancy in women with Tuberculosis by site of disease.

Outcome	No. of studies	Extra-pulmonary OR (95% CI)	No. of studies	Pulmonary OR (95% CI)	P value
Maternal morbidity	2	2·9 (95% CI 1·8–4·6)	1	1·7 (95% CI 1·3–2·3)	0·057
Caesarean delivery	2	4·2 (95% CI 2·1–8·6)	2	1·5 (95% CI 0·6–4·0)	0·087
Perinatal death	1	4·2 (95% CI 0·57–31·2)	1	2·4 (95% CI 0·53–11·2)	0·663
Low birth weight	1	2·7 (95% CI 1·02–7·1)	3	2.2 (95% CI 0·91–5·1)	0·757
Pre-term birth	2	1·3 (95% CI 0·56–2·8)	2	1·5 (95% CI 0·68–3·4)	0·867
Acute fetal distress	1	1·7 (95% CI 0·5–5·8)	1	2·7 (95% CI 1·3–5·7)	0·526
Asphyxia	1	3·1 (95% CI 1·4–6·8)	1	7·7 (95% CI 4·0–14·8)	0·082
Congenital anomaly	1	0·78 (95%CI 0·04–16·6)	1	3·3 (95% CI 0·41–26·6)	0·441

7.44: Breakdown of outcomes by timing of diagnosis and treatment

Breakdown of outcomes by timing of diagnosis and treatment showed significantly better outcomes when treatment was initiated in first trimester in comparison to second and third trimester. In one study of women who were treated in the first trimester none had preterm birth compared to 33% who initiated treatment in second and third trimester.[137] For those who were treated in first trimester there were no cases of perinatal death compared to 23% in those treated in second and third trimester. In mothers who were treated in the first trimester 28% developed complications compared to 60% in those who were treated in second and third trimester. Another study [138] also found that no woman who were treated in first trimester had a baby with low birth weight compared to 60% in those treated in second and third trimester

7.44: Discussion

Our systematic review highlights that maternal and fetal outcomes were consistently poorer in pregnant women with active TB compared to those without. There is a high-risk of maternal morbidity, anaemia, perinatal death, preterm birth, low birth weight and fetal distress in pregnant women with active TB and this risk was higher when anti tuberculous treatment (ATT) was started late or not received at all.

The systematic review was carried out with an exhaustive literature search. It is the first review that systematically evaluates the risk of active TB in pregnancy. The review was carried out in a stringent manner to reduce bias. Although the studies included a significant number of patients with active TB, not all studies had data available for all maternal and fetal outcomes. Not all studies included information on disease location, type, length or complications of ATT, limiting sub- group analysis. Some maternal and fetal outcomes had moderate to high heterogeneity but there was insufficient data to do a subgroup analysis to explore this further. The strength of this review is that it provides the current best evidence summary exploring studies' characteristics quality and results, which leads to a deeper insight into the topic than that afforded by individual studies.

The effects of active TB on pregnancy may be influenced by many factors, including the extent of the disease, the presence of pulmonary TB vs extra-pulmonary, other comorbidities and the timing of diagnosis and initiation of treatment. Over 50% of maternal mortality occurring in mothers with TB in pregnancy is thought to be due to co-infection with HIV.[139] Unfortunately there were not many women with HIV co-infection included in our review but it is likely that the outcomes would be even worse in this group.

Clinical diagnosis of active TB in pregnant women can be difficult and there is often a delay in diagnosis due to the non-specific symptoms related to the physiological response to pregnancy[140]. Women who are pregnant are more likely to access healthcare, making pregnancy an important screening opportunity for TB especially in developing countries. Different screening tests for active TB have been used in antenatal care such as symptom check, routine sputum examination by smear [141, 142], and the Xpert® MTB/RIF assay[143], however there are no guidelines for routine screening for active TB in pregnancy. The tuberculin skin test and the interferon gamma release assays have been used to screen for latent TB infection (LTBI) in pregnancy.[144] The WHO recommends LTBI treatment for all HIV-positive pregnant women, however there are no WHO guidelines for LTBI screening and management of latent disease in HIV-negative pregnant women. In order to reduce poor maternal and fetal outcomes routine screening for active and latent TB needs to be part of standard antenatal screening (ANC) in order to identify active TB early and reduce the risk of progression in those who are latently infected. Early treatment especially in low-income countries, which have the greatest burden of disease, will decrease maternal and fetal morbidity and mortality**.**

Future large prospective studies are needed to examine the effect of active TB on maternal and fetal outcomes in pregnancy. Risk factors affecting outcomes such as HIV co-infection, site of disease, pulmonary or extra-pulmonary involvement, timing, type and length of ATT need to be further studied.

7.5: Conclusion

Active TB in pregnancy leads to poor maternal and fetal outcomes. There is an urgent need for active case finding and screening for LTBI in antenatal care in high incidence TB countries in order to initiate treatment promptly and improve outcomes.

Chapter 8: Conclusion

8.1:Summary of findings

This chapter provides an overview of the results of the individual chapters. Detailed results are included in the individual chapters. I have addressed the objectives pre-specified in my thesis by quantifying the rates of maternal death associated with pregnant women requiring anaesthesia in LMIC and associated risk factors including type of anaesthesia and type of

practitioner. I also quantified risk associated with type of anaesthesia in women with pre-eclampsia who are particularly high risk. I quantified the rates of maternal death and perinatal death associated with caesarean sections and associated risk factors including type of caesarean section, and type of surgeon. I explored causes of maternal death from both anaesthesia and caesarean sections. I explored the diagnostic accuracy of point of care tests used to diagnose anaemia and I investigated pregnancy outcomes in pregnant women with Tuberculosis.

The table below summarises the objectives of my thesis and a column of findings from the chapters of this thesis.

Table 14: summary of thesis

Chapter Number	Population	Intervention	Outcome(s)	Research Design	Results
Obstetric anaesthesia and caesarean section related mortality and morbidity					
3	Pregnant women in LMIC undergoing surgical procedure	Anaesthetic interventions	-Rate of anaesthesia attributable maternal deaths. -Rates of anaesthesia attributable deaths in women undergoing a surgical procedure.	Meta-analysis of observational studies	Anaesthesia was the primary cause of death in 1.2 per 1000 (95% CI 0.8 to 1.7, I^2 =83%) pregnancies exposed to surgery (44 studies; 632,556 pregnancies). Anaesthesia accounted for 2.8% (95% CI 2.4 to 3.4, I^2=75%) of all maternal deaths (95 studies; 32,149,636 pregnancies, 36,144 maternal deaths), 3.5% (95% CI 2.9 to 4.3, I^2=79%) of direct maternal deaths, and 13.8% (95% CI 9.0 to 20.7, I^2=84%) of deaths during or after caesarean section.
4	Pregnant women in LMIC undergoing anaesthesia for surgical procedure	Setting (urban/ rural) Practitioner (Physician / non physician) Type of anaesthesia (general/ regional)	Odds of Maternal death, admission to ITU and PPH. Fetal: Perinatal death, low Apgar scores. Odds of Maternal: Death, admission	Meta-analysis of comparative studies	Exposure to general anaesthesia increased the odds of maternal (OR 3.3, 95% CI 1.2 to 9.0, I^2=58%), and perinatal deaths (OR 2.3, 95% CI 1.2 to 4.1, I^2=73%) compared with regional anaesthesia (25 studies; 414,069 pregnancies).

			to ITU and PPH. Fetal: Perinatal death, low Apgar scores		The rates of any maternal death were higher when anaesthesia was administered by non-physician (9.8/1000, 95% CI 5.2 to 15.7, I^2 =92%) than physician anaesthetists (5.2/1000, 95% CI 0.9 to 12.6, I^2=95%).
4	Pregnant women with pre-eclampsia in LMIC undergoing anaesthesia for surgical procedure	Type of anaesthesia (general/ regional)	Odds of Maternal: Death, admission to ITU and PPH. Fetal: Perinatal death, low Apgar scores	Meta-analysis of comparative studies	Included 14 studies (10411 pregnant women with varying severity of pre-eclampsia) There was a seven-fold increase (OR 7.70, 95% CI 1.9- 31.0, I^2=58%)in maternal death in pre-eclamptic women undergoing caesarean section with general anaesthesia compared to regional anaesthesia, there was also an increase in pulmonary oedema (OR 5.16, 95% CI 2.5-10.4, I^2=0%) and Intensive care unit admissions ((OR 16.25, 95% CI 9.0- 29.5, I^2=65%). Administration of general compared with regional anaesthesia also increased the odds of perinatal death by two fold (OR 3.01, 95% CI 1.4-6.5, I^2=56%). and the odds of low Apgar score at 1 minute (OR 2.50, 95% CI 1.3-4.6, I^2=50%) and at 5 minutes (OR2.75, 95% CI 1.5-5.0,)
5	Pregnant women in LMIC	Cesarean section	Rates of maternal and perinatal mortality and morbidity in women having a caesarean section	Systematic review and meta-analysis	Of all maternal deaths 24% (95% CI 21.7 to 27, I^2=93.7%) had undergone a caesarean section with the highest rates in Latin America and the Caribbean and the lowest in East Asia and Pacific The overall rate of death in women undergoing a caesarean section was 4.8 per 1000 (95% CI 4.23 to 5.6, I^2 = 97%) procedures, with the highest rates in sub-Saharan Africa. The overall rate of stillbirth in women undergoing a caesarean section was 44 per 1000 procedures (95% CI 35.0 to 54.9, I^2 = 99%), and perinatal death was 73 per 1000

					caesarean sections (95% CI 60.0 to 88.4, I^2 = 99%).
5	Pregnant women in LMIC undergoing caesarean section	Type of caesarean section (emergency / elective & second / first stage) Type and grade of operating surgeon/ practitioner	Odds of Maternal death, admission to ITU, PPH, post partum infections, and surgical complications. Fetal: Perinatal death, low Apgar scores.	Meta-analysis of comparative studies	The odds of maternal death was doubled (95% CI 1.20 to 3.82, I^2=62%), and perinatal death was quadrupled (OR 4.24, 95% CI 2.56 to 7.10, I^2=83%) with emergency compared to elective caesarean section. Caesarean section that was performed in the second stage of labour increased the odds of maternal death by 12 fold (OR 12.27, 95% CI 2.87 to 52.49, I^2=0%), and perinatal death (OR 9.23, 95% CI 4.24 to 20.10 compared to those performed before full dilatation. There was an increase in wound dehiscence by non-physicians clinicians, and there was an increase in hysterectomy by physicians performing caesarean sections.
	Testing for anaemia in pregnancy				
6	Pregnant women in LMIC with suspected anaemia	Tests used to diagnose anaemia: -WHO colour scale - HemoCue -Copper sulphate, -NBM 80, -Sahli's test -Clinical assessment	Sensitivity and specificity of tests to diagnose anaemia.	Meta-analysis of diagnostic test accuracy studies	Ten studies (4023 pregnant women) were included. Of the tests identified to detect anaemia at a haemoglobin concentration of <110 g/l, Copper sulphate had a sensitivity 97% (95% CI 88-100) and specificity 71% (95% CI 55-85), Sahli's method had a sensitivity 86% (95% CI 75-94) and a specificity 83.3% (95% CI 68-93) and HemoCue had sensitivity of 85% (95% CI 79-90) and a specificity 80% (95% CI 76-83).
	Infectious diseases: Tuberculosis in Pregnant women.				
7	Pregnant women in LMIC	Tuberculosis	Maternal death, maternal morbidity, anaemia, and caesarean delivery. Perinatal mortality, low Apgar score, low birth weight and preterm birth.	Systematic review and meta-analysis of controlled studies.	We included 13 studies (3384 pregnancies associated with active TB, 112530 pregnant women without TB). There was a significantly increased risk of poor fetal outcomes; perinatal death (OR 4.2 95% CI 1.5-11.8 I2 57.2%) preterm birth (OR 1.7, 95% CI 1.2-2.4, $I^2$66..5%), low birth rate (OR1.7 95% CI 1.2 -2.4, I^2

	53.7%) and birth asphyxia (OR 4.6 95%CI 2.4-8.6, I I^2 46.3). Maternal outcomes were also significantly worse; maternal morbidity (OR 2.8, 95%CI 1.7-4.6, I^2 60.3%), anaemia (OR 3.9, 95%CI 2.2-6.7, I^2 29.8%) and Caesarean delivery (OR 2.1, 95%CI 1.2-3.8, I^2 61.1%), compared to pregnant women without active TB.

Anaesthesia and caesarean section-attributed maternal and perinatal mortality, and risk factors for complications in LMIC

I undertook the largest systematic reviews to-date on maternal and fetal outcomes associated with anaesthesia and caesarean section. Anaesthesia and caesarean sections are major contributors to maternal and perinatal deaths in LMIC. General anaesthesia is associated with worse outcomes for the mother and fetus and should be avoided unless clinically necessary. The main cause of death from general anaesthesia was airway complications. I found worse outcomes when non- physician anaesthetists administered anaesthesia, this cadre of health workers need better training and support to ensure safe care. Second stage caesarean section was a particular risk factor for caesarean section outcomes, with high rates of mortality and morbidity. I found the main causes of death following caesarean section so that these can be prevented. I identified regions and countries where outcomes were poor so interventions can be targeted.

Anaesthesia-attributed maternal and perinatal mortality in women with pre-eclampsia in LMIC

I found that in women with pre-eclampsia the risk of maternal mortality following general anaesthesia was almost double that of the general obstetric population. I also found a significant risk of intensive care admission, pulmonary oedema, postpartum haemorrhage and hypertension intra- and postoperatively following general anaesthesia. Training is needed in general anaesthesia to reduce risk when this method is required and regional anaesthesia should be otherwise recommended.

Anaemia in pregnancy: testing in antenatal care

Anaemia is associated with maternal mortality and morbidity; furthermore anaemia is very prevalent in pregnancy although the severity of disease varies. In settings where full blood count testing is not available, we found on-site haemoglobin testing with a haemoglobinometer should be recommended over the use of the haemoglobin colour scale which was previously recommended or clinical tests as the method for diagnosing anaemia in pregnancy. Older tests were also found to be accurate like the copper sulphate and Sahlis method, however more research is needed into why the use of these methods are no longer prevalent or advocated.

TB In pregnancy: maternal and perinatal outcomes

I found that pregnant women with TB suffered worse outcomes compared to those without the disease; women with an early diagnosis and appropriate treatment for the disease had better outcomes than those who were diagnosed late.

8.2: Strengths and limitations

The reviews were prospectively registered and followed appropriate protocols. Extensive literature searches using major databases were done without language restrictions to avoid missing studies. Study selection, data extraction and quality assessments were done in duplicate to minimise bias and ensure accuracy of data. Sensitivity analyses were planned a priori and Meta-analyses was performed where appropriate; We also assessed for heterogeneity and carried out meta-regression where possible to explore potential sources.

The main limitation throughout the reviews was heterogeneity of data. There was significant heterogeneity in our findings despite adjusting for various factors, reflecting the variation in population, risk factors, setting and outcome. Due to the non-randomised nature of the studies used, there were confounding factors, which could not always be controlled for. For the reviews on rates of anaesthesia and caesarean section mortality, the majority of studies used were observational, which has limitations. We were limited by the differences in reporting of outcomes, and accepted the author's definitions, which may have created heterogeneity. There were paucity of data from some regions and countries so comprehensive global analysis could not be achieved.

8.3: Implications for clinical practice, research and policy

Efforts are needed to provide safe obstetric surgery by improving training, infrastructure and resources. Training is needed in general anaesthesia administration including the management of airway complications, to be able to deal with problems swiftly. Training is also needed in anaesthetic management of high risk women such as those with pre-

eclampsia where the potential for complications is much greater, regional anaesthesia in this subgroup should be recommended unless otherwise contraindicated.

More needs to be done to ensure that caesarean section is performed for clinical indication, and alternate options such as instrumental delivery should be considered prior to embarking on second stage caesarean section. Strategies to reduce maternal mortality should include increasing the number of anaesthetists and obstetricians, resources including the availability of blood, and the level of training in LMIC. Implementation of simple measures, such as the WHO 'Safer Surgery' checklist before and during surgery would minimise the adverse outcomes.[58]

Further prospective research is needed to help address the gap in data regarding rates of maternal morbidity related to caesarean section. Large studies are required to compare the outcomes of physician and non-physician anaesthetists to ensure the safety of non-physician anaesthetists before task shifting can be recommended. No doubt they are a very valuable group of anaesthetic workers however further training, continuing professional development and supervision is required at present.

Diagnosing anaemia in pregnancy is important. Increasing access of accurate point of care tests should improve the diagnosis of anaemia in LMIC, firstly so treatment can be initiated, but also especially in severe cases the appropriate place of delivery can be advised. Preventative measure and maternal education of the importance of a good diet and engagement with antenatal care providers is required. Large-scale tests are needed into the testing of anaemia and to also investigate if the trimester tested or type of blood sample affects the results.

Women make up a large proportion of the TB burden and pregnancy is a good time to capture women who would otherwise not interact with healthcare workers. Concerted effort is needed to integrate tuberculosis prevention, diagnosis, and treatment into maternity health services with active screening especially in TB endemic areas and high HIV regions, this will not only lead to better maternal and perinatal outcomes but also help with the overall WHO END TB agenda.[145] Treatment for latent tuberculosis infection can also be initiated for pregnant women who are at high risk of disease progression.[146] Women with TB should also be better monitored throughout pregnancy in order to detect any potential complications and act on these early. More research is needed into the screening methods used in pregnancy for active and latent disease. Studies are also needed to investigate if latent TB also carries high maternal and perinatal morbidity and if prophylaxis should be given in endemic areas. Large prospective studies are needed to examine the effect of active TB on maternal and fetal outcomes in pregnancy. Risk factors affecting outcomes such as HIV co-infection, site of disease, timing, type and length of treatment also need to be further studied.

APPENDICES

APPENDIX 1: My role in the thesis

Chapter 3:

I was involved in the conception of the research question, and designed the protocol. Along with Dr. Kuhan D, I undertook literature search, study selection and data extraction. I carried out the

data analysis with help from Javier Zamora and David. I designed the tables, figures and appendices and wrote the first draft of the manuscript.

Chapter 4

I was involved in the conception of the research question, and designed the protocol. Along with Dr. Kuhan D, I undertook literature search, study selection and data extraction, I also carried out the data analysis. I designed the tables, figures and appendices and wrote the first draft of the manuscript.

Chapter 5

I was involved in the conception of the research question, and designed the protocol. Along with Nilaani Murugesi. Joshua Vogel from WHO provided access to WHO multi country and global survey data. I undertook literature search, study selection and data extraction. Javier Zamora and David M helped with statistical analysis. I designed the tables, figures and appendices and wrote the chapter.

Chapter 6

I was involved in the conception of the research question, and designed the protocol. Along with Ewelina Rogozinska , I undertook literature search, study selection and data extraction. Ewelina helped with statistical analysis. I designed the tables, figures and appendices and wrote the first draft of the manuscript.

Chapter 7

I was involved in the conception of the research question, and designed the protocol. Along with Dr Heinke Kunst, I undertook literature search, study selection and data extraction. I carried out the statistical analysis with advice from Javier Zamora. I designed the tables, figures and appendices and wrote the first draft of the manuscript, with input from Prof Khalid khan, and Dr. Heinke Kunst

APPENDIX 2. Search strategy for systematic review on anaesthesia-related maternal mortality in low- and middle-income countries

Search History

1. EMBASE; exp PREGNANCY/; 568978 results.

2. EMBASE; pregnant.ti,ab; 154162 results.

3. EMBASE; (pregnant AND woman).ti,ab; 13995 results.

4. EMBASE; maternal.ti,ab; 205956 results.

5. EMBASE; gravid.ti,ab; 4241 results.

6. EMBASE; parturient.ti,ab; 3490 results.

7. EMBASE; exp PREGNANT WOMAN/ OR exp PREGNANCY COMPLICATION/; 140046 results.

8. EMBASE; pregnan*.ti,ab; 446261 results.

9. EMBASE; mother.ti,ab; 94305 results.

10. EMBASE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9; 872145 results.

11. EMBASE; exp DEVELOPING COUNTRY/; 77721 results.

12. EMBASE; (developing AND countr*).ti,ab; 61196 results.

13. EMBASE; (low AND income AND countr*).ti,ab; 10718 results.

14. EMBASE; (low-income AND countr*).ti,ab; 5313 results.

15. EMBASE; (middle- AND income AND countr*).ti,ab; 6413 results.

16. EMBASE; (middle AND income AND countr*).ti,ab; 6413 results.

17. EMBASE; (low AND resource AND country).ti,ab; 657 results.

18. EMBASE; (low-resource AND country).ti,ab; 211 results.

19. EMBASE; poverty.ti,ab; 17059 results.

20. EMBASE; africa.ti,ab; 76548 results.

21. EMBASE; asia.ti,ab; 52712 results.

22. EMBASE; (south AND america).ti,ab; 13075 results.

23. EMBASE; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22; 253960 results.

24. EMBASE; exp ANAESTHESIA/ OR exp ANESTHESIA COMPLICATION/ OR exp ANESTHESIA NURSING/
OR exp EPIDURAL ANESTHESIA/ OR exp GENERAL ANESTHESIA/ OR exp NURSE ANESTHESIA EDUCATION/ OR exp OBSTETRIC ANESTHESIA/ OR exp REGIONAL ANESTHESIA/; 263973 results.

25. EMBASE; exp ANESTHESIST/; 17645 results.

26. EMBASE; anesthetist.ti,ab; 1633 results.

27. EMBASE; anaesthetist.ti,ab; 3663 results.

28. EMBASE; anesthesiologist.ti,ab; 5812 results.

29. EMBASE; (nurse AND anesthetist).ti,ab; 394 results.

30. EMBASE; anesthesia.ti,ab; 145229 results.

31. EMBASE; exp ANESTHESIST/ OR exp ANESTHETIC/; 235989 results.

32. EMBASE; c-section.ti,ab; 1482 results.

33. EMBASE; exp CESAREAN SECTION/; 64117 results.

34. EMBASE; c-section.ti,ab; 1482 results.

35. EMBASE; exp INSTRUMENTAL DELIVERY/; 68177 results.

36. EMBASE; (caesarian AND delivery).ti,ab; 638 results.

37. EMBASE; (caesarian AND section).ti,ab; 1361 results.

38. EMBASE; (clinical AND officer).ti,ab; 894 results.

39. EMBASE; (physician AND assistant).ti,ab; 1590 results.

40. EMBASE; (medical AND assistant).ti,ab; 2602 results.

41. EMBASE; CRNA.ti,ab; 3351 results.

42. EMBASE; (operative AND obstetrics).ti,ab; 1277 results.

43. EMBASE; 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38

OR 39 OR 40 OR 41 OR 42; 522070 results.

44. EMBASE; 10 AND 23 AND 43; 1116 results

APPENDIX 3: Characteristics of studies evaluating rates of anaesthesia attributed maternal mortality in low- and middle-income countries

a. Studies reporting rates of anaesthesia-attributed maternal deaths

Ref No. *	Author, Yr	Country	Setting	Method used to ascertain cause of death	No. of pregnancies	No. of anaesthesia attributable deaths	No. of maternal Deaths (direct and indirect)
(147)	E. Abdel-Hady, 2007	Egypt	Multicentre	Prospective confidential enquiry	251016	7	164
(148)	J. Larsen, 1996	South Africa	Multicentre	Prospective study	41779	9	45
(149)	Z. Amarin, 2010	Jordan	Multicentre	RAMOS/ Confidential enquiry	397588	3	76
(150)	S. Ara, 2012	Pakistan	Urban	Retrospective hospital based audit	24667	1	168
(151)	M. Akar, 2004	Turkey	Urban	Retrospective	430559	9	174
(152)	N. Bano, 2011	Pakistan	Multicentre	Prospective	47209	2	108
(153)	S. Begum, 2003	Pakistan	Urban	Retrospective	2040	3	26
(154)	C. Hoestermann, 1996	Gambia,	Urban	Retrospective hospital based audit	10590	1	75
(155)	A. Bashir, 1995	Pakistan	Urban	Retrospective hospital based audit	276717	8	215
(156)	N.Vink, 2013	Malawi	Rural	Retrospective hospital based audit	9800	2	61
(157)	X De Muylder, 1990	Zimbabwe	Multicentre	Retrospective	51058	3	70
(158)	J. Bolngaa, 2014	Madang	Urban	Retrospective hospital based audit	10891	1	64
(159)	S. Ngwan, 2011	Nigeria	Urban	Prospective hospital based audit	4443	2	56
(160)	A. Sule-Odu, 1999	Nigeria	Urban	Retrospective	5320	3	103
(161)	O. Oladapo, 2006	Nigeria	Urban	Retrospective hospital based audit	2709	1	75
(162)	N. Obiechina, 2013	Nigeria	Urban	Retrospective hospital based audit	8022	5	103

(163)	S. Mahbouli, 2003	Tunisia	Urban	Retrospective hospital based audit	29845	1	10
(164)	A. El Daba, 2010	Egypt	Urban	Retrospective hospital based audit	19619	15	187
(165)	R. Rahim, 2006	Pakistan	Urban	Retrospective hospital based audit	23720	5	311
(166)	S. Yang, 2014	China	Urban	Retrospective	629544	2	91
(167)	V. Soare, 2012	Brazil	Multicentre	Retrospective	461999	10	270
	V. Soare, 2012	Brazil	Multicentre	Retrospective	452444	11	252
(168)	U. Okfar, 2008	Nigeria	Urban	Retrospective hospital based audit	6798	6	160
(169)	E. Kongnyuy, 2009	Malawi	Multicentre	Retrospective	5080	1	43
(170)	I. Ujah, 2005	Nigeria	Urban	Retrospective hospital based audit	38768	11	267
(171)	S. Hodorogea, 2014	Moldova	Multicentre	Retrospective, National enquiry	114625	2	29
(172)	V. Paily, 2014	India	Multicentre	Prospective confidential enquiry	3307553	12	501
(173)	I. Ujah, 1999	Nigeria	Urban	Retrospective hospital based audit	12047	8	89
(174)	D. Goswami, 2013	India	Urban	Prospective study	42355	2	296
(175)	T. Kane, 1992	Egypt	Multicentre	Retrospective audit and Verbal autopsy	123810	31	156
(176)	G. Ganyaglo, 2012	Ghana	Urban	Retrospective hospital based audit	19965	3	191
(177)	A. Granja, 2001	Mozambique	Urban	Retrospective hospital based audit	74637	4	239
(178)	F. Font, 2000	Tanzania	Rural	Retrospective audit and sisterhood method	8929	2	40
(179)	K. Akpanza, 1994	Togo	Urban	Retrospective hospital based audit	21603	4	190
(180)	J. Okaro, 2001	Nigeria	Urban	Retrospective hospital based audit	12949	3	182
(181)	P. Onwuhafua, 2000	Nigeria	Urban	Retrospective hospital based audit	10572	6	69
(182)	J. Mukherji, 1995	India	Urban	Retrospective hospital based audit	38870	10	429

(183)	E. Abe, 2008	Nigeria	Urban	Retrospective hospital based audit	28186	1	135
(184)	M.Kassas, 1995	Egypt	Multicentre	Population-based retrospective review	443248	19	718
(185)	Egypt MOH, 2000	Egypt	Multicentre	Retrospective National survey	1752562	30	580
(186)	NCCEMD, 2007	South Africa	Multicentre	Confidential enquiry	2598357	107	3959
(187)	A. Aboyeji, 2007	Nigeria	Urban	Retrospective hospital based audit	13093	3	108
(188)	M. Bukar, 2013	Nigeria	Urban	Retrospective hospital based audit	8497	2	28
(189)	A. Mungra, 1999	Surinam	Multicentre	Prospective, confidential enquiry	28337	1	64
(190)	NCCEMD, 2012	South Africa	Multicentre	Confidential enquiry	1939673	70	2966
(191)	S. Munjanja 2007	Zimbabwe	Multicentre	Retrospective confidential enquiry	45240	3	316
(192)	Jayashree, 2014	India	Urban	Prospective hospital based audit	43799	1	34
(193)	P.N. Makinga, 2012	South Africa	Multicentre	Retrospective	29883	3	61
(194)	Botswana MOH, 2012	Botswana	Multicentre	Confidential enquiry	50048	2	74
(190).	NCCEMD, 2010	South Africa	Multicentre	Confidential enquiry	2761888	121	4867
(195)	S. Fawcus, 2005	Cape town	Urban	Prospective	176822	1	52
(196)	M. Kharouf, 1992	Tunisia	Urban	Retrospective hospital based audit	42028	5	29
(197)	F. Madzimbamuto 2014	Botswana	Multicentre	Retrospective	50328	2	55
(198).	U. Okeh, 2009	Nigeria	Urban	Retrospective	1645	4	45
(199)	H. Bashour, 2009	Syria	Multicentre	RAMOS Design	Unknown	10	129
(200)	S. Rutgers, 2001	Zimbabwe	Multicentre	Retrospective	35050	2	92
(201)	A. Kampikaho, 1991	Uganda	Multicentre	Retrospective	174915	30	580
(202).	B. Khan, 2012	Pakistan	Urban	Retrospective hospital based audit	21120	14	163
(203)	S. Kauser, 2006	Pakistan	Urban	Retrospective hospital based audit	15885	3	46
(204)	A. Fawad, 2011	Pakistan	Urban	Retrospective hospital based audit	7380	4	767

(205)	A.G. Mairiga, 2009	Nigeria	Urban	Prospective hospital based audit	44281	6	767
(57)	A. Dalina, 1996	Malaysia	Multicentre	Confidential enquiry	1033099	10	475
(206)	Malaysia MOH, 1993	Malaysia	Multicentre	Confidential enquiry	536883	6	246
(207)	Malaysia MOH, 1994	Malaysia	Multicentre	Confidential enquiry	533333	6	208
(208)	Malaysia MOH, 1995-1996	Malaysia	Multicentre	Confidential enquiry	1075721	11	471
(209)	Malaysia MOH, 1997-2000	Malaysia	Multicentre	Confidential enquiry	2101361	9	654
(210)	Malaysia MOH, 2001-2005	Malaysia	Multicentre	Confidential enquiry	2434604	2	671
(211)	Malaysia MOH, 2006-2008	Malaysia	Multicentre	Confidential enquiry	1424602	2	396
(212).	P. Wagaarachchi, 2002	Sri-Lanka	Urban	Retrospective hospital based audit	135320	10	133
(213)	E. Nelissen, 2013	Tanzania	Rural	Prospective cross sectional study	9136	1	32
(214)	M. Bouvier-Colle, 2001	West Africa: including ivory coast, Mali, Niger, Mauritania, Burkina Faso and Senegal	Multicentre	Prospective study and questionnaires of pregnant population and Verbal autopsy for maternal deaths.	17694	1	52
(215)	A. L. Montgomery, 2007	India	Multicentre	Maternal death survey/ verbal autopsy	431496	4	1096
(216)	A. Pal, 2005	West Bengal	Rural	Retrospective hospital based audit	83244	4	519
(217)	V. Ashok, 2008	India	Urban	Retrospective hospital based audit	18793	1	65
(218)	K. Khatum, 2015	Bangladesh	Urban	Retrospective hospital based audit	5246	2	96
(219)	M. Cetin, 2002	Turkey	Urban	Retrospective hospital based audit	7424	1	34
(220)	Swaziland MOH, 2001	Swaziland	Multicentre	Maternal death review audit	16898	2	43

(221)	Kavoo-Linge, 1992	Kenya	Rural	Prospective hospital based audit	2171	1	6
(222)	M. Rakotoarimanana, 2000	Madagascar	Urban	Retrospective hospital based audit	91032	23	997
(223)	J. Oyieke 2006	Kenya	Urban	Retrospective hospital based audit	27455	4	203
(224).	R. Ali, 2012	Pakistan	Urban	Retrospective hospital based audit	7529	3	31
(225)	G. Igberase, 2007	Nigeria	Rural	Retrospective hospital based audit	5153	1	115
(226)	B. Asamoah, 2011	Ghana	Multicentre	Maternal health survey and verbal autopsy	Unknown	4	605
(227)	Botswana MOH, 2010	Botswana	Multicentre	Confidential enquiry	50328	1	82
(228)	Botswana MOH, 2011	Botswana	Multicentre	Confidential enquiry	45008	2	85
(229)	Botswana MOH, 2013	Botswana	Multicentre	Confidential enquiry	49839	1	91
(230)	Turkey MOH, 2005	Turkey	Multicentre	Confidential enquiry	763585	2	218
(231)	Salvador MOH, 2006	El-Salvador	Multicentre	Confidential enquiry/ RAMOS	Unknown	2	82
(232)	E. Farhat, 2012	Tunisia	Multicentre	Confidential enquiry	1194329	15	506
(233)	K. Issah, 2011	Ghana	Multicentre	Maternal death notifications and audits	Unknown	2	47
(234)	M. Glenshaw,2005	Zimbabwe	Rural	Retrospective	18718	5	77

Ramos- Reproductive Age Mortality Studies (RAMOS) use varied sources, depending on the context, to identify all deaths of women of reproductive age and ascertain which of these are maternal or pregnancy-related; http://www.maternal-mortality-measurement.org.uk

Verbal Autopsy- a research method that helps determine probable causes of death in cases where there was no medical record or formal medical attention given. In the case of the maternal deaths, full-time, non-medical field workers are trained to record written narratives from families or other reliable informants in the local language describing the events that preceded the death. In addition, answers to standard questions about key symptoms were also recorded. These records were then scanned and sent to trained physicians, who independently assigned a probable underlying cause of death to each case. In cases where the physicians did not agree on the cause of death, the conflicting physicians were given the other physician's notes, and cases were anonymously reviewed again. Further disagreements were resolved by the opinion of a third, senior physician. http://www.cghr.org/projects/million-death-study-project/what-is-verbal-autopsy/

Sisterhood method- the sisterhood method is an indirect measurement technique, which has been adapted to maternal mortality. It reduces sample size requirements because it obtains information by interviewing respondents about the survival of all their adult sisters. (The sisterhood method for estimating maternal mortality, WHO

b. Studies reporting anaesthesia-attributed deaths in pregnant women undergoing surgical procedures, risk factors for complications in low and middle-income countries

Ref	Author, Yr.	Setting	Study design	Population	Procedures	Anaesthetic provider	Anaesthesia	Outcomes
(235)	A.McKenzie, 1998	Central hospital, Ethiopia. Urban	Prospective review	Unselected	9833 operative obstetric procedures	Physician and non physician	General 8965, Spinal 868	Anaesthetic associated deaths- death within 24hrs of anaesthesia
(236)	Z. Abdissa, 2013	Teaching hospital, Ethiopia Urban	Prospective Cross sectional study	Exclusions: LSCS mothers with medical conditions, pre-eclampsia and diabetes. LSCS for bradycardia, haemorrhage or haemodynamic instability. Intrauterine foetal death	315 CS, 92% emergency	Physician anaesthetists	General 188, Spinal 97	Birth outcomes by C-sections under general and spinal anaesthesia, Apgar score and perinatal death
(237)	B. Fente, 2013	Niger Delta University Teaching hospital, Nigeria Rural/ semi urban	Retrospective observational study	Mixed surgical population	840 CS	Non Physician (88%)	General & Spinal	Anaesthesia related morbidity and mortality- 24 hrs.
(238)	B. Ozumba, 2001	Teaching Hospital, Enugu Nigeria Urban	Retrospective	Unselected	1684 CS, 68% emergency	Physician anaesthetists; residents and consultants involved in all deaths.	Not specified	C- Section related mortality- till discharge. Anaesthesia related maternal death

(239)	C. Chang, 2011	Taiwan Country wide	Population based study using dataset and registry	Excluded patients with APH, Placenta praevia and who were induced	67328 CS	Not specified	General Regional, numbers not specified	Risk of PPH within 24hrs following anaesthesia for C-section
(240)	K.O. Enohumah-2006	Tertiary hospital Nigeria Urban	Retrospective observational study	Unselected	2323 CS, 390 Cerclage	Physician	General 2339, Regional 332	To determine the incidence of maternal mortality related to anaesthesia and analyse the causes.
(168)	U.V. Okafor-2009	Teaching Hospital, Enugu, Nigeria Urban	Retrospective observational study	Unselected	729 CS	Not specified	General 347, Regional 374	The trends of different forms of anaesthesia for caesarean section in Eastern Nigeria and the morbidity associated
(241).	P. Fenton-2003	23 district and two central hospitals in Malawi. Rural and urban	Multicentre prospective study	Unselected	8070 ~~caesarean sections~~CS	Physician and non physician	General and spinal	Associations between maternal or perinatal deaths in the first 72 hours and various quantifiable risk factors
(242)	A. O. Okezie, 2007	Teaching hospital, Enugu, Nigeria Urban	Retrospective observational study	Unselected	740 CS	Not specified	Not specified	To analyse subjects delivered by CS, determine the CS rate, indication, maternal and foetal outcomes.
(243)	S.A. Okogbenin-2004	Tertiary hospital, Benin Nigeria Urban	Retrospective observational study	Unselected	2218 CS	Not specified	General, Spinal and Local	Incidence, associations, and outcome of cardiac arrest associated during CS in a Nigerian tertiary centre.
(244)	U.Okafor-2008	University of Nigeria Teaching Hospital, Enugu	Retrospective observational study	Unselected	1579 CS	Physicians- Senior trainees (more than 24 months training)	General & spinal – rate of use increased from 1.3	To determine the causes and risk factors of maternal deaths during C-sections

		Urban					(2000)-71%(2006) All deaths under GA	
(245).	E.I Nwobodo, 2011	Tertiary hospital, sokoto, Nigeria Urban	Retrospective	Excluded emergency CS	498 elective CS	Not specified	General 253, spinal 219	To determine the CS rate and trend, indication and maternal mortality associated
(246)	C.O. Imarengiaye, 2001	Teaching hospital, Benin Nigeria Urban	Retrospective	Unselected	2686 CS; 78% emergency	Not specified	General 2597, Regional- 89	To determine the anaesthesia related complication after Lscs, especially ICU admissions and maternal deaths.
(247)	A.Imtiaz, 2010	Tertiary hospital, Pakistan Urban	Randomised prospective study	Healthy pregnant women- ASA1	60 elective CS	Physician anaesthetists	General 30, Spinal 30	To compare the effects of general v spinal Anaesthesia on APGAR score in term neonates born by elective CS,
(248)	K. Tomta, 2003	University hospital, Lome, Togo Urban	Prospective	2% ASA 3	318 CS; 89% emergency	Non physician (74 in Togo) or Physician anaesthetist (1 in Togo)	General 299, Spinal- 13	Deaths within 24hrs after anaesthesia
(249)	W. Chau-2010	Thailand Multicentre	Prospective survey	Unselected	16697 CS; 35% emergency	Physicians or surgeons for spinal, Nurse in 34% of general	General 4,677 Spinal 11,310	To determine the incidence of maternal mortality related to anaesthesia and analyse the causes.
(250)	S.charuluxanananan- 2008	Thailand Multicentre-20 centres	Prospective survey	Those having spinal anaesthesia	17,382 CS	Unspecified.	All spinal	Incidence of cardiac arrest with spinals for CS
(251)	A. Rukewe 2014	Teaching hospital, Nigeria Urban	Retrospective	Unselected	3389 CS	Not specified	General 469, Regional 2920	To investigate potential trends and the rate of maternal complications associated with general or regional anaesthesia

(252)	O.A. Soyannwo-1995	2 hospitals and 3 health centres, Gambia Urban and rural	Retrospective	Unselected	2792 O&G procedure	Mainly nurse anaesthetists with 1-2 physician anaesthetists overseeing at the referral hospital	Not specified	Review of the development of anaesthesia and role of nurse anaesthetists-maternal death post procedures
(253).	S.A. Solangi, 2012	Medical college Nawabshah, Pakistan Urban	Randomised controlled trial	Term pregnant women, ASA-1, singleton pregnancy. Normal foetal growth and liquor, no congenital anomalies or foetal distress. No maternal co-morbidity.	160 elective C-Sections	Physician anaesthetists	General 80, Spinal 80	To compare the effects of general v spinal anaesthesia on APGAR scar in neonates born to full term elective C/S
(254)	G. O. Igberase, 2009	A mission tertiary hospital, EKU, delta state-Rural	Retrospective	Unselected	1777 CS, 63% emergency	Not specified	Not specified	C/S rates and related maternal mortality
(255)	A.I.Eshiet 2003	Teaching hospital, Calabar Nigeria Urban	Retrospective	General anaesthesia group: ASA2 (49.7%), ASA3 (21%), ASA4 (5.9%)	920 Emergency ~~C sections~~CS	Physician anaesthetists of varying seniority	General 550, Spinal 365	Anaesthesia related complications within 24 hrs.
(256)	A.D. Ekanem, 2008	Teaching hospital, Calabar, Nigeria	Retrospective	Emergency CS only	349 CS	Consultant anaesthetist administered in (12.9%), Senior registrar (43.8%) Junior registrar (43.8%)	General 117, Spinal 232	Anaesthesia related complications within 24 hrs.

(257)	S.Adisso, 2006	National hospital, Benin Urban	Retrospective case control study	Unselected	304 ~~C-section~~CS	Not specified	General 152, spinal 152	Anaesthetic related complications
(258)	P.Imbert, 2003	Principal hospital in Dakar, Senegal Urban	Prospective	Unselected	370 emergency CS	Nurse anaesthetist in majority of cases	General 182, Spinal 188	C-section related maternal mortality and morbidity
(259)	C.O. Imarengiaye, 2008	Teaching hospital, Benin, Nigeria Urban	Retrospective	Those with placenta praevia	81 CS	Not specified	General 52, Spinal 29	To determine the anaesthetic management and outcome in placenta praevia.
(260)	T. Kandasamy, 2009	Government maternity hospital, Kabul Urban	Retrospective	Unselected	392 CS	Not specified	General 114, Spinal 5	Fetal outcomes following CS
(261)	M.I. Nwafor, 2014	University of Nigeria teaching hospital Urban	Retrospective	Women with preterm deliveries.	236 CS	All cadres of anaesthetists	General 151, Spinal 85	Perinatal outcome in preterm caesarean sections, Apgar score, perinatal deaths
(262).	M.A. ljiya 2001	University Hospital Ilorin, Nigeria Urban	Retrospective	Unselected	2764 CS	Nurse anaesthetists- 2465, Physician anaesthetists- 299	General 2764 Regional 0	CS related maternal mortality and morbidity
(263).	Sri Wahjoeningsih 2007	Urban	Retrospective	C-section for foetal distress	240 CS	Resident anaesthetists under supervision from the anaesthetic consultant	General 172, Spinal 66	Apgar scores with general and spinal for CS in those with foetal distress

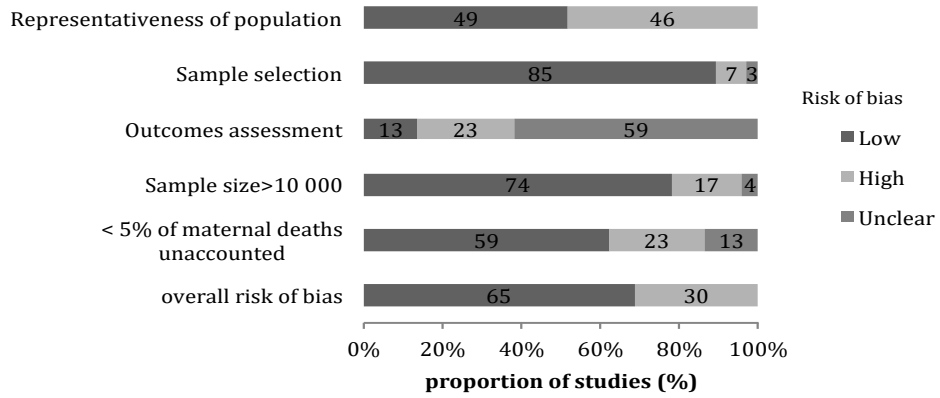
(264).	U.Okafor/ E.fefie 2008	University hospital, Nigeria Urban	Retrospective	Parturient with severe co-morbidity- ASA 3	270 CS	Physician anaesthetists	General 202, Regional 68	Outcomes from high risk CS
(234)	Glenshaw, 2005	Mission hospital, Zimbabwe Rural	Retrospective	Unspecified	2054 obstetric procedures	The surgeon would give the anaesthetic before operating and a nurse would monitor.	General/ mainly Ketamine, & spinal	All patients who died within 24hrs of an anaesthestic
(265)	C.J. Huang, 2010	Taiwan, Multicentre	Retrospective	CS with and without pre-eclampsia	295295 CS	Unspecified	General-11496 Regional – 283799	Risk of Stroke, ITU admissions and PPH post CS
(266)	S.Rasouli, 2014	University hospital, Iran	Retrospective	Exclusions: Underlying disease, Pre-eclampsia/, cord prolapse, prematurity, severe foetal bradycardia, foetal growth restriction or malformations.	324 CS	Not specified	General-117 Spinal- 207	Apgar scores with general and spinal in C-section
(267)	O.Almomani, 2012	Regional hospital, Jordan Urban	Prospective	All elective CS with exclusions; IUFD, growth restriction or malformations.	161 CS	Not specified	GA- 104 Spinal- 42 Epidural 15	Apgar scores with general and spinal in elective C-section
(268)	EOV Ugwu, 2011	Teaching hospital, Enugu, Nigeria Urban	Retrospective	Unselected	980 CS; 94% emergency	Not specified	Not specified	To determine the rate, pregnancy outcomes, indication and complications of CS.
(269).	T. Mekbib 1994	12 hospital, Addis Ababa, Ethiopia Urban	Retrospective	Unselected	647 CS; 90% emergency	Not specified	Not specified	Fetal outcomes and maternal mortality and morbidity post CS.

(270)	P. Foumane, 2014	Women's and children's hospital, Cameroon Urban	Retrospective	Unselected	219 CS; 58% emergency	Not specified	Not specified	Comparison of maternal outcomes following elective and emergency CS
(271)	CT. Cisse, 1998	Senegal Multicentre	Retrospective	Unselected	2269 CS	Not specified	Not specified	Maternal outcomes following CS
(272)	A.O Sayonnwo 94	Gambia	Retrospective	Ectopic pregnancies	Laparotomy	Non physician anaesthetists	All under general	Anaesthetic complication following surgery for ectopic pregnancy.
(273)	A.F. Ouro-Bangna Maman- 2005	Teaching hospital, Togo	Retrospective	Mixed population 28% O&G surgery	410 O&G procedures	Mainly nurse anaesthetists	General- 90% of cases	Anaesthetic outcomes
(274)	C.Nwosu, 2004	Sub-urban health centre, Nigeria	Retrospective	Unselected-	1254 CS	Nurse anaesthetist	Mainly General	CS related mortality
(275)	E Ojiyi, 2012	University hospital, Nigeria Urban	Retrospective	Unselected	363 CS; 53.6% emergency	Not specified	Not specified	CS related mortality
(276)	G.kamilya 2010	Medical college Kolkata, India Urban	Retrospective	Exclusions: those with obstetric complications	13627 CS	Not specified	Not specified	CS related mortality
(277)	I.Kambo, 2002	30 colleges and hospitals, India	Prospective	Unselected-	7017 CS	Not specified	Not specified	Outcomes of CS
(278)	H.Abbassi, 2000	University hospital, Morocco	Retrospective	Unselected- all undergoing C-section	3231 CS	Physicians	Not specified	Outcomes of CS
(279)	K.M. Chu, 2010	13 developing countries	Retrospective	Mixed population	7939 Obstetric procedures	Mainly nurse anaesthetists	Not specified	Surgical morbidity
(280).	Malaysia MOH, 1992	Malaysia	Retrospective	Unselected	37 CS deaths	Not specified	Not specified	Anaesthesia related CS deaths

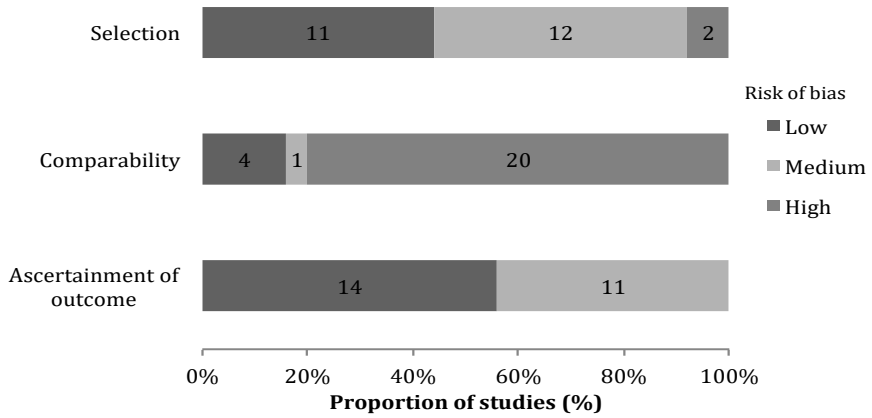
(281)	M. Ajmal-2011	Faisalabad, Pakistan	Retrospective	Unselected	2114 CS	Physicians	100% GA	To report rates of regurgitation and failed intubations with GA

APPENDIX 4: Quality assessment of studies included in the systematic review of anaesthesia-related risk factors for maternal mortality and complications in low- and middle-income countries

a. Studies on anaesthesia-attributed maternal mortality rates



b: Risk of bias assessment by Newcastle Ottawa Scale in studies evaluating anaesthesia-related risk factors and maternal and fetal complications



APPENDIX 5: Anaesthesia attributed maternal deaths in pregnant women undergoing surgical procedures in individual low- and middle-income countries- country specific prevalence's.

A) Anaesthesia-attributed maternal death as a proportion of all obstetric surgical procedures

Country	Prevalence /1000 women
Benin	1.1
Cameroon	9.1
Ethiopia	1.6
Gambia	3.6
Ghana	0.8
India	0.3
Kenya	3.4
Malawi	3.0
Nigeria	1.4
Senegal	3.4
South Africa	0.2
Tanzania	4.5
Thailand	0.4
Togo	15.9
Zimbabwe	0.8

B) Anaesthesia-attributed deaths as a proportion of all maternal deaths

Country	Prevalence
Bangladesh	2.04%
Botswana	1.7%
Brazil	4.0%
China	2.2%
East Africa;	1.9%
Burkina Faso	1.9%
Ivory Coast	1.9%
Mauritania	1.9%

Níger	1.9%
Senegal	1.9%
Mali	1.9%
Egypt	6.85%
El-salvador	2.4%
Gambia	1.33%
Ghana	0.91%
India	1.12%
Kenya	2.03%
Madagascar	2.31%
Malawi	2.81%
Malaysia	1.41%
Moldova	6.9%
South Africa	2.78%
Sri-lanka	7.52%
Surinam	1.56%
Swaziland	4.65%
Syria	7.75%
Tanzania	3.96%
Togo	2.11%
Tunisia	7.96%
Turkey	2.7%
Uganda	5.17%
Zimbabwe	2.39%

APPENDIX 6: Study characteristics of included studies for systematic review of maternal and fetal outcomes related to type of anaesthesia in women with pre-eclampsia in low- and middle-income countries.

Author, yr	Year	Setting	Study design	Population	Procedures and anaesthesia	Objectives and outcome measured	Findings
J.Moodley, 2001 [282]	1995-1999	Hospital in south Africa	Retrospective	All women with Stable Eclampsia [a]Stable" eclampsia was defined as: 1. Glasgow coma score >14; 2. Rapidly acting anti-hypertensive agent not required; 3. Platelet count>100,000/mm^3; 4. Cooperative; 5. Central venous pressure >5 cm H2O; 6. Normal fetal heart rate pattern on electronic monitoring. 7. No additional maternal or Fetal complications.	66 C-sections GA- 27 Epidural-37 Spinal- 2 (not analysed)	Maternal, neonatal and anaesthetic complications	Maternal and neonatal outcomes are not affected adversely by the use of epidural anaesthesia in selected cases of eclampsia.
S.Chattoadhyay, 2014 [283]	2012-2013	Medical college & Hospital Kolkata	Prospective	Women with Severe pre-eclampsia undergoing emergency caesarean section. **Exclusions:** < 34 weeks, eclamptic patients; history of medical disorders, severe allergic reaction; abruption or placenta previa; coagulopathy, thrombocytopenia with platelet count less than 80, sepsis, neurological problems, hypovolemia, or pulmonary edema; multiple gestations or	173 C-sections, 27 GA 146 spinal	Maternal, neonatal and anaesthetic complications	Mothers with Severe Pre-eclampsia receiving general anaesthesia and their babies required more critical care support. Maternal as well as neonatal mortality was significantly higher with general anaesthesia.

				any congenital anomalies			
M.A. Ul-Haq, 2005 [67]	2002-2003	Naval hospital, Karachi, Pakistan	Retrospective	Women with severe pre-eclampsia	60 C-sections GA -30 Spinal -30	Perioperative morbidity and mortality in severe pre eclampsia,	Spinal anaesthesia should be used as first choice for severe pre eclamptic patients, which is safer than general anaesthesia, with less postoperative morbidity and mortality.
C-J. Huang, 2010 [265]	2002-2006	Taiwan National Health Insurance Research Database.	Registry data	Women with pre-eclampsia. Mild PET- 3751 Severe PET-4816 **Exclusions**: those younger than 16 or older than 49, hx of stroke, those with missing data	8567 C-sections, GA- 1027 Regional- 7540	Mode of anaesthesia on outcomes especially stroke, other morbidities and mortality	general anaesthesia for CS delivery was associated with increased risk of stroke when compared with regional anaesthesia in pre-eclamptic women.
U.V.Okafor, 2005 [284]	1998-2002	Teaching hospital, Enugu, Nigeria	Retrospective	Women with pre-eclampsia/ eclampsia Mild PET- 34 Severe PET-76 Eclampsia- 15	125 C-sections, GA- 116 Spinal- 9	Perioperative morbidity and mortality in pre eclampsia/ eclampsia	Maternal and fetal mortality were high. Use of spinal anaesthesia should be encouraged
U.V.Okafor, 2009 [285]	1998-2006	Teaching hospital, Enugu, Nigeria	Retrospective	Women with pre-eclampsia/ eclampsia Mild pre-eclampsia- 59, Severe pre-eclampsia-107, Eclampsia-30	196 C-sections GA- 157 Spinal- 34 Epidural- 5	Perinatal outcomes in women with pre-eclampsia/ eclampsia	Pre-eclampsia/eclampsia continues to be a cause of foetal loss. Early onset management of severe pre-eclampsia with maintenance of adequate placental perfusion during anaesthesia may result in lower perinatal deaths.
U.V.Okafor, 2009 [286]	2002-2006	Teaching hospital, Enugu, Nigeria	Retrospective	Women with pre-eclampsia/ eclampsia, Mild pre-eclampsia- 25, Severe pre-eclampsia-31, Eclampsia-15	71 C-sections, GA- 41 Spinal- 25 Epidural- 5	Perioperative morbidity and mortality in pre eclampsia/ eclampsia	Maternal outcomes improved from previous study due to increase in regional anaesthesia
Obinna V. Ajuzieogu, 2011[287]	2005-2009	Teaching hospital Enugu, Nigeria	Retrospective	Women with severe pre-eclampsia defined as: Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg with ≥ 2+ of Proteinuria on dipstix urinalysis.	96 C-sections GA- 59 Spinal- 37	To compare the outcome of spinal and general anaesthesia in Cesarean delivery for women with severe pre-eclampsia.	There was no significant difference in the maternal and perinatal mortality outcome of cesarean delivery by type of anaesthesia. There was significantly higher

				Exclusions: mild pre-eclampsia, other medical disorders, multiple pregnancies, gestational age less than 32 weeks, cases of eclampsia.			proportion of birth asphyxia in babies of women who received general anaesthesia.
JM Afolayan, 2014 [288]	2011-2012	Teaching hospital, Benin, Nigeria Retrospective	Retrospective	82 women with eclampsia **Exclusions:** concurrent medical ailments.	82 C-sections GA- 17 Spinal- 65	Anaesthetic management methods, maternal and perinatal outcome measures	Maternal and perinatal survival and well being are better in eclamptics who had spinal anaesthesia for caesarean section compared to those who had general anaesthesia.
K. Keerath, 2012 [68]		Tertiary hospital, South Africa	Retrospective	Women with severe pre-eclampsia presenting for emergency caesarean section Exclusions: antepartum haemorrhage, cardiac disease, poor record keeping/missing data.	84 C-sections, GA- 21 Spinal- 58 Other regional-5 (not analysed)	Postoperative maternal outcomes, maternal mortality or morbidity, as well as any neonatal mortality or morbidity.	Maternal morbidity and mortality were not significantly different between the two groups. Neonatal outcomes were poorer in the GA group. This study supports spinal anaesthesia as an appropriate anaesthetic choice in patients with severe pre-eclampsia.
S.Chupathang, 2016 [289]		University hospital, Thailand	Retrospective	Women with severe pre-eclampsia, managed according to homogenous guidelines. Exclusions: epidurals and combined spinal-epidural, incomplete data	701 patients GA- 84 Spinal-617	Anaesthetic management methods, maternal and perinatal outcome measures	Spinal anaesthesia Can be safely administered in women with severe preeclampsia patients
R.Dyer 2003 [290]		University hospital South Africa	Randomised study	Women with pre-eclampsia and a non-reassuring fetal heart rate. Mild PET- 30 Severe PET-40 Exclusions: BMI>35, mallampati score>2, clinical	70 Patients GA- 35 Spinal- 35	To assess maternal heamodynamics and markers of neonatal hypoxia in women with pre-eclampsia.	Maternal heamodynamics were similar with either anaesthetic technique. Spinal was associated with a lower mean umbilical arterial pH, the clinical significance remains to be

			signs of hypovolemia, abruption, placenta previa, platelets<70, cord prolapse, < 30 weeks, twins.			established.
P. Indira 2016 [291]	Government maternity hospital, Hyderabad, India	Randomised study	Women with severe Pre-eclampsia as per ACOG diagnostic criteria Exclusions: Cardio vascular and pulmonary disease, Diabetes, HELLP syndrome, Gestational age <34 weeks , Fetal bradycardia and any contraindications of regional anaesthesia including patients refusal, severe haemorrhage, coagulopathy and sepsis.	60 patients GA- 30 Spinal 30	Anaesthetic management methods, maternal and perinatal outcome measures	Spinal anaesthesia is a safe alternative to general anaesthesia in severe preeclampsia patients
F.Moslemi 2007[292]	University hospital, Iran	Randomised study	Women with severe pre-eclampsia: BP> 160/90, proteinuria > 5g/24h with at least one associated symptom. Exclusion criteria: Cardiovascular/ pulmonary disease, HELLP, < 34 weeks, fetal bradycardia and any contraindication to regional anaesthesia.	60 patients GA- 30 Spinal- 30	Hemodynamic status of severe pre-eclamptic women and neonatal outcomes	No difference In BP or neonatal outcomes in the two groups.

APPENDIX 7: Study characteristics of studies included in in caesarean section related maternal and perinatal mortality and morbidity review.

Author, yr	Country	Type of hospital , setting	Study design	Characteristics , inclusion and exclusion criteria	No. of Caesarean sections	Outcomes
S.Kilsztajn, 2007[293]	Sao Paulo, Brazil	Public health hospital	Retrospective	All Caesarean sections	371981	To evaluate c/s in both public and private sectors; maternal mortality associated with mode of delivery in the public sector in Sao Paulo, Brazil
J.M.Afolayan, 2014[294]	Nigeria	Teaching hospital	Retrospective	Inclusion criteria: eclamptic women who had c/s Exclusion criteria: patients with previous history of incurrent medical ailment/pre-existing disease	87	To evaluate the comparative advantage of general and spinal anaesthesia on maternal and perinatal outcomes in eclamptics, after c/s
L.Cebekulu, 2006[295]	South Africa	Referral hospital	Cohort	Inclusion criteria: singleton live pregnancies at 36 weeks or more of gestation with cephalic presentations. Exclusion: women with previous c/s	5765	To determine maternal and neonatal complications associated with c/s done in the second stage of labour. (primary outcome: intraoperative difficulties, blood loss, operating time and neonatal morbidity)
A.Ghazi, 2012 [296]	Pakistan	Tertiary hospital	Prospective	All mothers admitted through OPD or emergency recruited. Patients having previous myomectomy, hysterectomy or classical c/s were excluded)	100	To compare maternal morbidity and determine its cause in elective and emergency c/s
L.A.O.Ujah, 1999 [173]	Nigeria	Teaching hospital	Retrospective	All women dying in pregnancy, labour and puerperium		Maternal mortality ratio, trend of maternal mortality, age, antenatal booking status, educational status, main causes of maternal death, factors contributing to maternal deaths
J.Mukherji, 1995 [182]	India	Teaching hospital	Retrospective	MD following Caesarea~~Caesarea~~ sections	8017	To evaluate the associated factors resulting in MD following c/s
I.K.Sorbye, 2011 [297]	Tanzania	Zonal referral hospital	Retrospective	all deliveries including Caesarea sections	6765	To compare c/s rates among women formally referred to a tertiary care centre vs self-referred women, and to assess the effect of referral status on adverse outcomes after CS
I.K.Sorbye, 2011	Nairobi	Tertiary/teaching hospital	Retrospective	All ~~Caesarea~~Caesareann sections	1229	To compare total c/s rates, their indication and perinatal outcome in 2001 and 2004
V.Ashok, 2008[298]	India	Government medical college hospital	Retrospective	All maternal deaths		To study maternal mortality and common complications leading to MD
B.Onankpa, 2009[299]	Nigeria	Teaching hospital	Prospective	All ~~Caesarea~~Caesareann sections	216	To evaluate fetal outcome for the various indications for c/s
S.J.Etuk, 2001[300]	Nigeria	Teaching hospital	Retrospective	All c/s deaths, excluding those who had uterine rupture	1540	To identify the avoidable factors in maternal mortality following c/s
R.Koigi-Kamau, 2005[301]	kenya	District hospital	Prospective	All ~~Caesarea~~Caesareann sections	153	To determine the incidence of post-caesarean wound infection
N.P.Khawaja, 2004[302]	Pakistan	Tertiary hospital	Prospective?	All Caesarean sections	300	To determine the rate of c/s, indications and outcome

S.Pothinam, 1992[303]	Thailand	Teaching hospital	Prospective	Patients delivered by Caesarean sections. Exclusion criteria: intrapartum fever developed before c/s, gestational age of less than 28 weeks and loss of medical records	548	Post-c/s puerperal morbidity, incidence and risk factors
E.A.Wright, 1991[304]	Nigeria	Teaching hospital	Prospective	Perinatal deaths on patients delivered by c/s	757	To determine the perinatal mortality rate based upon c/s deliveries
T.F.Urrio, 1991[305]	Tanzania	Regional hospital	Retrospective	All maternal deaths		Maternal deaths
F.F.Wirakusumah, 1995 [306]	Indonesia	Referral/teaching hospital	Retrospective	MD associated with ~~Caesarea~~Caesarean sections	2704	To compare frequencies of MD and perinatal mortality, and severe morbidity among cases of c/s
O.T.Oladapo, 2007[161]	Nigeria	Teaching hospital	Retrospective	All elective Caesarean ~~Caesarea~~ sections	164	To estimate the maternal morbidity and mortality associated with elective c/s at a Nigerian university hospital
E.Gomathy, 2013[307]	India	Referral hospital; rural	Retrospective	Maternal deaths over a 6 year period		To find the frequency and the causes of MD in a rural medical college hospital
C.Pereira, 1996 [308]	Mozambique	Central/university hospital	Prospective	~~Caesarea~~Caesarean sections delivered by ~~Asistant~~Assistant medical officer vs obstetricians	2071	Post-operative complications and duration of post-operative hospital stay of women delivered by c/s performed by AMO and obstetricians
E.Tadesse, 1996 [309]	Ethiopia	Teaching hospital	Prospective	All Caesarean~~rea~~ sections	318	To obtain base-line data on the rates of c/s, pregnancy out-come, major indications for c/s and c/s complications
F.O.Njokanma, 2002 [310]	Nigeria	Private hospital	descriptive	All Caesarean sections	1140	Perinatal asphyxia rate, stillbirth rate, END rate, maternal mortality rate
M.Bukar, 2009 [188]	Gombe (Nigeria)	Federal medical Centre/tertiary institution	Retrospective	All Caesarean sections	264 (	To determine the indications and outcome of c/s
S.Kumari, 1990 [311]	India	District; urban	Prospective	Neonates delivered by Caesarea sections xcept those with prom>24hrs and major malformations	573	Neonatal outcome following c/s
A.O.Longombe, 1990 [312]	Zaire	Medical referral center; rural	Retrospective	All Caesarean sections	1014	Indications and risks of c/s in rural Zaire
A.Picaud, 1990 [313]	Gabon	Centre hospital	Prospective	All Caesarean sections	1213	Indications of c/s and their evolution in the Centre Hospitalier of Libreville
N.Dey, 1991 [314]	India	Referral hospital	Prospective	Unselected cases of Caesarea sections	200	To make an overall assessment of the complications of mother and the neonate following c/s under improved state of anaesthesia, skilled operative technique, antibiotics and neonatal services
S.P. Munjanja, 2007 [191]	Zimbabwe	Mixed	Retrospective	All maternal deaths in the population-based birth survey		To establish precisely the national estimates for indicators relating to mortality of mothers and newborns.
P. Yaïch, 2012 [315]	Ivory Coast	University hospital	Retrospective	All emergency Caesarean sections	618	To determine the rate of emergency c/s and the factors influencing the maternal/foetal prognosis.
N.M.Burshan, 2015 [316]	Libya	Al-khaddar hospital	Cross-sectional	All Caesarean sections	511	To review the complications of emergency c/s during and post-operative period and epidemiological and

						obstetric factors which could be associated with such morbidity.
A.Gessessew, 2011[317]	Ethiopia	11 hospitals and 2 health centers	Retrospective	All deliveries	2835	To assess the contribution of non-physician clinicians to comprehensive emergency obstetric care in Tigray, Ethiopia.
N.G. Omamalin, [318]	Philippines	University hospital	Retrospective	All emergency Caesarean sections	703	To determine the leading indications for emergency c/s and the clinical maternal and neonatal outcomes following emergency c/s in the hospital from 2005 to 2007
C.McCord, 2009[319]	Tanzania	District hospitals	Prospective	All emergency obstetrical operations, plus all cases of eclampsia, postpartum haemorrhage or puerperal sepsis	1087	To address the question the quality of care delivered by various non-physician clinicians.
S.Basak, 2011[320]	India	Teaching hospital	prospective	Inclusion: obstructed labour due to CPD with: fetus alive, vertex presentation, advanced cervical dilatation, well engaged fetal head; obstructed labour after failed ventouse/forceps; trapped after coming head in vaginal breech delivery; shoulder dystocia Exclusion: Dead baby, musculoskeletal disorders, severe obesity of mother, major degree of CPD, previous CS, baby weight > 4kg	50	To compare the maternal and neonatal outcomes of symphysiotomy and c/s when they were performed in women presenting with obstructed labour.
KS Begum, 2014[321]	Bangladesh	Tertiary hospital	prospective	Mothers with previous one lower segment Caesarean sections who presented at term	115	To determine the factors affecting the pregnancy outcome in patients with previous one c/s
V.Briand, 2012[322]	Mali and Senegal	Referral hospitals	Cross-sectional	All women with single pregnancy, living in Senegal or mali who delivered in the selected health facilities a newborn weighing more than 500g were included. excluded women with immediate life threatening maternal or fetal complication (placenta praevia, severe pre-eclampsia, prerupture or rupture of the uterus, transverse lie, brow presentation, or major cephalo-pelvic disproportion	11255	To assess maternal and perinatal adverse outcomes associated with mode of delivery in 41 referral hospitals of Mali and Senegal
CN Daniel, 2016 [323]	Nigeria	Tertiary hospital	Cross-sectional	Women who had a c/s hysterectomy following uterine rupture were excluded	504	To assess the overall c/s rate, indications and outcomes
F.E.Abebe, 2016 [324]	Ethiopia	Referral hospital	Retrospective	All Caesarean sections Exclusions: uterine rupture	723	To assess the rate and factors associated with c/s
M.Jabir, 2013 [325]	Iraq	6 public hospitals	Cross-sectional	All maternal deaths and near misses in 6 hospitals		To study the characteristics and quality of care provided to women with severe complications
Y.kim, 2012 [326]	Afghanistan	Referral facilities	Cross-sectional	All Caesarean sections	173	To gain a greater understanding of the clinical indications, timeliness and outcomes of CS deliveries

H.Litorp, 2014 [327]	Tanzania	University and regional hospital	Cross-sectional	All maternal deaths and near misses All women with complications during pregnancy, childbirth or within 42 days after termination of pregnancy		To describe the occurrence and panorama of maternal near-miss and death and explore their association with CS complications
N.Maaloe, 2012 [328]	Tanzania	rural hospitals	Retrospective	All emergency Caesarean sections	400	To investigate in depth to what extent indications for emergency c/s followed evidence-based audit criteria for realistic best practice.
G.B.Madoue, 2015 [329]	Chad	Tertiary hospital	Prospective	All Caesarean sections	170	To determine the frequency and main indications of c/s
P.I.Okonta, 2003 [330]	Nigeria	Teaching hospital	Retrospective	All Caesarean sections	1031	To audit c/s done over a 5 year period and to compare such with those from the same hospital 20 years ago
S.Rahlenbeck, 2001 [331]	Rwanda	District hospital	Retrospective	All deliveries	896	To obtain data on pregnancy outcomes and maternal mortality at a district hospital in Rwanda
B.Sebhatu [332]	Eritrea	Maternity hospital	Retrospective	All Caesarean sections	931	1.To describe the practice of caesarian section in Orotta Hospital in terms of the rate of caesarian section, the indication of the caesarian section, the type of caesarian section, the mode of anaesthesia used, the rate of post operative infection, the neonatal outcome and the maternal morbidity and mortality attributed to the procedure
W.K.Sekirime, 2009 [333]	Uganda	Tertiary referral	Prospective	All Caesarean sections	478	To assess whether asymptomatic HIV infection could be contributing to the increased morbidity following emergency c/s in the form of wound and GTI with consequent prolonged stay in the hospital
B.Utoo, 2013 [334]	Nigeria	Health facility	Retrospective	All nulliparaous Caesarean sections	109	To assess the primary c/s rate, indications and fetal outcome amongst nulliparous women at a health facility in southern Nigeria
Y.Berhan, 2004 [335]	Ethiopia	Teaching hospital	Retrospective	Major emergency obstetric performances included	961	To analyse the rates of variables-specific perinatal deaths, maternal and perinatal case fatality rates and to determine common indications of operative deliveries with their outcome indicators.
S.H.Hounton, 2009 [336]	Burkina Faso	National/regional and district hospitals Rural and urban	Retrospective	All Caesarean sections	2305	To evaluate the effectiveness and cost-effectiveness of alternative training strategies for increasing access to emergency obstetric care in Burkina Faso.
E.landry, 2014 [337]	9 facilities in Bangladesh (rural), Guinea (urban), Mali (urban), Niger (urban), Uganda (rural)	Referral, private, public, faith based	Retrospective	All Caesarean sections	2941	To review 350 c/s from 2008 from each hospital in study, randomly selected from operating room register, if less than 350 at site all reviewed. To assess the quality of record keeping for c/s
O.Asicioglu, 2014 [338]	Turkey	Tertiary/teaching hospital	Prospective	Inclusion: singleton live pregnancies at term	8072	To investigate the maternal and perinatal complications of c/s performed in the 2nd stage

				Exclusion: multiple pregnancies, pregnancies with major fetal abnormalities, significant maternal disease or pregnancy complications		compared with the 1st stage of labour at the tertiary hospital.
O.Kor-anantakul, 2008 (339)	Southern Thailand	Tertiary	Prospective	All women admitted for delivery and if they resided within 5km radius of the hospital	403	To compare the various complications found in vaginal and c/s deliveries based on the original elected intended mode of delivery.
S.L.Seal, 2010 (340)	Eastern India	Teaching	Prospective	inclusion: singleton live pregnancies at term in nulliparous women with vertex presentation exclusion criteria: pregnancies with major fetal abnormalities, mal-presentations, significant maternal disease or pregnancy complications	4185	To evaluate the maternal and perinatal complications of c/s deliveries performed in the 2nd stage compared with the first stage of labour in nulliparous women.
I.Teguete, 2012 (341)	Mali	Tertiary care referral center/hospital	Retrospective	All deliveries	4517	To assess the trends of c/s delivery at the Point G national hospital in Bamako, Mali over a period of 2 decades.
A.Diawara, 2014 (342)	Mali	Mixed	Retrospective	All Caesarean sections	262	To assess the impact of free c/s on emergency obstetric care
J. Ngowa, 2015 (343)	Cameroon	2 University hospitals	Prospective	All Caesarean sections	460	To determine the incidence of maternal complications related to c/s in two university hospitals in Yaoundé.
F.B.Diallo, 1998 (344)	guinea	University hospital	Prospective	All elective Caesarean sections, Uterine rupture excluded	434	To determine the frequency of c/s, the problems linked to c/s and to determine in which cases c/s can be a factor in reducing morbidity and foetal and maternal mortality.
A.Sucak, 2011 (345)	Turkey	Teaching hospital; rural	Prospective	Inclusion: Nulliparous women undergoing c/s, fetuses with vertex presentation and gestational age older than 36 weeks of gestation, and having no maternal comorbid disease or not associated obstetric problems	1389	To compare neonatal and maternal outcomes of the primary c/s performed in first stage versus second stage of labour.
D.Geelhoed, 2003 (346)	Ghana	District hospital, rural	Retrospective	All maternal deaths		To measure the impact of the Safe Motherhood Initiative on hospital-based maternal mortality since its start in 1987.
G.F.Gonzales, 2013(347)	Peru	43 public health facilities (40 hospitals and 3 health centers); rural and urban	Retrospective	All Caesarean sections Exclusions: domiciliary deliveries, if no data for newborn, incoherent birth weight data in relation to gestational age, congenital malformation.	152110	To estimate c/s rates over time during the period between 2000 and 2010 in Peru and to present outcomes for each mode of delivery.
J. Dillen, 2007 (348)	Northern Namibia	District hospital, semi-rural	Retrospective	All Caesarean sections	576	To identify the indications for c/s deliveries. To help identify factors associated with variations in CSR and help assess the quality of clinical care.
E. Nelissen, 2013 (349)	Tanzania	Referral hospital; rural	prospective	Inclusion: all maternal near misses and maternal deaths	74	The aim of this study is to assess the occurrence of severe maternal morbidity and mortality in a rural referral hospital in Tanzania as proposed by the WHO

						near miss approach and to assess implementation levels of key evidence-based interventions in women experiencing severe maternal morbidity and mortality.
K.Nahar, 2009 [350]	Bangladesh	Medical college hospital	Prospective	100 c/s patients randomly selected	225	To determine incidence and indications of LSCS, to find out unnecessary indications which may in future reduce the incidence rate in the country.
A.P. Aboyeji, 2007 [187]	Nigeria	teaching	Retrospective	All MD between 1997-2002	2016	To determine the maternal mortality ratio in a Nigerian tertiary health institution.
B.C.Ozumba, 2008 [351]	Nigeria	teaching	Retrospective	MD		The aim of this study was to identify avoidable factors in maternal mortality in Enugu, Nigeria.
A. I. Eshiet, 2003 [255]	Nigeria	Teaching	Retrospective	All emergency Caesarean sections	1533	To evaluate the morbidity and mortality from anaesthesia during the period under review.
B.C. Ozumba, 2002 [238]	Nigeria	teaching	Retrospective	All MD associated with c/s	1684	MD associated with c/s
E. Ojiyi 2012 [275]	Nigeria	Teaching	Retrospective	All Caesarean sections	363	To determine the rate and the complications associated with Caesarean section at the Imo State University Teaching Hospital, Orlu
E. Ugwu, 2011 [268]	Nigeria	Teaching	Retrospective	All Caesarean sections	980	To determine the rate of caesarean section, pregnancy outcome, major indications and complications of caesarean section.
E.Y. Kwawukume, 2001 [352]	Ghana	Teaching; urban	Retrospective	All Caesarean sections	23171	c/s in developing countries
G. Chilopora, 2007 [353]	Malawi	District hospital	Prospective	All Caesarean sections	2131	To validate the advantages and disadvantages of delegation of major obstetric surgery to non-doctors.
G.O. Igberase, 2009 [254]	Nigeria; rural	tertiary	Retrospective	All Caesarean sections	1777	To determine the trend in caesarean section rate, pattern of presentation and associated maternal morbidity and mortality in a tertiary centre in the Niger Delta.
I. Kambo, 2002 [277]	India	Teaching	Prospective	7017 consecutive caesareans	7017	To obtain an estimate of caesarean section rates and examine the indications and consequences at teaching hospitals in India
A.G. McKenzie, 1998 [235]	Zimbabwe	Central hospital	Prospective	major obs procedures	8502	To review anaesthetic-associated deaths (AAD) and their avoidable factors.
N.A. Garba, 2011 [354]	Nigeria	Teaching	Retrospective	All Caesarean sections	1005	To determine the cs rate, its morbidity and mortality in Aminu Kano teaching hospital, Kano.
E. Nwobodo, 2011 [245]	Nigeria	Tertiary	Retrospective	All Caesarean sections	2284	to determine the caesarean section rate together with the trend, indications, and maternal mortality associated with elective caesarean operation.

U.V. Okafor, 2009 [168]	Nigeria	teaching	Retrospective	All Caesarean sections	729	To present the trends of different forms of anaesthesia for caesarean section in Eastern Nigeria
A.O. Okezie, 2007 [242]	Nigeria	Teaching	Retrospective	All Caesarean sections	740	To analyse subjects delivered by caesarean sections in the University of Nigeria Teaching Hospital (UNTH) to determine the caesarean section rate, indications and fetal outcome and possible ways of reducing the caesarean section rate.
S.A. Okogbenin, 2004 [243]	Nigeria	Teaching	Retrospective	c/s women with cardiac arrest	2218	To review the incidence, associations, and outcome of cardiac arrest associated with caesarean section.
T. Kandasamy, 2009 [260]	Afghanistan	Public maternity hospital; urban	Retrospective	All Caesarean sections	392	To use an active facility-based maternal and new-born surveillance system to describe caesarean delivery practices and outcomes in a resource-poor setting.
K. Tomta, 2003 [248]	Togo	Teaching	Prospective	All Caesarean sections	306	The objective of this study is to know the results of anaesthesia practices, and allow for observation in a particularly deprived area.
W. Wu, 2000 [355]	China	Teaching hospital	Retrospective	All Caesarean sections	1922	This study examined the frequency and indications of caesarean birth in Shantou, a southern city in China
N.Fesseha, 2011[356]	Ethiopia	Mixed	Retrospective	All caesarean sections	17145	To describe Ethiopian national population-based and institutional caesarean delivery rates by sector, and to describe indications for caesarean delivery, fetal and maternal outcomes, and aspects of quality of care.
D.A.Adekanle, 2013 [357]	Nigeria	Teaching; semi-urban	Retrospective	All caesarean sections	1004	To look at the trends over six years and the corresponding perinatal outcome in our health facility.
C.Nwosu, 2004 [274]	Nigeria	General hospital; sub-urban town	Retrospective	All Caesarean sections	1254	To review the incidence, indications and outcomes of Caesarean
K.Chu, 2012 (358)	Sub-Saharan Africa	District hospital	Prospective	All Caesarean sections	1276	This study reports Caesarean sections rates and indications in Democratic Republic of Congo, Burundi, and Sierra Leone, and describe the main parameters associated with maternal and early neonatal mortality.
K.M. Chu, 2010 [279]	CAR, South sudan, Ivory coast, DRC, Haiti, Somalia, Chad, Niger, Burundi, siera leone, mali,	Mixed	Prospective	All Caesarean sections	3233	To determine operative mortality in surgical programs from resource-limited settings.
J.Davies 2016 (359)	DRC, CAR, South sudan	District	Prospective	All Caesarean sections	4646	To investigate the POMR of surgical procedure including caesarean sections
M.R. Festin, 2009 [360]	Indonesia, Malaysia,	Tertiary and district hospitals	Prospective	All Caesarean sections	2592	This audit aimed to report rates and reasons for caesarean and associated clinical care practices

	Philippines, Thailand					amongst nine hospitals in the four South East Asian countries participating in the South East Asia-Optimising Reproductive and Child Health in Developing countries (SEA-ORCHID) project.
H.F.Akasheh, 2000 [361]	Jordan	Military	Retrospective	All Caesarean sections	1339	To review the cs performed at QAMH over a 6 year period
F.Richard, 2008 [362]	Burkina Faso	District; urban	Before and after	All Caesarean sections	1371	To assess the effects of a comprehensive intervention (staff training, equipment, internal clinical audits, cost sharing system, patients–providers meetings) in improving caesarean delivery access and quality in an urban district of Burkina Faso.
P.M.Fenton, 2003 [241]	Malawi	23 district and 2 central hospitals; rural and urban	Prospective	All Caesarean sections	8070	To examine potentially modifiable factors that may influence the high maternal and perinatal mortality associated with caesarean section in Malawi.
G.Kamilya, 2010 [276]	India	Teaching	Retrospective	All deliveries after exclusion of medical or obstetric comorbidities	13628	to evaluate the intrinsic risk of maternal death, directly attributed to caesarean delivery (CD) compared to vaginal delivery (VD), and to evaluate further the differential risk associated with antepartum and intrapartum CD.
P.N.Nana, 2011[363]	Cameroon	Referral ; semi-urban Faith based ; rural	Prospective	All C-sections (those without a clear indication were excluded from the analysis)	61	The aim of the study was to determine maternal, foetal outcomes and cost
A.Moges, 2015 [364]	Ethiopia	Faith based hospital	Retrospective	All Caesarean sections after 28 weeks	1547	To determine the prevalence, common indications, outcomes and complications of c/s in Attat Hospital, Ethiopia.
O.Akinola, 2010 [365]	Nigeria	University hospital; urban	Retrospective	All Caesarean sections	327	an audit of blood reservation and transfusion practices for caesarean section at this centre with a view to recommending modifications wherever it is found to be suboptimal.
H.Abbassi, 2001[366]	Morocco	Teaching; urban	Retrospective	All Caesarean sections	3231	To assess the maternal mortality and morbidity associated with c/s
O.M. Abiodun, 2009 [367]	Nigeria	Teaching; suburban	Retrospective	All Caesarean sections-	923	To determine the perinatal mortality rate among women who delivered through caesarean section in a tertiary health institution in Nigeria and evaluate how various social and obstetric factors influence the perinatal deaths.
R.C.Onoh, 2015[368]	Nigeria	Teaching	Retrospective	All Caesarean sections	2323	To appraise the cesarean deliveries and the associated fetal and maternal outcomes.

Y. ali, 1995 [369]	Ethiopia	Teaching	Prospective	All Caesarean sections	100	To provide base line information about the incidence, indications and complications of c/s, and suggest possible ways of reducing avoidable complications
S.A.Feresu, 2005 [370]	Zimbabwe	Central hospital; urban	Retrospective	All births	2990	To assess demographic and obstetric risk factors for stillbirth and early neonatal death
Swende, 2008[371]	Nigeria	tertiary	Retrospective	All Caesarean sections	420	To determine the c/s rate, ascertain the trend of emergency c/s, indications for c/s and emergency c/s morbidity and mortality at the Federal Medical Centre Makurdi.
S.Wanyonyi, 2006 [372]	Kenya	University hospital	Retrospective	All deliveries at the hospital in 2001 and 2004	1229	To compare the c/s rate, their indications and the perinatal outcome at the Aga Khan University hospital for the years 2001 and 2004.
O.C.Ezechi, 2009 [373]	Nigeria	Tertiary hospital	Retrospective	All Caesarean sections	5195	To review the perinatal mortality associated with c/s in 4 hospitals in the south western Nigeria
M.I.Nwafor, 2014 [261]	Nigeria	University hospital	Retrospective	Pre-term Caesarean sections excluding those for ruptured uterus and multiple pregnancy	1961	To evaluate perinatal outcome in preterm caesarean sections conducted under general anaesthesia (GA) and subarachnoid block (SAB) with the aim to ascertain any difference in outcome between the two methods.
S.Moodliar, 2007 [374]	South Africa	Tertiary; urban	Retrospective	All Caesarean sections	744	This study was designed to determine the prevalence of complications associated with abdominal delivery in a setting of high caesarean section (C/S) and HIV rates.
obgyn.net, 2011 (Evaluation of Risk Factors Associated with Recurrent Cesarean Section Morbidity)	Egypt	University	Prospective	1000 women undergoing Caesarean sections under general anaesthesia	1000	To determine the risk factors related to recurrent c/s morbidity and to suggest a morbidity scoring system based on these risk factors which can help in the prediction of c/s morbidity.
U. Okafor, 2008 [244]	Nigeria	Teaching hospital	Retrospective	Deaths during c/s	1579	To examine the changing trend in maternal deaths during caesarean delivery in a tertiary care hospital in Nigeria over an 8 year period
M.A.Ijaiya, 2001 [375]	Nigeria	University hospital	Retrospective	All Caesarean sections	2764	c/s delivery trend over 10 years at Ilorin, Nigeria
C.O.Imarengiaye, 2001 [246]	Benin	Tertiary/teaching hospital	Retrospective	Admitted to ICU following c/s due to anaesthesia-related complications	2686	To determine the anaesthesia-related complications after c/s in a tertiary hospital
J.R. Ekoundzola, 2001 [376]	DRC	University hospital	Retrospective	All Caesarean sections	745	Babies born by c/s
P.Foumane, 2014 [270]	Cameroon	Women and children's hospital	Retrospective	All Caesarean sections	219	To identify the risk factors for emergency caesarean deliveries and assess the effects of the emergency situation on maternal and fetal prognosis.

L. Foumsou, 2014 [377]	Chad	Maternity hospital	Prospective	All Emergency Caesarean sections	370	The aim of this study was to determine the incidence of emergency caesarean in Mother and Child Hospital of N'Djamena (Chad).
M.G.Diarra, 2006	Mali	Mixed	Prospective	All Caesarean sections	200	To determine the frequency, indications, prognosis, temporary characteristics and cost of c/s. To investigate the sociodemographic and psychologic profile of women having c/s and to formulate recommentions.
S.Adisso, 2006 [257]	Benin	University	Retrospective	All Caesarean sections but focus on anaesthetic mortality	1745	Maternal prognosis following c/s with regards to type of anaesthesia used
P.Imbert, 2003 [258]	Senegal	Principal hospital	Prospective	All Emergency Caesarean sections	402	Maternal and paediatric prognosis following emergency c/s
C.T.Cisse, 1998 [271]	Senegal	Surgical maternity hospitals	Prospective	All Caesarean sections	2436	The epidemiology and quality of c/s were investigated
A.Khan, 2014 [378]	Bangladesh	Teaching hospital	Prospective	130 Caesarean sections randomly selected	130	TO identify the different types & rate of caesarean section indications, the outcome of different indications, estimate the rate of caesarean section proportion of the elective & emergency indications and evaluate the complications of caesarean sections.
A.Rasoarimahandry 2001 [379]	Madagascar	Central university hospital	Retrospective		529	To evaluate the indications and prognosis of c/s, in order to improve caesarean's management and consequently to reduce maternal death.
D.Goswami, 2013 [174]	India	Tertiary hospital	Prospective	All Maternal deaths	8451	The aim of this study was to identify causes of maternal mortality at the facility and to assess the standard of care, deficiencies in health services and preventability of these deaths using facility-based maternal death reviews.
M.E. Akar, 2004 [380]	Turkey	Research hospital	Retrospective	All maternal deaths	126779	To determine the incidence and causes of maternal deaths in a 20-year period at the Women's Health Hospital, Ankara, Turkey
A.N.Johnson, 2012 [381]	South Africa	Academic hospital	Prospective	Exclusions: Women who were less than 18 years of age, had unknown HIV status or refused to participate	272	To determine the incidence of puerperal sepsis after c/s at the hospital
J. Beltman, 2011 [382]	Malawi	District hospital; rural	Retrospective	all cases of obstetric haemorrhage	375	To identify substandard care factors in the management of obstetric haemorrhage at district level in rural Malawi
C.Chang, 2011 [239]	Taiwan	Rural and urban	Retrospective	All c/s, excluded those with antepartum haemorrhage and haemorrhage from placenta preavia. Outcome focus on obstetric haemorrhage	69533	To compare the risk of PPH for patients who underwent c/s with general vs spinal/epidural anaesthesia

A.Zongo, 2015 [383]	Senegal and Mali	46 hospitals (mixed types); urban and rural	Prospective	All deliveries with analysis don't by mode of delivery	40975	To explore the differential effect of a multifaceted intervention on hospital-based maternal mortality between patients with cesarean and vaginal delivery in low-resource settings.
V.Govender 2010 [384]	South Africa	Tertiary	Prospective	All Caesarean sections	1091	An audit of second stage caesarean section (C/S) at a tertiary hospital to compare the frequency of perinatal and maternal complications between first and second stage C/S and to evaluate the training level of physicians.
T. Belay, 2014 [385]	Ethiopia, Addis Ababa	Teaching hospital	Prospective	For every second stage C/D, the next three consecutive first stage C/D cases were taken as controls	388	To compare maternal and perinatal outcomes of caesarean delivery (C/D) performed in the second stage of labor compared with the first stage in the Ethiopian setting.
J.Moodly, 2009 [386]	South Africa	District hospital, Durban	Retrospective	All Caesarean sections	1257	To investigate risks associated with second stage caesarean sections
Rabiu 2011 [387]	Nigeria	Teaching; urban	Retrospective	All intrapartum c/s multiple pregnancy, previous scar, congenital anomalies, mal-presentation, significant maternal disease excluded.	3061	To compare maternal and neonatal outcomes between caesarean section performed in the first and second stages of labour at the maternity unit of the Lagos State University Teaching Hospital, Lagos, Nigeria.
A.Suwal 2013[388]	Nepal	Teaching hospital/ referral hospital; urban	Prospective	All lower segment caesarean sections (classical excluded)	254	To compare the maternal and fetal outcome in elective and emergency cesarean section.
M Bokossa 2008 [389]	Ivory coast	University hospital; urban	Retrospective	197 elective and 197 randomly selected form the emergency patients	1264	To compare outcomes of elective and emergency caesarean sections
K Kizonde 2006 [390]	DRC	Tertiary hospital	Retrospective	All caesarean sections	625	To explore maternal and neonatal outcomes following caesarean section
E Ugwa 2015 [391]	Nigeria	Tertiary; semi-urban	Retrospective	All Caesarean sections	590	To review the caesarean section rate and perinatal mortality in Federal Medical Centre.
C Tshissuz 2014	DRC	Tertiary; urban	Retrospective	All Emergency Caesarean sections,	312	Outcome focussed on pph and transfusion rate associated with caesarean section
J. Villar, 2006 [64]	Argentina, brazil, Cuba, Ecuador, Mexico, Nicaragua, Paraguay, Peru	Urban and rural	Retrospective	All Emergency Caesarean sections: pre-labour c/s ,	31821	Aim was to assess the association between caesarean delivery and pregnancy outcome at the institutional level
X.De Muylder, 1990 [157]	Zimbabwe	All health facilities in a province in *Zimbabwe*	Retrospective	All the delivery deaths occurring in all the health facilities during the study period. Exclusions: deaths due to abortion, ectopic pregnancy or choriocarcinoma	3602	To identify which avoidable factors were involved most frequently with maternal deaths.
W.Chau-in, 2010 [249]	Thailand	Mixed	Prospective		16697	to determine the incidence of maternal mortality related to anesthesia, to analyze the causes and to suggest measures to improve anesthetic safety for the parturients.

G.Urbani, 2001[392]	South Africa	Teaching hospitals	Prospective	All women undergoing c/s who accepted to take part, except for those with diabetes mellitus.	307	To document complications associated with cesarean section in HIV-infected women.
A. Nakimuli, 2015[393]	Uganda	Referral Hospital	Prospective	Elective Caesarean sections for singleton pregnancies	5763	The primary objective was to assess the incidence and determinants of neonatal morbidity after elective caesarean section deliveries. The secondary objective was to describe the maternal morbidity associated with elective caesarean section.
W. van den Boogaard, 2016 [394]	Burundi	Rural Hospital	Prospective	All Caesarean sections	228	To determine the maternal status of women 2 years following a C-section in a district hospital in rural Burundi.
C.M. Ouedraogo, 2015 [395]	Burkina Faso	District	Retrospective	All Caesarean sections	3381	To study the epidemiology, clinical and prognostic aspects of c/s
A.Nyamtema, 2016 [395, 396]	Tanzania	10 rural centers< Tanzania	Retrospective	All Caesarean sections	5868	To describe the results of increasing availability and quality of caesarean deliveries and anaesthesia in rural Tanzania.
A.D.Ekanem, 2008 [256]	Nigeria	Teaching hospital	Retrospective	All Caesarean sections	431	To assess the maternal outcome of emergency caesarean sections in University of Calabar Teaching Hospital in relationship to the seniority and experience of medical personnel involved in the operation
S.Benzounia, 2016 [397]	Morocco	Tertiary maternity hospital.	Prospective	All the cases of elective and emergency caesarean section Mothers who had definite antenatal complications that would adversely affect fetal outcome were excluded from the study.	588	The objective of the study was to compare the fetal outcome and the indications in elective versus emergency caesarean section performed in a tertiary maternity hospital.
R.Soren, 2016 [398]	India	Teaching hospital	Prospective	All subjects undergoing elective and emergency Caesarean were included over the study period	2060	To compare emergency and elective Caesarean section with regard to intra operative and post-operative complications in both mother and child.
A.A. El Daba, 2010 [399]	Egypt	University hospital	Retrospective	All maternal deaths.	Unknown	The aim of the study is to estimate the prevalence, causes and risk factors of maternal mortality related to anaesthesia.
E.Abe, 2008 [400]	Nigeria	Central hospital	Retrospective	MD but Deaths due to abortion and ectopic pregnancy were excluded	Unknown	To document the maternal mortality rate and pattern of obstetric deaths at the Central Hospital, Benin City, Edo State, Nigeria.
G.S. Gebhardt, 2015 [401]	South Africa	Mixed	Retrospective	MD and c/s in South Africa	Unknown	To scrutinise the contribution or effect of the surgical procedure on the ultimate cause of death by a cross-cutting analysis of the 2011 - 2013 national data.
P.N. Makinga, 2012 [193]	South Africa	District hospital	Retrospective	All reported MD	Unknown	To determine the clinical and demographic profile of maternal deaths, determine the most common primary

						causes of maternal deaths at district hospital level, compare the causes of deaths at district hospital, provincial and national level, and to investigate the quality of care that was provided to maternal deaths patients and to make recommendations.
C.F.L. Hoestermann, 1996 [402]	Gambia	Referral	Retrospective	All Maternal deaths	Unknown	To analyse the maternal mortality in the main referral hospital in The Gambia, West Africa.
A. L. Montgomery, 2014 [403]	India	Mixed	Retrospective	All Maternal deaths	Unknown	To estimate the national and regional distribution of maternal death and uptake of obstetric service indicators among women who died while pregnant or postpartum.
Jayashree, 2014[192]	India	Government teaching hospital	Prospective	All Maternal deaths	Unknown	To study the MD and the common causes and complications leading to MD over a period of 7 years from 2008-2014
M.Bouvier-Colle, 2001 [404]	West Africa	Mixed	Prospective	All Maternal deaths	Unknown	To describe the maternal mortality, estimation of the rates and distribution of obstetric causes, from a population based survey of pregnant women carried out in West Africa.
P.M.Tebeu, 2007 [405]	Cameroon	Provincial hospital	Retrospective	All Maternal deaths	Unknown	The aim of this study was to establish baseline data on maternal mortality for future evaluation of pregnancy-related mortality trends in this city.
M.N.El-Gharib, 2010 [406]	Egypt	University hospital	Retrospective	All Maternal deaths	Unknown	To assess the etiology, trends and causes of maternal mortality in Tanta University Hospital.
P.Charoenweerakul, 2009 [407]	Thailand	University hospital	Retrospective	All Maternal deaths	Unknown	To analyse the characteristics, leading causes and trend of MD at the hospital between the 20th and 21st century
S.J.Pal, 2014 [408]	South India	District hospital	Retrospective	Inclusion: all MD occurring during pregnancy and within 42 days of delivery, ectopic pregnancies, septic abortions, molar pregnancies Exclusion: all MD occurring after 42 days of termination of pregnancy, and accidents	Unknown	To study the causes behind MD in the 3 yr review period, to analyse the trend of MMR over 3 years of study and to evaluate preventable causes and use the data to take measures to reduce MMR.
A.C.L Granja, 2001 [177]	Mozambique	Central hospital	~~retrospective~~ Retrospective	All Maternal deaths	Unknown	To describe adolescent maternal mortality and analyse its avoidability.
E. Abdel-Hady, 2007 [409]	Egypt	Mixed	~~retrospective~~ Retrospective	All Maternal deaths	Unknown	To investigate the causes of maternal mortality in the Dakahlia Governorate in Egypt.
A. Bashir, 1995 [410]	Pakistan	Mixed	~~retrospective~~ Retrospective	All Maternal deaths	Unknown	A study regarding maternal death in Faisalabad City, Pakistan
A.A.Mohammed, 2011 [411]	East Sudan	Mixed	Retrospective	Maternal deaths in that community	Unknown	To investigate the causes and contributing factors of maternal deaths and to identify any discrepancies in rates and causes between different areas

N. Bano, 2011 [412]	Pakistan	Mixed	~~prospective~~Prospective	All Maternal deaths	Unknown	To determine maternal mortality to assess the achievement of Millennium Development Goal 5 in Pakistan and suggest remedial measures.
O.T. Oladapo, 2006 [413]	Nigeria	teaching	~~retrospective~~ Retrospective	All Maternal deaths	Unknown	This study presents the magnitude and distribution of causes of maternal mortality at the beginning of the 21st century in a Nigerian referral hospital and derives recommendations, to reduce the frequency of maternal deaths in this centre and in other centres in similar setting.
L.A.O.Ujah, 2005 [170]	Nigeria	Teaching hospital	Retrospective	All Maternal deaths	Unknown	To determine the magnitude, trends, causes and characteristics of maternal deaths before and after the launch of the Safe Motherhood Initiative in Nigeria, with a view to suggesting strategic interventions to reduce these deaths.
J.W.Bolnga, 2014 [414]	Papau New Guinea	General hospital	Retrospective	All Maternal deaths	Unknown	To assess the frequency, causes, and reporting of maternal deaths at a provincial referral hospital in coastal Papua New Guinea (PNG), and to describe delays in care.
S.Ray, 2013 [415]	Botswana	Mixed	Retrospective	Reported MD	Unknown	To investigate the underlying circumstances of MD in Botswana
T.T.Kane, 1992 [416]	Egypt	Mixed	Retrospective	All Maternal deaths	Unknown	To determine the incidence and causes of MD in Giza
Z.Amarin, 2010 [417]	Jordan	Mixed	Retrospective	All Maternal deaths	Unknown	To estimate the number of maternal among Jordanian women; to identify the causes of maternal mortality
P.T.Wagaarachchi, 2002 [418]	Sri Lanka	Tertiary care hospital	Retrospective	All Maternal deaths	Unknown	To assess the trends in maternal mortality and factors affecting substandard care at a tertiary care hospital in a developing country.
A.Kampikaho, 1991 [201]	Uganda	Mixed	Retrospective	All Maternal deaths	Unknown	To estimate MMR, to identify type and cause of MD in 5 Kampala hospitals
S.Mahbouli, 2003 [419]	Tunisia	Military hospital	Retrospective	10 cases of MD	Unknown	To determine maternal mortality rate during the last decade as revealing the quality of obstetrical follow-up and the necessary measures to be taken.
M. Kassas, 1995 [420]	Egypt	Mixed	Retrospective	All Maternal deaths	Unknown	To discover avoidable factors and identify the major problems and issues that require action concerning maternal mortality in Egypt.
A.Mungra, 1999 [189]	Surinam	Nationwide (5 hospitals)	Retrospective	All Maternal deaths	Unknown	To assess the magnitude, causes and associated factors of maternal mortality in Surinam
S. Mukherjee, 2014 [421]	India	Tertiary teaching institute	Retrospective	All Maternal deaths	Unknown	To study the incidence of maternal deaths and the causes at a tertiary (teaching) institute over 6 years from January 2006 – December 2010
A.O. Sule-Odu, 2000 [160]	Nigeria	Mixed	Retrospective	All Maternal deaths	Unknown	To investigate factors responsible for the high maternal deaths so as to reduce it substantially, if not eliminate it completely.

M.Ashraf, 2015 [422]	India	Tertiary care center	Retrospective	All Maternal deaths	Unknown	To study the maternal mortality and the causes resulting in maternal death over 5 years in a tertiary care centre,
W Saleh 2013 [423]	Egypt	University hospital, Cairo	Retrospective	All Maternal deaths	Unknown	The aim was to calculate Maternal Mortality Ratio (MMR) as well as identify the causes and predisposing factors to maternal deaths.
Karimi-Zarchi 2016[424]	Iran	Health centers, yazd	Retrospective	All Maternal deaths	Unknown	The aim of this study was to determine the frequency and causes of pregnancy-related mortality rates in Yazd Province.
MOH confidential enquiries Malaysia, 1991	Malaysia	Mixed	Retrospective	All Maternal deaths	Unknown	To identify trends in maternal mortality and to analyse maternal deaths.
MOH confidential enquiry Malaysia, 1992 [280]	Malaysia	Mixed	Retrospective	All Maternal deaths	Unknown	To identify trends in maternal mortality, analyse maternal deaths and formulate recommendations.
confidential enquiry Malaysia, 1993	Malaysia	Mixed	Retrospective	All Maternal deaths	Unknown	To statistically analyse maternal deaths that occurred in Malaysia, in 1993.
confidential enquiry Malaysia, 1994 [207]	Malaysia	Mixed	Retrospective	All Maternal deaths	Unknown	To investigate factors contributing to maternal death
Confidential enquiry Malaysia 1995-96[209]	Malaysia	Mixed	Retrospective	All deliveries	95529	To identify the major contributory factors to maternal death, to then institute remedial measures to reduce the likelihood of a maternal death occurring.
Confidential enquiry Malaysia, 1997-2000 [209]	Malaysia	Mixed	Retrospective	All Maternal deaths	Unknown	To study the trend of maternal deaths in Malaysia
Confidential enquiry Malaysia 2006-2008	Malaysia	Mixed	Retrospective		Unknown	To investigate factors contributing to maternal death
Confidential Enquiry in South Africa 2005-2007 [186]	South Africa	All hospitals; rural and urban	Retrospective	All maternal deaths	477210	To investigate maternal mortality in South African, to aid make recommendations.
Confidential Enquiry in South Africa 2006-2008 [190]	South Africa	All hospitals; rural and urban	Retrospective		564271	To investigate maternal mortality in South African, to aid make recommendations.
Saving maternal lives 2008-10 [190]	South Africa	Mixed	Retrospective	All maternal deaths	Unknown	To summarise the findings on confidential enquiries into maternal deaths in South Africa for 2008-2010;
Confidential Enquiry in South Africa 2011-13[425]	South Africa	All hospitals; both rural and urban	Retrospective	All Maternal deaths	655686	To investigate maternal mortality in South African, to aid make recommendations.
Ministry of Health and Population – Egypt, 2000 [185]	Egypt	Mixed	Retrospective		Unknown	To investigate maternal mortality in egypt

APPENDIX 8: Rate of caesarean section deaths as a proportion of postpartum maternal deaths- sensitivity analysis.

Factors		Studies/ Cohorts	n	N	Prevalence (%)	Heterogeneity I^2	Subgroup P Value
Region	East Asia and Pacific	17	611	2,049	27.5 (22.6; 32.5)	64.2%	<0.001
	Europe and Central Asia	1	50	135	37.0 (29.3; 45.4)	-	
	Latin America and the Carribean	16	239	455	73.5 (56.3; 88.4)	37.8%	
	Middle-East and North Africa	8	305	1,434	35.7 (14.8; 59.5)	98.2%	
	South Asia	18	371	1,517	30.6 (23.7; 37.9)	82.9%	
	Sub-saharan Africa	27	1,981	4,528	36.6 (30.6; 42.8)	90.1%	
Year of study	<2000	21	1,158	3,882	31.0 (24.0; 38.5)	95.7%	0.025
	>2000	66	2,399	6,236	40.4 (33.9; 47.0)	91.7%	
Study design	Prospective	49	370	1,003	42.8 (35.6; 50.2)	63.5%	0.009
	Retrospective	38	3,187	9,115	32.6 (26.9; 38.6)	96.9%	
Income setting	Low	14	420	835	42.9 (30.5; 55.7)	89.7%	0.261
	Lower-Middle	41	974	3,874	32.1 (25.3; 39.2)	93.1%	
	Upper-Middle	32	2,163	5,409	37.6 (30.8; 44.6)	87.9%	
Quality	Low	5	141	350	37.0 (26.8; 47.8)	71.4%	0.840
	High	82	3,416	9,768	36.9 (31.6; 42.2)	93.8%	
Overall		**87**	**3557**	**10,118**	**36.7 (31.7; 41.7)**	**93.5%**	

APPENDIX 9: Individual country rates of caesarean section fatality rates/ 1000 procedures.

Country	Rate / 1000 CS
Bangladesh	0.000
Jordan	0.000
Namibia	0.000
China	0.018
Viet Nam	0.239
Mexico	0.253
Sri Lanka	0.261
Thailand	0.322
Turkey	0.333
Ecuador	0.393
Cuba	0.437
Mongolia	0.518
Brazil	0.601
South Africa	0.697
Nicaragua	0.85
Argentina	0.87
Algeria	0.912
Paraguay	0.912
Peru	1.005
Cambodia	1.038
Malaysia	1.078
Benin	1.146
Lebanon	1.24
Cameroon	1.394
Burundi	1.47
Indonesia	1.849
Philippines	2.253
Nepal	2.309
Pakistan	2.314
India	2.329
Kenya	2.336
Morocco	2.786
Zimbabwe	3.506
Uganda	6.016
Ethiopia	6.71
Ghana	7.337
Cote d'Ivoire	7.552
Mozambique	8.209
Congo, Dem. Rep.	8.951
Angola	9.675
Gabon	9.688
Rwanda	10.045
Malawi	10.537

Niger	10.606
Burkina Faso	11.35
Sierra Leone	11.834
Nigeria	13.348
Tanzania	14.78
Madagascar	20.794
Guinea	25.246
Mali	28.066
Chad	28.21
Senegal	29.967
Afghanistan	31.639
Togo	39.216
Iraq	56.122

APPENDIX 10: Rates of deaths in women undergoing caesarean section / 1000 caesarean sections- a sensitivity analysis excluding studies that included only subsets of the population.

Outcome		CS deaths of total CS (Sensitivity)					
Analysis		Studies/ Cohorts	n	N	Prevalence (x1,000)	Heterogeneity I2	Subgroup P Value
Region	East Asia and Pacific	15	140	150,828	0.6 (0.2; 1.0)	74.1%	<0.001
	Europe and Central Asia	2	51	130,596	0.3 (0.2; 0.4)	98.2%	
	Latin America and the Carribean	17	202	215,982	0.6 (0.4; 0.8)	33.4%	
	Middle-East and North Africa	6	13	9,021	0.7 (0.1; 1.8)	28.9%	
	South Asia	20	258	75,668	2.1 (1.1; 3.3)	83.4%	
	Sub-saharan Africa	88	5,737	1,887,464	9.5 (8.2; 10.9)	97.8%	
Year of study	<2000	28	919	299,499	7.5 (4.7; 11.0)	98.4%	0.015
	>2000	121	5,522	2,173,001	3.8 (3.2; 4.5)	96.5%	
Study design	Prospective	89	1,585	285,217	3.1 (1.9; 4.5)	96.1%	<0.001
	Retrospective	60	4,856	2,187,283	7.6 (6.5; 8.7)	97.8%	
Income setting	Low	52	1,759	131,481	10.6 (7.8; 13.9)	95.4%	<0.001
	Lower-Middle	39	525	137,595	1.8 (1.0; 2.9)	89.3%	
	Upper-Middle	57	4,117	2,200,483	2.5 (2.0; 3.0)	96.0%	
Quality	Low	23	1,303	120,363	7.5 (5.0; 10.5)	95.1%	0.005
	High	125	5,132	2,350,077	3.8 (3.2; 4.4)	96.2%	
Type of Hospital	District hospital	19	135	17,308	5.7 (3.3; 8.7)	66.9%	0.013
	Mixed	18	4,713	2,033,020	5.8 (4.3; 7.5)	99.2%	
	Private hospital	2	3	1,470	1.5 (0.0; 4.6)	100.0%	
	Teaching hospital	38	1,041	224,118	8.8 (5.3; 13.1)	98.2%	
	Tertiary hospital	23	281	40,729	8.3 (5.3; 11.8)	89.5%	
Overall		**149**	**6,441**	**2,472,500**	**4.5 (3.9; 5.2)**	**97.1%**	

APPENDIX 11: Caesarean section risk factors related to maternal and fetal outcomes

a. *Emergency vs. Elective CS*

Outcome	NO. of studies	Emergency C/S		Elective C/S		Estimate	Lower CI (95%)	Upper CI (95%)	P-Value	I^2
		Events	No events	Events	No events	OR				
Maternal death	21	419	129,035	120	125,534	2.17	1.19	3.95	0.011	64.6%
ITU Admissions	3	282	19,215	391	133,317	2.18	0.39	12.09	0.372	85.5%
Hysterectomy	6	219	49,018	120	39,806	1.60	0.89	2.89	0.116	64.5%
Blood transfusion	9	1,844	49,433	794	39,978	1.74	1.02	2.98	0.044	92.8%
Postpartum haemorrhage	8	153	1,732	47	983	2.87	1.08	7.68	0.035	82.1%
Anaemia	5	518	1,581	43	479	2.20	1.10	4.39	0.026	65.3%
Febrile illness	5	350	2,536	68	1,096	1.57	0.87	2.83	0.136	67.9%
Postpartum infection	3	59	315	6	333	10.16	4.36	23.69	<0.001	0.0%
Postpartum endometritis	4	33	1,890	9	638	1.171	0.56	2.47	0.677	0.0%
Wound infection	8	272	3,064	64	837	1.30	0.59	2.89	0.521	82.7%
Wound dehiscence	2	22	1,464	4	670	3.87	1.26	11.89	0.018	0.0%
Urinary tract infection	3	41	495	12	447	5.09	1.93	13.42	0.001	24.0%
Respiratory complications	2	73	1,413	20	654	2.48	1.13	5.43	0.023	48.5%
Bladder / bowel injury	4	17	2,286	3	975	2.69	0.87	8.18	0.081	0.0%
Maternal morbidity	1	48	240	19	197	2.07	1.18	3.64	0.011	-
Uterine extensions	1	28	22	3	47	19.94	5.47	72.71	<0.001	-
Perinatal death	11	1,624	31,214	105	16,522	4.35	2.86	7.32	<0.001	83.9%
Low Apgar score- 5 mins.	4	183	608	55	547	3.89	1.83	8.27	<0.001	71.7%
Neonatal death	1	359	19,700	140	24,523	3.19	2.62	3.88	<0.001	-
Stillbirth	1	553	20,106	107	24,682	6.34	5.15	7.81	<0.001	-

b. *Second vs. First stage of labour CS*

Outcome	No. of studies	Second stage C/S		First stage C/S		Estimate				I^2
		Events	No events	Events	No events	OR	Lower CI (95%)	Upper CI (95%)	P-Value	
Maternal death	4	6	557	1	5,504	12.27	2.87	52.49	0.001	0.0%
ITU Admissions	3	10	255	3	1,983	16.68	4.90	56.77	<0.001	0.0%
Hysterectomy	5	20	633	3	5,309	22.08	7.56	64.43	<0.001	0.0%
Blood transfusion	7	79	2,402	172	6,001	1.99	1.03	3.84	0.041	71.9%
Postpartum haemorrhage	4	136	441	212	5,307	5.19	1.83	14.73	0.002	83.0%
Intraoperative complications	3	103	416	220	5,292	17.84	3.34	95.33	0.001	89.7%
Bladder injury	5	33	778	42	7,617	5.62	2.99	10.58	<0.001	36.9%
Lower segment tears	3	25	491	26	4,713	7.81	4.28	14.23	<0.001	0.0%
Febrile illness	4	87	281	125	1,439	4.07	2.95	5.61	<0.001	0.0%
Postpartum endometritis	2	27	373	172	3,592	1.71	1.11	2.62	0.015	0.0%
Wound infection	7	72	757	249	6,575	2.77	1.18	6.49	0.019	80.0%
Uterine extensions	4	86	554	155	6,286	11.45	4.20	31.23	<0.001	85.3%
Bladder / Uterine extensions	1	4	93	0	291	28.06	1.50	526.01	0.026	-
Uterine vessel injury	1	13	285	25	3,494	6.38	3.23	12.60	<0.001	-
Perinatal death	5	23	606	10	5,551	9.23	4.24	20.10	<0.001	0.0%
Low Apgar score- 5 mins.	3	14	312	7	2,225	11.89	1.09	130.27	0.043	65.8%
Low Apgar score- 1 mins.	1	15	24	1	38	23.75	2.94	191.59	0.003	
NICU admission	6	134	697	223	6,791	3.57	2.20	5.79	<0.001	- 69.4%

APPENDIX 12: Search history: Accuracy of on-site tests to detect anaemia in antenatal care: a systematic review

1. EMBASE; pregnancy.af; 730804 results

2. EMBASE; exp PREGNANCY/; 595416 results

3. EMBASE; pregnan*.af; 790375 results

4. EMBASE; antenatal.af; 33986 results

5. EMBASE; ante-natal.af; 603 results

6. EMBASE; gravid*.af; 21782 results

7. EMBASE; parturient.af; 3942 results

8. EMBASE; prenatal.af; 205568 results

9. EMBASE; gestation*.af; 233292 results

10. EMBASE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9; 963515 results

11. EMBASE; an$emia.ti,ab; 113762 results

12. EMBASE; exp HEMOGLOBIN/; 222340 results

13. EMBASE; H$emoglobin.af; 259243 results

14. EMBASE; Hb.ti,ab; 42341 results

15. EMBASE; haemoglobin.ti,ab; 35287 results

16. EMBASE; 12 OR 13 OR 14 OR 15; 292011 results

17. EMBASE; anaemia.ti,ab; 113762 results

18. EMBASE; anaemia.ti,ab; 33352 results

19. EMBASE; 11 OR 17 OR 18; 145584 results

20. EMBASE; 10 AND 16 AND 19; 3895 results

21. EMBASE; f$et*.ti,ab,af; 466110 results

22. EMBASE; cord.ti,ab,af; 289892 results

23. EMBASE; neonat*.ti,ab,af; 297624 results

24. EMBASE; placenta.ti,ab; 51372 results

25. EMBASE; 21 OR 22 OR 23 OR 24; 986330 results

26. EMBASE; 20 NOT 25; 2372 results

APPENDIX 13: Study characteristics of accuracy studies for tests to detect anaemia in pregnancy.

Author, Yr	Country and setting	No. of women	Index test	Reference test
Pistorius 1996[117]	Pretoria, South Africa, Public Hospital.	100	Copper sulphate	Coulter Counter
Wilkinson 1997 [118]	Kwala Zulu, South Africa. One mobile clinic team serving 14 clinic points across the district.	449	Copper sulphate	Sysmex Analyser
Van den broek1999 [112]	Malawi. Three rural hospitals and two health centres	644	Clinical signs, *HCS, HemoCue.	Coulter Counter
Shulman 2001[111]	Mombasa, Kenya District hospital	1787	Clinical signs	Coulter Counter
Fourn 2004[115]	Benin Rural maternity clinic	480	Clinical signs	Spectrophotometry Labarotory test
Prathapan 2011[116]	Colombo district, Sri Lanka Field antenatal clinics in 11out of 13 ministry of health areas in the Colombo district	101	HCS	Spectrophotometry Laboratory test
Chathurani 2012 [114]	Anuradhapura district, Sri Lanka Ministry of health field clinics Anuradhapura district	115	Clinical signs HCS	Cyanmethaemoglobin Method
Khan 2015 [113]	Karachi, Pakistan. Community-based antenatal clinics in the towns of Gadap, Bin Qasim, Kemari, and New Karachi	194	Clinical signs HCS	Calorimetric Hemoglobinometry
Agnihotri 2015[119]	India ANC-O&G department JNMC, Sawangi, Wardha ANC clinic, civil hospital	100	Sahil's method Copper sulphate	Cyanmethaemoglobin Method
Ahankari 2016[120]	India 33 villages in Tuljapur and Lohara blocks of Osmanabad district, Maharashtra.	269	NBM2000, noninvasive haemoglobin sensor	Sysmex analyser XP-100

APPENDIX 14: QUADAS-2 quality assessment tool for risk of bias of test accuracy studies for the detection of anaemia in pregnancy.

Study ID	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Pistorius 1996	☺	☺	☺	☺	☺	☺	☺
Wilkinson 1997	☺	☺	☺	☺	☺	☺	☺
Van den berk 1999	?	☺	☺	☺	☺	☺	☺
Shulman 2001	☺	☺	☺	☺	☺	☺	☺
Fourn 2004	☺	☺	☺	☺	☺	☺	☺
Chathurani 2010	☹	☹	☺	☺	☺	☺	☺
Prapathan 2011	☺	☹	☺	☺	☺	☺	☺
Khan 2015	☺	☺	☺	☺	☺	☺	☺
Agnihotri 2015	?	☺	☺	?	☺	☺	☺
Ahankari 2016	?	☺	☺	☺	☺	☺	☺

☺= low risk of bias, ☹ High risk of bias,? Unclear risk of bias

APPENDIX 15: Search strategy for systematic review on pregnancy outcomes in women with Tuberculosis.

1. EMBASE; TB.ti,ab; 42940 results.

2. EMBASE; exp MYCOBACTERIUM TUBERCULOSIS/ OR exp TUBERCULOSIS/; 223787 results.

3. EMBASE; exp LATENT TUBERCULOSIS/; 2831 results.

4. EMBASE; 1 OR 2 OR 3; 236001 results.

5. EMBASE; (maternal AND mortality).ti,ab; 24924 results.

6. EMBASE; MATERNAL MORTALITY/; 17214 results.

7. EMBASE; (maternal AND morbidity).ti,ab; 15710 results.

8. EMBASE; exp MATERNAL MORBIDITY/; 5705 results.

9. EMBASE; exp PERINATAL MORTALITY/; 17980 results.

10. EMBASE; exp PERINATAL MORBIDITY/; 9648 results.

11. EMBASE; (still AND birth).ti,ab; 11733 results.

12. EMBASE; (preterm AND birth).ti,ab; 32257 results.

13. EMBASE; "low birth weight".ti,ab; 25555 results.

14. EMBASE; "early neonatal death".ti,ab; 476 results.

15. EMBASE; (congenital AND TB).ti,ab; 124 results.

16. EMBASE; exp CONGENITAL TUBERCULOSIS/; 91 results.

17. EMBASE; exp PREGNANCY/; 598759 results.

18. EMBASE; exp PARAMETERS CONCERNING THE FETUS, NEWBORN AND PREGNANCY/ OR exp
PREGNANCY COMPLICATION/ OR exp PREGNANCY DISORDER/ OR exp PREGNANCY OUTCOME/; 582087
results.

19. EMBASE; 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 16 OR 18; 603296 results.

20. EMBASE; 4 AND 17 AND 19; 1035 results

APPENDIX 16: Characteristics of studies included in a systematic review on TB in pregnancy.

Author/Year	Study dates	Setting	Study design	Study population	Site of TB disease (number of women)	Anti-tuberculous Treatment	Outcomes
Asuquo B, et al 2012 [426]	2004–2006	Three inner-city hospitals, Birmingham, United Kingdom	Retrospective cohort study	Cases: 24 pregnant women with active TB Controls: 72 apparently healthy pregnant women matched for age and socio-economic status N.B. Only one woman had HIV/TB co-infection	Pulmonary (13) Extra-pulmonary (10): -TB lymph-8 -TB milliary- 2 - TB arthritis- 1 TB- Meningitis- 2 Multi-site (1)	Rifampicin, isoniazid, pyrazinamide, and ethambutol	Preterm birth, Mean birth weight
Lin HC et al, 2010 [427]	2001–2003	National database, Taiwan	Cross–sectional retrospective study	Cases: 761 pregnant women with active TB Controls: 3805 apparently healthy pregnant women matched for age and year of delivery N.B. HIV/TB co-infected women were excluded	Not documented	Rifampicin, isoniazid, pyrazinamide, and ethambutol	Preterm birth, small-for-gestational age, and low birth weight
Tripathy SN et al, 2003 [138]	1986–2001	Teaching hospital plus a private clinic, Calcutta, India	Prospective cohort study	Cases: 111 pregnant women with active TB Controls: 51 apparently healthy pregnant women matched for age, parity and socio-economic status	Pulmonary (101) Extra-pulmonary (10)/ Glandular	Either rifampicin, isoniazid, pyrazinamide, plus ethambutol; or rifampicin, isoniazid, and ethambutol	Maternal death and neonatal birth weight
Figueroa- Damian R et al, 1998 [137]	1990–1995	Perinatal Institute, Mexico city, Mexico	Prospective cohort study	Cases: 25 pregnant women with active TB Controls: 75 apparently healthy pregnant women matched for age, gestational age and socioeconomic status	Pulmonary (13) Extra-pulmonary (12): Renal Tb - 7	Either rifampicin plus isoniazid; or rifampicin, isoniazid, and ethambutol; or rifampicin, isoniazid, and pyrazinamide	Obstetric morbidity, preterm labour, and neonatal mortality
Figueroa- Damian R et al, 2001 [428]	1990–1998	Perinatal Institute, Mexico city,	Retrospective cohort study	Cases: 35 pregnant women with active TB Controls: 105 apparently healthy pregnant women matched for age, gestational age and socio-economic status	Pulmonary (17) Extra-pulmonary (18): Renal Tb- 11 Lymph node Tb- 6 Cutaneous Tb- 1	Triple therapy of Isoniazid, Rifampicin and Ethambutol or Pyrazinamide	Obstetric morbidity, preterm birth, and perinatal death
Jana N et al, 1994 [429]	1983–1991	Two clinics, Chandigarh, India	Prospective cohort study	Cases: 79 pregnant women with active TB Controls: 316 apparently healthy pregnant women matched for age, parity and socio-economic status	Pulmonary (79)	48% received isoniazid, rifampicin, and ethabutol.11% isoniazid and rifampicin, 15% isoniazid and rifampicin. 2 patients had quadruple therapy.	Preterm labour, small-for-gestational age, low birth weight, and perinatal death .

Jana N et al, 1999 [136]	1983–1993	One clinic, Chandigarh India	Prospective cohort study	Cases: 33 pregnant women with active TB Controls: 132 apparently healthy pregnant women matched for age, parity and delivered within 48 hours of each other	Extra-pulmonary (33): Lymph node Tb-12 Intestine Tb- 9 Skeletal Tb- 7 Renal Tb- Tb meningitis- 2 Endometrial Tb- 1	62% received isoniazid, rifampicin and ethambutol. 21% received ethambutal, rifampicin and pyrazinamide.	Maternal morbidity, perinatal mortality, preterm birth and low birth weight.
Ali et al, 2011[430]	2008–2010	Maternity hospital, Kassala, Sudan	Retrospective cohort study	Cases: 42 pregnant women with active TB Controls: 42 apparently healthy unmatched pregnant women attending the same hospital N.B. 5 women were HIV/TB co-infected	Pulmonary (35) Extra-pulmonary (7)	Rifampicin, isoniazid, pyrazinamide, and ethambutol	Maternal anaemia, preterm birth, and low birth weight
Maryonawski A et al, 1971 [431]	1963–1970	France	Retrospective cohort study	Cases: 1188 pregnant women with active TB Controls: 2007 apparently healthy pregnant women with past history of active TB or exposure to TB	Pulmonary (1188)	The majority had no treatment.	Preterm birth
Kavganko PA et al, 2003 [432]	1992–2001	TB hospital, Moscow, Russia	Retrospective cohort study	Cases: 371 pregnant women with active TB Controls: 121 apparently healthy unmatched pregnant women	Pulmonary (371)	Not all received treatment – regimen unknown	Perinatal death, asphyxia, congenital anomaly, and low birth weight
Kavganko PA et al, 2004 [433]	1996–2002	TB hospital, Moscow, Russia	Retrospective cohort study	Cases: 96 pregnant women with active TB Controls: 120 apparently healthy unmatched pregnant women	Extra-pulmonary (96)	Not documented	Maternal morbidity and preterm birth
Bjerkedal T et al, 1975 [434]	1967–1968	Norway	Retrospective cohort study	Cases: 542 pregnant women with active TB Controls: 112530 apparently healthy unmatched pregnant women	Pulmonary (542)	Not documented	Maternal morbidity, perinatal death, low birth weight, preterm birth, congenital anomaly, and miscarriage
Pranevicius A, et al 2003 [435]	1993–1997	Teaching hospital, Lithuania	Retrospective cohort study	Cases: 77 pregnant women with active TB Controls: 72 pregnant healthy women	Pulmonary TB (64) Extra-pulmonary (13)	Only 49.3% of women received treatment during pregnancy.	Perinatal death and asphyxia

Appendix 17: Published manuscript

Anaesthesia-related maternal mortality in low-income and middle-income countries: a systematic review and meta-analysis

Soha Sobhy*, Javier Zamora*, Kuhan Dharmarajah, David Arroyo-Manzano, Matthew Wilson, Ramesan Navaratnarajah, Arri Coomarasamy, Khalid S Khan, Shakila Thangaratinam

Summary

Background The risk factors contributing to maternal mortality from anaesthesia in low-income and middle-income countries and the burden of the problem have not been comprehensively studied up to now. We aimed to obtain precise estimates of anaesthesia-attributed deaths in pregnant women exposed to anaesthesia and to identify the factors linked to adverse outcomes in pregnant women exposed to anaesthesia in low-income and middle-income countries.

Methods In this systematic review and meta-analysis, we searched major electronic databases from inception until Oct 1, 2015, for studies reporting risks of maternal death from anaesthesia in low-income and middle-income countries. Studies were included if they assessed maternal and perinatal outcomes in pregnant women exposed to anaesthesia for an obstetric procedure in countries categorised as low-income or middle-income by the World Bank. We excluded studies in high-income countries, those involving non-pregnant women, case reports, and studies published before 1990 to ensure that the estimates reflect the current burden of the condition. Two independent reviewers undertook quality assessment and data extraction. We computed odds ratios for risk factors and anaesthesia-related complications, and pooled them using a random effects model. This study is registered with PROSPERO, number CRD42015015805.

Findings 44 studies (632 556 pregnancies) reported risks of death from anaesthesia in women who had an obstetric surgical procedure; 95 (32 149 636 pregnancies and 36 144 deaths) provided rates of anaesthesia-attributed deaths as a proportion of maternal deaths. The risk of death from anaesthesia in women undergoing obstetric procedures was 1·2 per 1000 women undergoing obstetric procedures (95% CI 0·8–1·7, I^2=83%). Anaesthesia accounted for 2·8% (2·4–3·4, I^2=75%) of all maternal deaths, 3·5% (2·9–4·3, I^2=79%) of direct maternal deaths (ie, those that resulted from obstetric complications), and 13·8% (9·0–20·7, I^2=84%) of deaths after caesarean section. Exposure to general anaesthesia increased the odds of maternal (odds ratio [OR] 3·3, 95% CI 1·2–9·0, I^2=58%), and perinatal deaths (2·3, 1·2–4·1, I^2=73%) compared with neuraxial anaesthesia. The rate of any maternal death was 9·8 per 1000 anaesthetics (5·2–15·7, I^2=92%) when managed by non-physician anaesthetists compared with 5·2 per 1000 (0·9–12·6, I^2=95%) when managed by physician anaesthetists.

Interpretation The current international priority on strengthening health systems should address the risk factors such as general anaesthesia and rural setting for improving anaesthetic care in pregnant women.

Funding Ammalife Charity and ELLY Appeal, Bart's Charity.

Lancet Glob Health 2016; 4: e320–27

See Comment page e290

*Joint first authors

Women's Health Research Unit (S Sobhy MBBS, Prof J Zamora PhD, Prof K S Khan MSc, Prof S Thangaratinam PhD), Multidisciplinary Evidence Synthesis Hub (mEsh) (Prof J Zamora, Prof K S Khan, Prof S Thangaratinam), Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS, CIBERESP), Madrid, Spain (Prof J Zamora, D Arroyo-Manzano MSc); Northwick Park Hospital, Harrow, Middlesex, UK (K Dharmarajah MRCOG); School of Health and Related Research, University of Sheffield, Sheffield, UK (M Wilson MD); Barts Health NHS Trust, Whitechapel, London, UK (R Navaratnarajah MRCOG); and School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK (Prof A Coomarasamy MD)

Correspondence to: Prof Khalid S Khan, Women's Health Research Unit, Multidisciplinary Evidence Synthesis Hub (mEsh), Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AD, UK
k.s.khan@qmul.ac.uk

Introduction

A quarter of a million women die every year during or after pregnancy and childbirth, and 99% of these are from low-income and middle-income countries.[1] Anaesthetic interventions are an integral part of emergency obstetric care.[2] However, there is a paucity of physician anaesthetists in many of the poorest countries, with an estimated ratio of one physician anaesthetist per million women.[3] There is also a lack of infrastructure, drugs, and equipment.

The need for safe, affordable surgery and anaesthesia in low-income and middle-income countries is recognised, with perioperative death as a global safety indicator.[4] In high-income countries, very few maternal deaths are attributed to anaesthesia.[5] However, no robust estimates are available of maternal deaths from obstetric anaesthesia, or of overall maternal mortality attributable to anaesthesia, in low-income and middle-income countries. Factors that contribute to maternal and perinatal mortality in women exposed to anaesthesia in low-income and middle-income countries need to be identified.

Individual studies have provided varied and imprecise results, with up to a fifth of all direct maternal deaths attributed to anaesthesia-related procedures.[6] Systematic reviews report estimates of complications in all individuals exposed to anaesthesia, not specifically in pregnant women.[7] We undertook a systematic review to obtain precise estimates of anaesthesia-attributed deaths

Appendix 18: Published manuscript

BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14408
www.bjog.org

Systematic review

Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis

S Sobhy,[a] ZOE Babiker,[b,c] J Zamora,[a,d,e] KS Khan,[a,d] H Kunst[f]

[a] Women's Health Research Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK [b] Department of Infection, Royal London Hospital, Barts Health NHS Trust, London, UK [c] Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, UAE [d] Multidisciplinary Evidence Synthesis Hub (mEsh), Centre of Primary Care and Public Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK [e] Clinical Biostatistics Unit, Hospital Ramon y Cajal (IRYCIS) and CIBER Epidemiology and Public Health, Madrid, Spain [f] Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Correspondence: Dr H Kunst, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK. Email h.kunst@qmul.ac.uk

Accepted 22 September 2016. Published online 11 November 2016.

Background There is a dearth of data on the clinical features and outcomes of active tuberculosis (TB) in pregnancy. Studies have shown varied results and the relationship between TB and adverse pregnancy outcomes remains unclear.

Objectives We conducted a systematic review and meta-analysis to evaluate pregnancy outcomes associated with TB.

Search strategy Major databases were searched from inception until December 2015 without restrictions using the terms: 'TB', 'pregnancy', 'maternal morbidity', 'mortality' and 'perinatal morbidity', 'mortality'.

Selection criteria We included studies that compared the outcomes of pregnant women with and without active TB.

Data collection and analysis We computed odds ratios for maternal and perinatal complications, and pooled them using a random effects model. We assessed for heterogeneity using chi-squared tests and evaluated its magnitude using the I^2 statistic. We used the Newcastle–Ottawa scale for quality assessment.

Main results Thirteen studies, including 3384 pregnancies with active TB and 119 448 without TB were included. Compared with pregnant women without TB, pregnant women with active TB was associated with increased odds of maternal morbidity [odds ratio (OR) 2.8, 95% CI 1.7–4.6; I^2 = 60.3%], anaemia (OR 3.9, 95% CI 2.2–6.7; I^2 = 29.8%), caesarean delivery (OR 2.1, 95% CI 1.2–3.8; I^2 = 61.1%), preterm birth (OR 1.7, 95% CI 1.2–2.4; I^2 = 66.5%), low birth weight (OR 1.7, 95% CI 1.2–2.4; I^2 = 53.7%), birth asphyxia (OR 4.6, 95% CI 2.4–8.6; I^2 = 46.3), and perinatal death (OR 4.2, 95% CI 1.5–11.8; I^2 = 57.2%).

Author's conclusion Active TB in pregnancy is associated with adverse maternal and fetal outcomes. Early diagnosis of TB is important to prevent significant maternal and perinatal complications.

Keywords Active, tuberculosis, maternal, perinatal, pregnancy outcomes.

Tweetable abstract Active tuberculosis in pregnancy is associated with adverse maternal and perinatal outcomes.

Please cite this paper as: Sobhy S, Babiker ZOE, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. BJOG 2016; DOI: 10.1111/1471-0528.14408.

Introduction

Tuberculosis (TB) is one of the world's deadliest communicable diseases.[1] In 2013, an estimated 9 million people developed active TB and 1.5 million died from the disease; 510 000 of these were women.[1] TB is one of the leading causes of death in women of reproductive age (15–45 years);[2] globally it is estimated that as many as 216 500 pregnant women have active TB.[3] Indirect maternal deaths now account for 28% of total maternal deaths; 15–35% of these deaths are due to TB.[2,4]

Although the greatest burden of TB infection is in resource-limited countries, resource-rich countries have seen a resurgence of TB, largely as a result of an increase

Appendix 19: Published abstract

PG.15

Maternal and fetal outcomes of tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis

Sobhy, S[1]; Khan, K[1]; Zahir, B[3]; Kunst, H[2]

[1]Womens Health Research Unit, Queen Mary's University, London, UK; [2]Queen Mary's University, London, UK; [3]Barts Health, London, UK

Introduction Our objective was to identify outcomes of pregnancies in women with maternal tuberculosis (TB).

Methods Systematic review and meta-analysis.

Data sources: Major electronic databases until October 2015.

Eligibility criteria: Studies that compared pregnant women with and without active TB for outcome data.

Data extraction and synthesis: Study selection, quality assessment and data extraction were carried out by two independent reviewers. Information on study design, setting, population characteristics, TB diagnosis and treatment as well as obstetric outcomes was obtained. Risk of bias was assessed using the Newcastle-Ottawa scale. Data were pooled and odds ratios using random effects modelling were calculated for maternal and perinatal outcomes.

Results Out of 7521 citations, 13 studies were included; (3384 pregnancies associated with active TB, 119 480 pregnant women without TB). Using the Newcastle-Ottawa scale, seven studies had a low risk or medium risk of bias and six had a high risk of bias. There was a significantly increased risk of poor fetal outcomes; with quadruple the odds of perinatal death and asphyxia and double the odds of preterm birth and low birth rate. Maternal outcomes were also significantly worse with double the odds of maternal morbidity, anaemia and caesarean delivery, compared with pregnant women without active TB. Women who were diagnosed and treated in first trimester had better outcomes than those diagnosed and treated in second and third trimester.

Conclusion TB in pregnancy results in poor maternal and fetal outcomes. A wider screening programme and case detection are needed to start early treatment and reduce poor outcomes.

Introduction Our objective was to assess the consumption of folate and the frequency of the main gene polymorphisms MTHFR-677C>T, MTHFR-1298A>C, MTRR-66A>G associated with folate cycle disorder in female students.

Methods A cross-sectional study. The questionnaire survey about the adequacy of nutrition and reproductive plans and genetic examination were conducted among 100 healthy female students aged between 19 and 25 years. Genomic DNA was extracted from blood leucocytes with a simple salting-out method. Gene polymorphisms were detected by the technique of real-time polymerase chain reaction. We have analysed the frequencies and Hardy–Weinberg equilibria.

Results We found that all female students consumed poor folate foods. Nobody took folic acid supplements or folate-containing combined oral contraceptives. No students excluded the possibility of pregnancy and childbirth during the period of study at the academy. The frequency of MTHFR-677TT mutant genotype was 6%, MTHFR-1298CC was 9%, MTRR-66GG was 31%. Combined MTHFR-677TT//MTHFR-1298CC and MTHFR-677TT//MTRR-66GG mutant genotypes, which significantly increased risk of pregnancy loss and neural-tube defects, were found in 2% of cases.

Conclusion Healthy female students are characterised by inadequate intake of folate with food, increased prevalence of the mutant genotype of the MTRR-66GG, the average frequency of mutant genotypes of the MTHFR-677TT and MTHFR-1298CC, that increases risks of fetal malformations and pregnancy complications. These facts in addition to a high frequency of unplanned pregnancies, explains the necessity to include in reproductive educational programmes for students information about the need of systematic and adequate intake of folate.

PG.17

Risks associated with anaesthesia in women with pre-eclampsia in low- and middle-income countries. Systematic review and mata-analysis

Sobhy, S[1]; Dharmarajah, K[2]; Zamora, J[3]; Wilson, M[4]; Coomarasamy, A[5]; Navaratnarajah, R[6]; Thangaratinam, S[1]

[1]Women's Health Research Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]Northwick Park hospital, London, UK; [3]Clinical Biostatistics Unit, Hospital Ramon y Cajal, Madrid, Spain; [4]School of Health & Related Research, University of Sheffield, Sheffield, UK; [5]School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK; [6]Barts Health NHS Trust, London, UK

REFERENCES:

1. Organization WH. ICD-10, International statistical classification of diseases and related health problems, 10th revision. 2010.
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014;2(6):e323-e33.
3. group Ud. UN Millenium project [cited 2015]. Available from: http://www.unmillenniumproject.org/goals/index.htm.
4. The millenium development goals report. United Nations, 2015.
5. Alkema L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. The Lancet. 2015.
6. sustainable development goals: United Nations. Available from: https://sustainabledevelopment.un.org.
7. Thaddeus S, Maine D. Too far to walk: maternal mortality in context. Social science & medicine (1982). 1994;38(8):1091-110.
8. TK S. The untold story: how the health care systems in developing countries contribute to maternal mortality. International journal of health services : planning, administration, evaluation. 1992;22(3):513-28.
9. Geller SE CS, Callaghan WM, Berg CJ. Morbidity and mortality in pregnancy: laying the groundwork for safe motherhood. Women's health issues : official publication of the Jacobs Institute of Women's Health. 2006;16(3):176-88.
10. Tabassum Firoz DC, Peter von Dadelszen, Priya Agrawal, Rachel Vanderkruik, Ozge Tunçalp, Laura A Magee, Nynke van Den Broek, Lale Say Measuring maternal health: focus on maternal morbidity 2013 [cited 2015]. Available from: http://www.who.int/bulletin/volumes/91/10/13-117564/en/.
11. Koblinsky MA. Beyond maternal mortality — magnitude, interrelationship and consequences of women's health, pregnancy-related complications and nutritional status on pregnancy outcomes. International Journal of Gynecology & Obstetrics. 1995;48:S21-S32.
12. Ogboli-Nwasor E. Maternal Mortality and Morbidity Will Not Reduce in Low Resource Countries without the Anaesthetists' Involvement. Open Journal of Obstetrics and Gynecology. 2014;04(05):228-33.
13. Organization. WH. Appropriate technology for birth. Lancet. 1985;2:436-7.
14. Ronsmans C, Holtz S, Stanton C. Socioeconomic differentials in caesarean rates in developing countries: a retrospective analysis. The Lancet. 2006;368(9546):1516-23.
15. Ologunde R, Vogel JP, Cherian MN, Sbaiti M, Merialdi M, Yeats J. Assessment of cesarean delivery availability in 26 low- and middle-income countries: a cross-sectional study. Am J Obstet Gynecol. 2014;211(5):504 e1-e12.
16. Dubowitz G, Detlefs S, McQueen KA. Global anesthesia workforce crisis: a preliminary survey revealing shortages contributing to undesirable outcomes and unsafe practices. World journal of surgery. 2010;34(3):438-44.
17. McAuliffe MS HB. Countries where anesthesia is administered by nurses. Journal of the American Association of Nurse Anesthetists. 1996;64(5):469-79.

18. Hendel S, Coonan T, Thomas S, McQueen K. The rate-limiting step: the provision of safe anesthesia in low-income countries. World journal of surgery. 2015;39(4):833-41.
19. Hodges SC, Mijumbi C, Okello M, McCormick BA, Walker IA, Wilson IH. Anaesthesia services in developing countries: defining the problems. Anaesthesia. 2007;62(1):4-11.
20. Hoyler M, Finlayson SR, McClain CD, Meara JG, Hagander L. Shortage of doctors, shortage of data: a review of the global surgery, obstetrics, and anesthesia workforce literature. World journal of surgery. Feb 2014;38(2):269-80.
21. Dennis AT. Management of pre-eclampsia: issues for anaesthetists. Anaesthesia. 2012;67(9):1009-20.
22. Lumbiganon P, Laopaiboon M, Intarut N, Vogel JP, Souza JP, Gulmezoglu AM, et al. Indirect causes of severe adverse maternal outcomes: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health. BJOG : an international journal of obstetrics and gynaecology. 2014;121 Suppl 1:32-9.
23. Vogel JP, Souza JP, Mori R, Morisaki N, Lumbiganon P, Laopaiboon M, et al. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG : an international journal of obstetrics and gynaecology. 2014;121 Suppl 1:76-88.
24. Lone FW, Qureshi RN, Emanuel F. Maternal anaemia and its impact on perinatal outcome. Tropical medicine & international health : TM & IH. 2004;9(4):486-90.
25. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion. 2015;55(12):2799-806.
26. Nielsen TF, Hokegard KH. Postoperative cesarean section morbidity: a prospective study. Am J Obstet Gynecol. 1983;146(8):911-6.
27. Tuberculosis (Fact sheet N°104): World Health Organisation; 2014. Available from: http://www.searo.who.int/thailand/factsheets/fs0017/en/.
28. Tuberculosis in women. Geneva, Switzerland: World health organisation 2015.
29. Tuberculosis: World health organisation; 2016. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/.
30. Loto OM, Awowole I. Tuberculosis in pregnancy: a review. Journal of pregnancy. 2012;2012:379271-.
31. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001;56(6):494-9.
32. Peker E, Bozdogan E, Dogan M. A rare tuberculosis form: congenital tuberculosis. Tuberk Toraks. 2010;58(1):93-6.
33. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. J R Soc Med. 2003;96(3):118-21.
34. Say L CD, Gemmill A, Tunçalp O, Moller A, Daniels J, Gülmezoglu A.M, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. 2014;2(6):e323–e33.
35. Clyburn P, Morris, S. and Hall, J. Anaesthesia and safe motherhood. Anaesthesia. 2007;62(s1):21-5.

36. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. The Lancet. 2015;386(9993):569-624.
37. Larsen JV, Janowski KA, Krolikowski A. Maternal mortality in hospitals in Zululand, July 1993 June 1994. South African Medical Journal. 1996;86(4):424-&.
38. Bainbridge D, Martin J, Arango M, Cheng D, Evidence-based Peri-operative Clinical Outcomes Research G. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. Lancet. 2012;380(9847):1075-81.
39. Sobhy S, Thangaratinam S, Zamora J, Damaraajah K. Anaesthesia related maternal and perinatal mortality and morbidity in developing countries: a systematic review and meta-analysis. . Prospero. 2015.
40. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
41. world bank. Available from: http://data.worldbank.org/.
42. WHO. Maternal and perinatal health [cited 2014 10/08/14]. Available from: http://www.who.int/maternal_child_adolescent/topics/maternal/maternal_perinatal/en/
43. Papile LA. The Apgar score in the 21st century. The New England journal of medicine. 2001;344(7):519-20.
44. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. The Lancet. 2006;367(9516):1066-74.
45. P G, L I, C B, G C. Frequency and rate. Systematic reviews in health care: a practical guide (2nd edn), : Cambridge University Press; 2001. p. 67–73.
46. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P, . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [10/08/14]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
47. Brockhaus AC, Bender R, Skipka G. The Peto odds ratio viewed as a new effect measure. Statistics in medicine. 2014;33(28):4861-74.
48. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP. 2015.
49. Fenton PM, Whitty CJM, Reynolds F. Caesarean section in Malawi: prospective study of early maternal and perinatal mortality. British medical journal. 2003;327(7415):587-90A.
50. Neilson J. Centre for Maternal and Child Enquiries- Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-8: a review. British journal of anaesthesia. 2011;107(2):66-70.
51. Hawkins JL. Maternal mortality: anesthetic implications. International anesthesiology clinics. 2002;40(4):1-11.
52. Afolabi BB, Lesi FE. Regional versus general anaesthesia for caesarean section. The Cochrane database of systematic reviews. 2012;10(10):CD004350.
53. Simonson DC AM, Hendryx MS. . Anesthesia staffing and anesthetic complications during caesarean delivery: A retrospective analysis. . Nursing Research 2007;56(1):9-17.
54. Needleman J, Minnick AF. Anesthesia provider model, hospital resources, and maternal outcomes. Health services research. 2009;44(2 Pt 1):464-82.

55. Lewis SR N, SmithAF, AldersonP. . Cochrane Database of Systematic Reviews2014, Issue 7. Art. No.: CD010357. DOI: 10.1002/14651858.CD010357.pub2. Physician anaesthetists versus non-physician providers of anaesthesia for surgical patients. Cochrane Database of Systematic Reviews. 2014(7):Art. No: CD010357.
56. Pinder A. Complications of obstetric anaesthesia. Current Anaesthesia & Critical Care. 2006;17(3-4):151-62.
57. Dalina AM, Inbasegaran K. Anaesthetic related maternal deaths in Malaysia--a review. The Medical journal of Malaysia. 1996;51(1):52-63.
58. Walker IA, Reshamwalla S, Wilson IH. Surgical safety checklists: do they improve outcomes? British journal of anaesthesia. 2012;109(1):47-54.
59. 68th World health assembly resolution: Strengthening Emergency and Essential Surgical Care and Anaesthesia as a Component of Universal Health Coverage,.
60. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014;4(2):97-104.
61. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. The Lancet. 2016;387(10022):999-1011.
62. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36(9):1465-74.
63. Duley L. The global impact of pre-eclampsia and eclampsia. Seminars in perinatology. 2009;33(3):130-7.
64. Villar J, Valladares E, Wojdyla D, Zavaleta N, Carroli G, Velazco A, et al. Caesarean delivery rates and pregnancy outcomes: the 2005 WHO global survey on maternal and perinatal health in Latin America. The Lancet. 2006;367(9525):1819-29.
65. Howell P. Spinal anaesthesia in severe preeclampsia: time for reappraisal, or time for caution? International Journal of Obstetric Anesthesia. 1998;7(4):217-9.
66. Gogarten W. Preeclampsia and anaesthesia. Current opinion in anaesthesiology. 2009;22(3):347-51.
67. Ul-Haq MA. Analysis of outcome of general versus spinal anaesthesia for caesarean delivery in severe pre-eclampsia with foetal compromise. . Biomedica . 2005;20-27.
68. Keerath K, Cronje L. Observational study of choice of anaesthesia and outcome in patients with severe pre-eclampsia who present for emergency Caesarean section. Southern African Journal of Anaesthesia and Analgesia. 2014;18(4):206-12.
69. Sobhy S, Zamora J, Dharmarajah K, Arroyo-Manzano D, Wilson M, Navaratnarajah R, et al. Anaesthesia-related maternal mortality in low-income and middle-income countries: a systematic review and meta-analysis. The Lancet Global Health. 2016;4(5):e320-e7.
70. Connell H, Dalgleish JG, Downing JW. General anaesthesia in mothers with severe pre-eclampsia/eclampsia. British journal of anaesthesia. 1987;59(11):1375-80.

71. Hood DD, Curry R. Spinal versus epidural anesthesia for cesarean section in severely preeclamptic patients: a retrospective survey. Anesthesiology. 1999;90(5):1276-82.
72. Henke VG, Bateman BT, Leffert LR. Spinal Anesthesia in Severe Preeclampsia. Anesthesia & Analgesia. 2013;117(3):686-93.
73. Betran AP, Merialdi M, Lauer JA, Bing-Shun W, Thomas J, Van Look P, et al. Rates of caesarean section: analysis of global, regional and national estimates. Paediatric and perinatal epidemiology. 2007;21(2):98-113.
74. Miller S, Abalos E, Chamillard M, Ciapponi A, Colaci D, Comandé D, et al. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. The Lancet. 2016;388(10056):2176-92.
75. Schuitemaker N vRJ, Dekker G, van Dongen P, , van Geijn H GJ. Maternal mortality after caesarean section in The Netherlands.
. Acta obstetricia et gynecologica Scandinavica. 1997;76:332-34.
76. Weiser TG, Uribe-Leitz T, Fu R, Jaramillo J, Maurer L, Esquivel MM, et al. Variability in mortality after caesarean delivery, appendectomy, and groin hernia repair in low-income and middle-income countries: implications for expanding surgical services. The Lancet. 2015;385:S34.
77. Pergialiotis V, Vlachos DG, Rodolakis A, Haidopoulos D, Thomakos N, Vlachos GD. First versus second stage C/S maternal and neonatal morbidity: a systematic review and meta-analysis. European journal of obstetrics, gynecology, and reproductive biology. 2014;175:15-24.
78. Spencer C, Murphy D, Bewley S. Caesarean delivery in the second stage of labour. BMJ. 2006;333(7569):613-4.
79. Maharaj D, Moodley J. Symphysiotomy and fetal destructive operations. Best practice & research Clinical obstetrics & gynaecology. 2002;16(1):117-31.
80. Singhal SR, Chaudhry P, Sangwan K, Singhal SK. Destructive operations in modern obstetrics. Arch Gynecol Obstet. 2005;273(2):107-9.
81. II O. Neglected Obstructed Labor
and the Need to Revive the “Dying
Obstetric Art of Fetal Destructive
Vaginal Operations” in the Developing
Countries. . Ann Clin Case Rep. 2016;1(1049):1-3.
82. Maswime S, Buchmann EJ. Why women bleed and how they are saved: a cross-sectional study of caesarean section near-miss morbidity. BMC pregnancy and childbirth. 2017;17(1):15.
83. Fesseha N, Getachew A, Hiluf M, Gebrehiwot Y, Bailey P. A national review of cesarean delivery in Ethiopia. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2011;115(1):106-11.
84. Harrison MS, Goldenberg RL. Cesarean section in sub-Saharan Africa. Matern Health Neonatol Perinatol. 2016;2:6.
85. Vogel JP, Betrán AP, Vindevoghel N, Souza JP, Torloni MR, Zhang J, et al. Use of the Robson classification to assess caesarean section trends in 21 countries: a secondary analysis of two WHO multicountry surveys. The Lancet Global Health. 2015;3(5):e260-e70.
86. Ye J, Zhang J, Mikolajczyk R, Torloni MR, Gulmezoglu AM, Betran AP. Association between rates of caesarean section and maternal and neonatal mortality in the 21st century: a worldwide population-based ecological study

with longitudinal data. BJOG : an international journal of obstetrics and gynaecology. 2016;123(5):745-53.
87. Betran AP, Torloni MR, Zhang J, Ye J, Mikolajczyk R, Deneux-Tharaux C, et al. What is the optimal rate of caesarean section at population level? A systematic review of ecologic studies. Reprod Health. 2015;12:57.
88. New S, Wirth M. Anaemia, pregnancy, and maternal mortality: the problem with globally standardised haemoglobin cutoffs. BJOG : an international journal of obstetrics and gynaecology. 2015;122(2):166-9.
89. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. The American journal of clinical nutrition. 2016;103(2):495-504.
90. Sukrat B, Wilasrusmee C, Siribumrungwong B, McEvoy M, Okascharoen C, Attia J, et al. Hemoglobin concentration and pregnancy outcomes: a systematic review and meta-analysis. Biomed Res Int. 2013;2013:769057.
91. Sanghvi TG HP, Wainwright E. Maternal iron-folic acid supplementation programs: evidence of impact and implementation. Food Nutr Bull 2010;31(2 suppl):S100-7.
.
92. Kalantri A, Karambelkar M, Joshi R, Kalantri S, Jajoo U. Accuracy and reliability of pallor for detecting anaemia: a hospital-based diagnostic accuracy study. PloS one. 2010;5(1):e8545.
93. Davis BH, Jungerius B, International Council for the Standardization of H. International Council for Standardization in Haematology technical report 1-2009: new reference material for haemiglobincyanide for use in standardization of blood haemoglobin measurements. Int J Lab Hematol. 2010;32(2):139-41.
94. Roberto Musi MLR. Point of Care Testing and Transfusion Safety in Resource Limited Settings: A Review. Journal of Blood Disorders & Transfusion. 2015;06(02).
95. Hiscock R KD, Simmons S. Systematic review and meta-analysis of method comparison studies of Masimo pulse co-oximeters (Radical-7™ or Pronto-7™) and HemoCue® absorption spectrometers (B-Hemoglobin or 201+) with laboratory haemoglobin estimation. Anaesthesia and intensive care. 2015;43.(3):341-50.
96. Marn H, Critchley JA. Accuracy of the WHO Haemoglobin Colour Scale for the diagnosis of anaemia in primary health care settings in low-income countries: a systematic review and meta-analysis. The Lancet Global Health. 2016;4(4):e251-e65.
97. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity Geneva: World Health Organisation,(WHO/NMH/NHD/MNM/11.1), 2011.
98. Mulherin SA. Spectrum Bias or Spectrum Effect? Subgroup Variation in Diagnostic Test Evaluation. Annals of Internal Medicine. 2002;137(7):598.
99. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
100. Adam I, Ahmed S, Mahmoud MH, Yassin MI. Comparison of HemoCue(R) hemoglobin-meter and automated hematology analyzer in measurement of hemoglobin levels in pregnant women at Khartoum hospital, Sudan. Diagn Pathol. 2012;7:30.

101. Paiva AD, Rondo PHC, Silva SSD, Latorre MDDO. Comparison between the HemoCue((R)) and an automated counter for measuring hemoglobin. Revista de saude publica. 2004;38(4):585-7.
102. Daae LN HS, Mathisen PM, Mironska K. A comparison between haematological parameters in 'capillary' and venous blood from healthy adults. Scand J Clin Lab Invest. 1988;48(7):723-6.
103. Saxena R, Malik R. Comparison of HemoCue method with the cyanmethemoglobin method for estimation of hemoglobin. Indian pediatrics. 2003;40(9):917.
104. Neufeld L, Garcia-Guerra A, Sanchez-Francia D, Newton-Sanchez O, Ramirez-Villalobos MD, Rivera-Dommarco J. Hemoglobin measured by Hemocue and a reference method in venous and capillary blood: a validation study. Salud Publica Mex. 2002;44(3):219-27.
105. Harbord RM WP. metandi: Meta-analysis of diagnostic accuracy using hierarchical logistic regression. . The Stata Journal 2009;9(2):211-29.
106. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ. 2004;329(7458):168-9.
107. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. The Lancet Global Health. 2013;1(1):e16-e25.
108. Diagnostic Post Test Probability of Disease Calculator. Available from: https://www.easycalculation.com/statistics/post-test-probability.php.
109. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005;58(9):882-93.
110. Song F. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. International journal of epidemiology. 2002;31(1):88-95.
111. Shulman CE, Levene M, Morison L, Dorman E, Peshu N, Marsh K. Screening for severe anaemia in pregnancy in Kenya, using pallor examination and self-reported morbidity. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2001;95(3):250-5.
112. van den Broek NR, Ntonya C, Mhango E, White SA. Diagnosing anaemia in pregnancy in rural clinics: assessing the potential of the Haemoglobin Colour Scale. Bulletin of the World Health Organization. 1999;77(1):15-21.
113. Khan AA, Fatmi Z, Kadir MM. Accuracy and Use of WHO Hemoglobin Color Scale for Diagnosis of Anemia Among Pregnant Women by Health Care Providers in Periurban Settings in Karachi, Pakistan. Asia-Pacific journal of public health / Asia-Pacific Academic Consortium for Public Health. 2015;27(6):610-9.
114. Chathurani U, Dharshika I, Galgamuwa D, Wickramasinghe ND, Agampodi TC, Agampodi SB. Anaemia in pregnancy in the district of Anuradhapura, Sri Lanka--need for updating prevalence data and screening strategies. The Ceylon medical journal. 2012;57(3):101-6.
115. Fourn L, Salami L. [Diagnostic value of tegument pallor in anemia in pregnant women in Benin]. Sante publique (Vandoeuvre-les-Nancy, France). 2004;16(1):123-32.
116. Prathapan S LG, Fonseka P, Lokubalasooriya A, Prathapan R. How good is the quality of antenatal care in the Colombo district of Sri Lanka in diagnosing and treating anaemia? Qual Prim Care. 2011;19(4):245-50.

117. Pistorius LR, Funk M, Pattinson RC, Howarth GR. Screening for anemia in pregnancy with copper sulfate densitometry. International Journal of Gynecology & Obstetrics. 1996;52(1):33-6.
118. Wilkinson D, Sach ME. Cost effective on-site screening for anaemia in pregnancy in primary care clinics. South African Medical Journal. 1997;87(4):463-5.
119. Agnihotri M, Ambad R, Rahule AS. Study of Evaluation of Sensitivity and Specificity of Simple Screening Methods for Assessment of Anaemia in Pregnant Women. Journal of Contemporary Medicine and Dentistry. 2015;3(1):62-6.
120. Ahankari AS, Fogarty AW, Tata LJ, Dixit JV, Myles PR. Assessment of a non-invasive haemoglobin sensor NBM 200 among pregnant women in rural India. BMJ Innovations. 2016;2(2):70-7.
121. Simel DL, Bossuyt PM. Differences between univariate and bivariate models for summarizing diagnostic accuracy may not be large. J Clin Epidemiol. 2009;62(12):1292-300.
122. Lewis SM, Stott GJ, Wynn KJ. An inexpensive and reliable new haemoglobin colour scale for assessing anaemia. J Clin Pathol. 1998;51(1):21-4.
123. PATH. Anemia detection in health services: Guidelines for program managers. . USAID, 1996.
124. R.Parikh AM, S. Parikh, G. Chandra Sekhar, R. Thomas. Understanding and using sensitivity, specificity and predictive values. Indian J Ophthalmol. 2008;56(1):45-50.
125. Pena-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. The Cochrane database of systematic reviews. 2015;7:CD004736.
126. Maxwell MJ, Wilson MJA. Complications of blood transfusion. Continuing Education in Anaesthesia, Critical Care & Pain. 2006;6(6):225-9.
127. Szondy D. HemoGlobe device works with a smartphone to detect anemia 2012. Available from: http://www.gizmag.com/hemoglobe/23453/.
128. Flash of Insight: Mobile App Tests for Anemia with Camera Flash AFRICARE; 2015. Available from: https://www.africare.org/flash-of-insight-mobile-app-tests-for-anemia-with-camera-flash/.
129. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. BJOG : an international journal of obstetrics and gynaecology. 2011;118(2):226-31.
130. World Health Organization. Global tuberculosis report 2014. Geneva, 2014.
131. http://www.who.int/mediacentre/factsheets/fs334/en/.
132. Sheriff FG, Manji KP, Manji MP, Chagani MM, Mpembeni RM, Jusabani AM, et al. Latent tuberculosis among pregnant mothers in a resource poor setting in Northern Tanzania: a cross-sectional study. BMC infectious diseases. 2010;10.
133. Loto OM, Awowole I. Tuberculosis in pregnancy: a review. Journal of pregnancy. 2012;2012:379271.
134. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. The Lancet Global Health. 2014;2(12):e710-e6.
135. WHO. Maternal and perinatal health [10/08/2015]. Available from: http://www.who.int/maternal_child_adolescent/topics/maternal/maternal_perinatal/en/

136. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. The New England journal of medicine. 1999;341(9):645-9.
137. Figueroa-Damian R, Arredondo-Garcia JL. Pregnancy and tuberculosis: influence of treatment on perinatal outcome. American journal of perinatology. 1998;15(5):303-6.
138. Tripathy SN. Tuberculosis and pregnancy. International Journal of Gynecology & Obstetrics. 2003;80(3):247-53.
139. Khan M, Pillay T, Moodley JM, Connolly CA, Durban Perinatal TBHIVSG. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. AIDS (London, England). 2001;15(14):1857-63.
140. Doveren R. Tuberculosis and pregnancy – a provincial study (1990–1996). The Netherlands Journal of Medicine. 1998;52(3):100-6.
141. Kancheya N, Luhanga D, Harris JB, Morse J, Kapata N, Bweupe M, et al. Integrating active tuberculosis case finding in antenatal services in Zambia. International Journal of Tuberculosis and Lung Disease. 2014;18(12):1466-72.
142. Gupta A, Chandrasekhar A, Gupte N, Patil S, Bhosale R, Sambarey P, et al. Symptom screening among HIV-infected pregnant women is acceptable and has high negative predictive value for active tuberculosis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;53(10):1015-8.
143. Bates M, Ahmed Y, Chilukutu L, Tembo J, Cheelo B, Sinyangwe S, et al. Use of the Xpert((R)) MTB/RIF assay for diagnosing pulmonary tuberculosis comorbidity and multidrug-resistant TB in obstetrics and gynaecology inpatient wards at the University Teaching Hospital, Lusaka, Zambia. Tropical medicine & international health : TM & IH. 2013;18(9):1134-40.
144. Mathad JS, Bhosale R, Sangar V, Mave V, Gupte N, Kanade S, et al. Pregnancy differentially impacts performance of latent tuberculosis diagnostics in a high-burden setting. PloS one. 2014;9(3):e92308.
145. http://who.int/tb/End_TB_brochure.pdf?ua=1. The END TB strategy. Geneva Switzerland: World Health Organisation, 2015.
146. Getahun H, Sculier D, Sismanidis C, Grzemska M, Raviglione M. Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. The Journal of infectious diseases. 2012;205 Suppl 2:S216-27.
147. Abdel-Hady el S, Mashaly AM, Sherief LS, Hassan M, Al-Gohary A, Farag MK, et al. Why do mothers die in Dakahlia, Egypt? The journal of obstetrics and gynaecology research. 2007;33(3):283-7.
148. Larsen JV JK, Krolikowski A. . Maternal mortality in hospitals in Zululand, July 1993 June 1994. . South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde. 1996;86(4):424.
149. Amarin Z, Khader Y, Okour A, Jaddou H, Al-Qutob R. National maternal mortality ratio for Jordan, 2007-2008. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2010;111(2):152-6.
150. Ara S, Tahir S, Rehman A. Maternal mortality in Faisalabad and millennium developmental goals. Pakistan Journal of Medical Sciences. 2012;28(3):371-5.

151. Akar ME, Eyi EG, Yilmaz ES, Yuksel B, Yilmaz Z. Maternal deaths and their causes in Ankara, Turkey, 1982-2001. Journal of health, population, and nutrition. 2004;22(4):420-8.
152. Bano N, Chaudhri R, Yasmeen L, Shafi F, Ejaz L. A study of maternal mortality in 8 principal hospitals in Pakistan in 2009. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2011;114(3):255-9.
153. Begum S, Aziz un N, Begum I. Analysis of maternal mortality in a tertiary care hospital to determine causes and preventable factors. Journal of Ayub Medical College, Abbottabad : JAMC. 2003;15(2):49-52.
154. Hoestermann CFL, Ogbaselassie G, Wacker J, Bastert G. Maternal mortality in the main referral hospital in The Gambia, West Africa. Tropical Medicine & International Health. 1996;1(5):710-7.
155. Bashir A, Aleem M, Mustansar M. A 5-year study of maternal mortality in Faisalabad City Pakistan. International Journal of Gynecology & Obstetrics. 1995;50, Supplement 2(0):S93-S6.
156. Vink NM, de Jonge HC, Ter Haar R, Chizimba EM, Stekelenburg J. Maternal death reviews at a rural hospital in Malawi. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2013;120(1):74-7.
157. De Muylder X. Maternal mortality audit in a Zimbabwean province. Archives of Gynecology and Obstetrics. 1990;247(3):131-8.
158. Bolnga JW, Hamura NN, Umbers AJ, Rogerson SJ, Unger HW. Insights into maternal mortality in Madang Province, Papua New Guinea. International Journal of Gynecology & Obstetrics. 2014;124(2):123-7.
159. Ngwan S, Swende T. Maternal mortality in JOS Nigeria: A facility based prospective Review. Int J Biol Med Res. 2011;2(2):565-8.
160. Sule-Odu AO. Maternal deaths in Sagamu, Nigeria. International Journal of Gynecology and Obstetrics. 2000;69(1):47-9.
161. Oladapo OT, Lamina MA, Sule-Odu AO. Maternal morbidity and mortality associated with elective Caesarean delivery at a university hospital in Nigeria. Austalian and New Zealand Journal of Obstetrics and Gynaecology. 2007;47(2):110-4.
162. Obiechina NJ OV, Okechukwu ZC, Oguejiofor CF, Udegbunam OI, Nwajiaku LSA, . Maternal mortality at nnamdi azikiwe university teaching hospital, southeast nigeria: A 10-year review (2003-2012). International Journal of Women's Health 2013;5(1):31-6.
163. Mahbouli S, Basli M, Messaoudi F, Messaoudi I, Chibani M, Rachdi R. [Maternal mortality: epidemiology, risk factors and evitability. About ten cases]. Gynecologie, obstetrique & fertilite. 2003;31(12):1018-23.
164. El Daba AA, Amr YM, Marouf HM, Mostafa M. Retrospective study of maternal mortality in a tertiary hospital in Egypt. Anesth Essays Res. 2010;4(1):29-32.
165. Rahim R ST, Faiz, N, . An analysis of direct causes o maternal mortality, . JPMI - Journal of Postgraduate Medical Institute. 2006;90(1):86-91.
166. Yang S, Zhang B, Zhao J, Wang J, Flick L, Qian Z, et al. Progress on the maternal mortality ratio reduction in Wuhan, China in 2001-2012. PloS one. 2014;9(2):e89510.
167. Soares VM, de Souza KV, de Azevedo EM, Possebon CR, Marques FF. [Causes of maternal mortality according to levels of hospital complexity]. Revista

brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia. 2012;34(12):536-43.
168. Okafor UV, Ezegwui HU, Ekwazi K. Trends of different forms of anaesthesia for caesarean section in South-eastern Nigeria. Journal of Obstetrics and Gynaecology. 2009;29(5):392-5.
169. Kongnyuy EJ, Mlava G, van den Broek N. Facility-based maternal death review in three districts in the central region of Malawi: an analysis of causes and characteristics of maternal deaths. Women's health issues : official publication of the Jacobs Institute of Women's Health. 2009;19(1):14-20.
170. Ujah LAO, Aisien OA, Mutihir JT, Vanderjagt DJ, Glew RH, Uguru VE. Factors contributing to maternal mortality in north-central Nigeria: a seventeen-year review. African Journal of Reproductive Health. 2005;9(3):27-40.
171. Hodorogea S, Friptu V. The Moldovan experience of maternal death reviews. BJOG : an international journal of obstetrics and gynaecology. 2014;121 Suppl 4:81-5.
172. Paily V, Ambujam K, Rajasekharan Nair V, Thomas B. Confidential review of maternal deaths in Kerala: a country case study. BJOG : an international journal of obstetrics and gynaecology. 2014;121 Suppl 4:61-6.
173. Ujah IA, Uguru VE, Aisien AO, Sagay AS, Otubu JA. How safe is motherhood in Nigeria?: the trend of maternal mortality in a tertiary health institution. East African medical journal. 1999;76(8):436-9.
174. Goswami D, Rathore AM, Batra S, Dubey C, Tyagi S, Wadhwa L. Facility-based review of 296 maternal deaths at a tertiary centre in India: could they be prevented? The Journal of Obstetrics and Gynaecology Research. 2013;39(12):1569-79.
175. Kane TT, el-Kady AA, Saleh S, Hage M, Stanback J, Potter L. Maternal mortality in Giza, Egypt: magnitude, causes, and prevention. Stud Fam Plann. 1992;23(1):45-57.
176. GY G. A 6-Year (2004-2009) Review of Maternal Mortality at the Eastern Regional Hospital, Koforidua, Ghana. Seminars in perinatology. 2012;36(1):79–83.
177. Granja AC, Machungo F, Gomes A, Bergstrom S. Adolescent maternal mortality in Mozambique. Journal of Adolescent Health. 2001;28(4):303-6.
178. Font F, Alonso Gonzalez M, Nathan R, Lwilla F, Kimario J, Tanner M, et al. Maternal mortality in a rural district of southeastern Tanzania: an application of the sisterhood method. International journal of epidemiology. 2000;29(1):107-12.
179. Akpadza K, Kotor KT, Baeta S, Adama A, Hodonou AK. [Maternal mortality at the Tokoin Lome University Hospital Center from 1990 to 1992]. Revue francaise de gynecologie et d'obstetrique. 1994;89(2):81-5.
180. Okaro JM, Umezulike AC, Onah HE, Chukwuali LI, Ezugwu OF, Nweke PC. Maternal mortality at the University of Nigeria Teaching Hospital, Enugu, before and after Kenya. African journal of reproductive health. 2001;5(2):90-7.
181. Onwuhafua PI, Onwuhafua A, Adze J. The challenge of reducing maternal mortality in Nigeria. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2000;71(3):211-3.
182. Mukherji J SJ. How Safe Is Caesarean Section. Journal of Obstetrics and Gynaecology. 1995;21(1):17-21.

183. Abe E, Omo-Aghoja LO. Maternal mortality at the Central Hospital, Benin City Nigeria: a ten year review. African journal of reproductive health. 2008;12(3):17-26.
184. Kassas M HM, Hanafi A, Campbell O. The national maternal mortality study of Egypt 1992–1993. International Journal of Gynecology & Obstetrics. 1995;50(2):S101–S8.
185. Ministry of health and population; The national maternal mortality study: Egypt 2000. June 2001.
186. National committee on confidential enquiries into maternal deaths; Saving Mothers 2005-2007: Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa. Department of health, Pretoria
, 2009.
187. Aboyeji AP, Ijaiya MA, Fawole AA. Maternal mortality in a Nigerian teaching hospital - a continuing tragedy. Tropical Doctor. 2007;37(2):83-5.
188. Bukar M, Audu BM, Massa AA. Caesarean delivery at the Federal Medical Centre Gombe: a 3-year experience. Nigerian Journal of Medicine. 2009;18(2):179-83.
189. Mungra A, van Kanten RW, Kanhai HH, van Roosmalen J. Nationwide maternal mortality in Surinam. British Journal of Obstetrics and Gynaecology. 1999;106(1):55-9.
190. National committee on confidential enquiries into maternal death; National committee on confidential enquiries into maternal death; Saving Mothers 2008-2010: Fifth report on the confidential enquiries into maternal deaths in South Africa. Department of health, Pretoria, 2012.
191. Munjanja S. Maternal and perinatal mortality study: Ministry of Health and child welfare, Zimbabwe; 2007. Available from: http://www.unicef.org/zimbabwe/ZMPMS_report.pdf.
192. Jayashree, Hanamshetty A. A study on Maternal Mortality – At BRIMS Bidar. Internation Journal of Recent Trends in Science and Technology. 2014;13(2):415-7.
193. Makinga PN, Moodley J, Titus MJ. The profile of maternal deaths in a district hospital: A five-year review of maternal deaths from 2006-2010. S Afr Fam Pract. 2012;54(6):518-24.
194. Confidential enquiries into maternal death. Ministry of health, Botswana, 2012.
195. Fawcus SR, van Coeverden de Groot HA, Isaacs S. A 50-year audit of maternal mortality in the Peninsula Maternal and Neonatal Service, Cape Town (1953-2002). BJOG : an international journal of obstetrics and gynaecology. 2005;112(9):1257-63.
196. Kharouf M, Ben Zineb N, Chelli H, Ettagourti H, Halouani L, Falfoul A, et al. [Maternal mortality at the Maternity and Neonatology Center in Rabta of Tunis from 1986 to 1989]. Journal de gynecologie, obstetrique et biologie de la reproduction. 1992;21(2):236-40.
197. Madzimbamuto FD, Ray SC, Mogobe KD, Ramogola-Masire D, Phillips R, Haverkamp M, et al. A root-cause analysis of maternal deaths in Botswana: towards developing a culture of patient safety and quality improvement. BMC pregnancy and childbirth. 2014;14(231).
198. Okeh U.M. Statistical analysis of the maternal death rate at the Ebonyi State University Teaching Hospital, Abakaliki, for the year ending 31 December

2007. African journal of primary healthcare and family medicine. 2009;1(1):118-20.
199. Bashour H, Abdulsalam A, Jabr A, Cheikha S, Tabbaa M, Lahham M, et al. Maternal mortality in Syria: causes, contributing factors and preventability. Tropical medicine & international health : TM & IH. 2009;14(9):1122-7.
200. Rutgers S. Two years maternal mortality in Matebeleland north Province, Zimbabwe. The Central African journal of medicine. 2001;47(2):39-43.
201. Kampikaho A, Irwig LM. Incidence and causes of maternal mortality in five Kampala hospitals, 1980-1986. East African medical journal. 1991;68(8):624-31.
202. Khan B, Deeba F, Khattak SN. Maternal mortality: a ten year review in a tertiary care setup. Journal of Ayub Medical College, Abbottabad : JAMC. 2012;24(3-4):124-7.
203. Kauser S KS, Yousaf F, Akbar M. MATERNAL MORTALITY IN A TERTIARY CARE HOSPITAL, LAHORE - A Four Year Review. Biomedica. 2006;22:5-8.
204. Fawad A, Naz H, Islam A, Zaffar S, Abbasi AU. Maternal mortality in a tertiary care hospital. Journal of Ayub Medical College, Abbottabad : JAMC. 2011;23(1):92-5.
205. Mairiga AG, Saleh W. Maternal mortality at the State Specialist Hospital Bauchi, Northern Nigeria. East African medical journal. 2009;86(1):25-30.
206. Ministry of health, Malaysia; Report on the confidential enquiries into maternal deaths in malaysia 1993. 1993.
207. Ministry of health, Malaysia; Report on the confidential enquiries into maternal deaths in malaysia 1994. 1997.
208. Ministry of health, Malaysia; Report on the confidential enquiries into maternal deaths in malaysia 1995-1996. 2000.
209. Ministry of health, Malaysia; Report on the confidential enquiries into maternal deaths in malaysia 11997-2000. 2005.
210. Malaysia; Moh. Report on the confidential enquiries into maternal deaths in malaysia . 2001-2005.
211. Ministry of health, Malaysia; Report on the confidential enquiries into maternal deaths in malaysia, 2006-2008.
212. Wagaarachchi PT, Fernando L. Trends in maternal mortality and assessment of substandard care in a tertiary care hospital. European journal of obstetrics, gynecology, and reproductive biology. 2002;101(1):36-40.
213. Nelissen EJT, Mduma E, Ersdal HL, Evjen-Olsen B, van JJM, Stekelenburg J. Maternal near miss and mortality in a rural referral hospital in northern Tanzania: A cross-sectional study. BMC pregnancy and childbirth. 2013;13.
214. Bouvier-Colle M OC, Dumont A, Vangeenderhuysen C, Salanave B, Decam C. Maternal mortality in West Africa. Acta obstetricia et gynecologica Scandinavica. 2001;80(2):113-9.
215. Montgomery AL RU, Kumar R, Jha P. Maternal Mortality in India: Causes and Healthcare Service Use Based on a Nationally Representative Survey. PloS one. 2014;9(1).
216. Pal A RP, Hazra S, Mondal TK. Review of changing trends in maternal mortality in a rural medical college in West Bengal. J Obstet Gynecol India. 2005;55(6):521-4.
217. Ashok V SM, Anupa S, . A study on Maternal Mortality. J Obstet Gynecol India, . 2008;58(2):226-9.

218. Khatun K, Ara R, Aleem NT, Khan S, Husein S, Alam S, et al. Maternal mortality in obstetrics and gynaecology in a tertiary care hospital. Mymensingh medical journal : MMJ. 2015;24(1):103-7.
219. Cetin M, Sumer H, Timuroglu T, Demirkoprulu N. Maternal mortality in the last decade at a university hospital in Turkey. International Journal of Gynecology and Obstetrics. 2003;83(3):301-2.
220. Ndavi PM DD. Report on maternal mortality review in the Kingdom of Swaziland 2001. Ministry of health, Swaziland 2001.
221. Kavoo L, Rogo KO. Factors influencing early perinatal mortality in a rural district hospital. East African medical journal. 1992;69(4):181-7.
222. Rasoarimahandry CL RM, Ranjalahy RJ. . Maternal mortality in the maternity ward of Befelatanana. University Hospital of Antananarivo. Journal de gynecologie, obstetrique et biologie de la reproduction. 2000;29(5):501-8.
223. Oyieke JB OS, Kigondu CS. Millennium development goal 5: a review of maternal mortality at the Kenyatta National Hospital, Nairobi. East Afr Med J 2006 Jan;83(1):4-6.
224. Ali R KA, Kausar S. Maternal Mortality: An Ice Berg One Year Review at DHQ Hospital, Faisalabad. APMC. 2012;6(2):180-5.
225. Igberase GO, Ebeigbe PN, Andrew BO. High caesarean section rate: a ten year experience in a tertiary hospital in the Niger Delta, Nigeria. Nigerian journal of clinical practice. 2009;12(3):294-7.
226. Asamoah BO, Moussa KM, Stafström M, Musinguzi G. Distribution of causes of maternal mortality among different socio-demographic groups in Ghana; a descriptive study. BMC public health. 2011;11:159.
227. Confidential enquiries into maternal death. Ministry of health, Botswana. 2010.
228. confidential enquiry into maternal deaths. Ministry of health, Botswana, 2011.
229. Confidential enquiries into maternal death. Ministry of health, Botswana, 2013.
230. Koç I, Schumacher R, Campbell O, Türkyılmaz A.S, Ergöçmen B, Yüksel I. Turkey, National maternal mortality study. Reproductive health programme, Hacettepe university, institute of population studies.
, 2005.
231. Ministerio de salud publica y assistencia publicia y asistencia social, linea de base de mortalidad maternaen el Salvador- Junio 2005-Mayo 2006
. Ministry of health salvador, 2006.
232. Farhat EB, Chaouch M, Chelli H, Gara MF, Boukraa N, Garbouj M, et al. Reduced maternal mortality in Tunisia and voluntary commitment to gender-related concerns. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2012;116(2):165-8.
233. Issah K, Nang-Beifubah A, Opoku CF. Maternal and neonatal survival and mortality in the Upper West Region of Ghana. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2011;113(3):208-10.
234. Glenshaw M, Madzimbamuto FD. Anaesthesia associated mortality in a district hospital in Zimbabwe: 1994 to 2001. The Central African journal of medicine. 2005;51(3-4):39-44.

235. McKenzie AG. Operative obstetric mortality at Harare Central Hospital 1992-1994: an anaesthetic view. International Journal of Obstetric Anesthesia. 1998;7:237-41.
236. Abdissa Z, Awoke T, Belayneh T, Tefera Y. Birth outcome after caesarean section among mothers who delivered by caesarean section under general and spinal anesthesia at Gondar University teaching hospital north-west Ethiopia. Journal of Anesthesia and Clinical Research. 2013;4(7).
237. Fente BG OO. Experience working with Nurse Anesthetists' as Non-Physician Anesthesia Providers in a temporary Semi-Urban Niger Delta University Teaching Hospital, Okolobiri and review of the literature. Journal of Dental and Medical Sciences. Dec 2013;3(6):36-40.
238. Ozumba BC, Anya SE. Maternal deaths associated with cesarean section in Enugu, Nigeria. International Journal of Gynecology & Obstetrics. 2002;76(3):307-9.
239. Chang CC, Wang IT, Chen YH, Lin HC. Anesthetic management as a risk factor for postpartum hemorrhage after cesarean deliveries. American Journal of Obstetrics and Gynecology. 2011;205(5):462.e1-7.
240. Enohumah KO, Imarengiaye CO. Factors associated with anaesthesia-related maternal mortality in a tertiary hospital in Nigeria. Acta anaesthesiologica Scandinavica. 2006;50(2):206-10.
241. Fenton PM, Whitty CJM, Reynolds F. Caesarean section in Malawi: prospective study of early maternal and perinatal mortality. British Medical Journal. 2003;327:587.
242. Okezie AO, Oyefara B, Chigbu CO. A 4-year analysis of caesarean delivery in a Nigerian teaching hospital: one-quarter of babies born surgically. Journal of Obstetrics and Gynaecology. 2007;27(5):470-4.
243. Okogbenin SA, Otoide VO. Cardiac arrest complicating cesarean delivery in a Nigerian center. International Journal of Gynecology and Obstetrics. 2004;86(1):50-1.
244. Okafor U, Ezegwui H. Maternal Deaths During Caesarean Delivery In A Developing Country-Perspective From Nigeria. The Internet Journal of Third World Medicine. 2008;8(1).
245. Nwobodo EI, Isah AY, Panti A. Elective caesarean section in a tertiary hospital in Sokoto, north western Nigeria. Nigerian Medical Journal. 2011;52(4):263-5.
246. Imarengiaye CO, Otoide VO, Ande AB, Obiaya MO. Anaesthesia related complications following caesarean delivery necessitating intensive care unit admissions in a tertiary centre. African Journal of Medicine and Medical Sciences. 2001;30(3):229-32.
247. Imtiaz A MS, Noor ul Haq M, Ali SH, Imtiaz K. Effect of Spinal and General Anaesthesia Over APGAR Score in Neonates Born After Elective Cesarean Section. JLUMHS. SEPT-DEC 2010;9(3):151-4.
248. Tomta K, Maman FO, Agbetra N, Baeta S, Ahouangbevi S, Chobli M. Maternal mortality: anesthetic implications at the University Hospital of Lome (Togo). Sante. 2003;13(2):77-80.
249. Chau-in W RO, Lekprasert V, Punjasawadwong Y, Charuluxananan S, Tanudsintum S. Anesthesia-related complications of caesarean delivery in Thailand: 16,697 cases from the Thai Anaesthesia Incidents Study. J Med Assoc Thai. 2010;93(11):1274-83.

250. Charuluxananan S, Thienthong S, Rungreungvanich M, Chanchayanon T, Chinachoti T, Kyokong O, et al. Cardiac arrest after spinal anesthesia in Thailand: a prospective multicenter registry of 40,271 anesthetics. Anesthesia and analgesia. 2008;107(5):1735-41.
251. Rukewe A FA, Adebayo K. Anaesthesia for caesarean deliveries and maternal complications in a Nige. Afr J Med Med Sci. 2014;43(1)::5-10.
252. Soyannwo OA. Nurse anaesthetists in the Gambia. World health forum. 1992;13(2-3):208-10.
253. Solangi SAS, S.M; Khaskheli M.S, Siddiqui M.A. Comparison of the effects of general vs spinal anesthesia on neonatal outcome. Anaesthesia, Pain & Intensive Care;. 2012;16(1):18.
254. Igberase GO, Ebeigbe PN, Andrew BO. High caesarean section rate: a ten year experience in a tertiary hospital in the Niger Delta, Nigeria. Nigerian Journal of Clinical Practice. 2009;12(3):294-7.
255. Eshiet AI, Udoma EJ, Ekanem AD, Dada A. Effect of Anaesthesia on Morbidity and Mortality in Emergency Caesarean Section Patients in Calabar, Nigeria. Nigeria Journal of Physiological Sciences. 2003;18(1-2):77-81.
256. Ekanem AD, Udoma EJ, Etuk SJ, Eshiet AI. Outcome of emergency caesarean sections in Calabar, Nigeria: Impact of the seniority of the medical team. Journal of Obstetrics and Gynaecology. 2008;28(2):198-201.
257. Adisso S TI, Teguete I, Gbegnide H, Chobli M, Alihonou E, . Pronostic maternel selon le type d'anesthésie pour la césarienne en milieu urbain au Bénin. 2006.
258. Imbert P, Berger F, Diallo NS, Cellier C, Goumbala M, Ka AS, et al. Maternal and Infant Prognosis of Emergency Cesarean Section: Prospective Study of the Principal Hospital in Dakar, Senegal. Medicine Tropicale. 2003;63(4-5):351-7.
259. Imarengiaye CO, Osaigbovo EP, Tudjegbe SO. Anesthesia for cesarean section in pregnancies complicated by placenta previa. Saudi Med J. 2008;29(5):688-91.
260. Kandasamy T, Merialdi M, Guidotti RJ, Betran AP, Harris-Requejo J, Hakimi F, et al. Cesarean delivery surveillance system at a maternity hospital in Kabul, Afghanistan. International Journal of Gynecology and Obstetrics. 2009;104(1):14-7.
261. Nwafor MI, Aniebue UU, Nwankwo TO, Onyeka TC, Okafor VU. Perinatal outcome of preterm cesarean section in a resource-limited centre: a comparison between general anaesthesia and subarachnoid block. Nigerian Journal of Clinical Practice. 2014;17(5):613-8.
262. Ijaiya MA AA. Caesarean Delivery: The Trend Over a Ten-Year Period at Ilorin, Nigeria. . Niger Nig J Surg Res. 2001;3(1):11-8.
263. Wahjoeningsih S, Witjaksono W. Evaluation of anasthesia methods in caesarean section for foetal distress. Malaysian Journal of Medical Sciences, . July 2007;14(2):41-6.
264. Okafor UV, Efetie ER, Ibe O. Anaesthesia And Outcome For Caesarean Delivery In The Parturient With Severe Co-Morbidity. The Internet Journal of Anesthesiology. 2008;21(2).
265. Huang CJ, Fan YC, Tsai PS. Differential impacts of modes of anaesthesia on the risk of stroke among preeclamptic women who undergo Caesarean delivery: a population-based study. British journal of anaesthesia. 2010;105(6):818-26.

266. Rasouli s, Moslemi F. Apgar scores and cord blood gas values on neonates from cesarean with general anesthesia and spinal anesthesia. Journal of Analytical Research in Clinical Medicine. 2014;2(1):11-6.
267. Almomani O. Effect of General Anesthesia Compared to Regional Anesthesia on the Apgar Score of Neonates. sudan JMS. 2012;7(3).
268. Ugwu EO, Obioha KC, Okezie OA, Ugwu AO. A five-year survey of caesarean delivery at a Nigerian tertiary hospital. Annals of Medical and Health Sciences Research. 2011;1(1):77-83.
269. Mekbib TA. Caesarean section and foetal outcome at Yekatit 12 hospital, Addis Abeba, Ethiopia, 1987-1992. Ethiopian medical journal. 1994;32:173-9.
270. Foumane P, Mve Koh V, Ze Minkande J, Njofang Ngantcha EA, Dohbit JS, Mboudou ET. Facteurs de risque et pronostic des césariennes d'urgence à l'hôpital gynéco-obstétrique et pédiatrique de Yaoundé (Cameroun). Médecine et Santé Tropicales. 2014;24(1):89-93.
271. Cisse CT, Faye EO, de Bernis L, Dujardin B, Diadhiou F. Cesarean Sections in Senegal: Coverage of Needs and Quality of Services. Cahiers Sante. 1998;8(5):369-77.
272. Soyannwo OA. Ectopic pregnancy and anesthesia in Gambia. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 1994;46(3):331-2.
273. Ouro-Bang'na Maman AF, Tomta K, Ahouangbevi S, Chobli M. Deaths associated with anaesthesia in Togo, West Africa. Tropical doctor. 2005;35(4):220-2.
274. Nwosu C, Agumor K, Aboyeji AP, Ijaiya MA. Outcome of Caesarean Section in a Sub-Urban Secondary Health Care Facility in Nigeria. Nigerian Medical Practitioner. 2004;46(4):77-9.
275. Ojiyi E, Dike E, Anolue F, Chukwulebe A. Appraisal Of Caesarean Section At The Imo State University Teaching Hospital, Orlu, Southeastern Nigeria. The Internet Journal of Gynecology and Obstetrics. 2012;16(2).
276. Kamilya G, Seal SL, Mukherji J, Bhattacharyya SK, Hazra A. Maternal mortality and cesarean delivery: an analytical observational study. The Journal of Obstetrics and Gynaecology Research. 2010;36(2):248-53.
277. Kambo I, Bedi N, Dhillon BS, Saxena NC. A critical appraisal of cesarean section rates at teaching hospitals in India. International Journal of Gynecology and Obstetrics. 2002;79(2):151-8.
278. Abbassi H, Aboulfalah A, Morsad F, Matar N, Himmi A, Mansouri AE. [Maternal complications of cesarean section: retrospective analysis of 3,231 interventions at the Casablanca University Hospital, Morocco]. Sante (Montrouge, France). 2000;10(6):419-23.
279. Chu KM, Ford N, Trelles M. Operative mortality in resource-limited settings: the experience of Medecins Sans Frontieres in 13 countries. Archives of surgery (Chicago, Ill : 1960). 2010;145(8):721-5.
280. Ministry of health, Malaysia; Report on the confidential enquiries into maternal deaths in malaysia 1992. 1992.
281. Ajmal M. General anaesthesia for caesarean sections: are anaesthetists dealing with exaggerated fear? European journal of anaesthesiology. 2011;28(11):815-6.
282. Moodley J, Jjuuko G, Rout C. Epidural compared with general anaesthesia for caesarean delivery in conscious women with eclampsia. BJOG: An International Journal of Obstetrics and Gynaecology. 2001;108(4):378-82.

283. Chattopadhyay S, Das A, Pahari S. Fetomaternal Outcome in Severe Preeclamptic Women Undergoing Emergency Cesarean Section under Either General Or Spinal Anesthesia. Journal of pregnancy. 2014;2014:1-10.
284. Okafor UV, Okezie O. Maternal and fetal outcome of anaesthesia for caesarean delivery in preeclampsia/eclampsia in Enugu, Nigeria: a retrospective observational study. Int J Obstet Anesth. 2005;14(2):108-13.
285. Okafor UV, Efetie ER, Igwe W, Okezie O. Anaesthetic management of patients with pre-eclampsia/eclampsia and perinatal outcome. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2009;22(8):688-92.
286. Okafor UV. Maternal and perinatal outcome after caesarean delivery in preeclampsia or eclampsia in Enugu, Nigeria: four years on. Int J Obstet Anesth. 2009;18(3):292-3.
287. Ajuzieogu OV, Ezike HA, Amucheazi AO, Enwereji J. A retrospective study of the outcome of cesarean section for women with severe pre-eclampsia in a third world setting. Saudi J Anaesth. 2011;5(1):15-8.
288. Afolayan JM NC, Esangbedo ES, Omu PO, Amadasun FE, Fadare JO. Evolving pattern of spinal anaesthesia in stable eclamptic patients undergoing caesarean section at University of Benin Teaching Hospital, Benin, Nigeria. Nigerian journal of medicine : journal of the National Association of Resident Doctors of Nigeria. 2014;23(4):288-95.
289. Chumpathong S, Sirithanetbhol S, Salakij B, Visalyaputra S, Parakkamodom S, Wataganara T. Maternal and neonatal outcomes in women with severe pre-eclampsia undergoing cesarean section: a 10-year retrospective study from a single tertiary care center: anesthetic point of view. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2016;29(24):4096-100.
290. Dyer RA, Els I, Farbas J, Torr GJ, Schoeman LK, James MF. Prospective, randomized trial comparing general with spinal anesthesia for cesarean delivery in preeclamptic patients with a nonreassuring fetal heart trace. Anesthesiology. 2003;99(3):561-9; discussion 5A-6A.
291. Pacharla Indira RR, Kota Raju, M.ChandraShekar. Analysis of Maternal Outcomes in Severe Pre-Eclampsia Patients under General versus Spinal Anaesthesia for Caesarean Delivery. Journal of Dental and Medical Sciences 2016;15(2):33-9.
292. Moslemi F, Rasooli S. Comparison of Spinal Versus General Anesthesia for Cesarean Delivery in Patients with Severe Preeclampsia. Journal of Medical Sciences(Faisalabad). 2007;7(6):1044-8.
293. Kilsztajn S, do Carmo MSN, Machado Jr. LC, Lopes ES, Lima LZ. Caesarean sections and maternal mortality in Sao Paulo. European Journal of Obstetric & Gynecology and Reproductive Biology. 2007;132(1):64-9.
294. Afolayan JM, Nwachukwu CE, Esangbedo ES, Omu PO, Amadasun FE, Fadare JO. Evolving Pattern of Spinal Anaesthesia in Stable Eclamptic Patients Undergoing Caesarean Section at University of Benin Teaching Hospital, Benin, Nigeria. Nigeria Journal of Medicine. 2014;23(4):288-95.
295. Cebekulu L, Buchmann EJ. Complications associated with cesarean section in the second stage of labor. International Journal of Gynecology and Obstetrics. 2006;95(2):110-4.

296. Ghazi A, Karim F, Hussain AM, Ali T, Jabbar S. Maternal morbidity in emergency versus elective caesarean section at a tertiary care hospital. J Ayub Med Coll Abbottabad. 2012;24(1):10-3.
297. Sorbye IK, Vangen S, Oneko O, Sundby J, Bergsjo P. Caesarean section among referred and self-referred birthing women: a cohort study from a tertiary hospital, northeastern Tanzania. BMC pregnancy and childbirth. 2011;11:55.
298. Ashok V, Santosh M, Anupa S. A study on Maternal Mortality. The Journal of Obstetrics and Gynecology of India. 2008;58(3):226-9.
299. Onankpa B, Ekele B. Fetal outcome following cesarean section in a university teaching hospital. J Natl Med Assoc. 2009;101(6):578-81.
300. Etuk SJ, Udoma EJ, Ekott MI. Avoidable factors in maternal mortality following caesarean section (excluding ruptured uterus) in Calabar, Nigeria. Tropical Doctor. 2001;31(2):108-9.
301. Koigi-Kamau R, Kabare LW, Wanyoike-Gichuhi J. Incidence of wound infection after caesarean delivery in a district hospital in central Kenya. East African Medical Journal. 2005;82(7):357-61.
302. Khawaja NP, Yousaf T, Tayyeb R. Analysis of caesarean delivery at a tertiary care hospital in Pakistan. Journal of Obstetrics and Gynaecology. 2004;24(2):139-41.
303. Pothinam S, Chanpoo T, Lumbiganon P. Post-cesarean section puerperal morbidity. The incidence and risk factors at Srinagarind Hospital. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 1992;75(3):173-7.
304. Wright EA, Kapu MM, Onwuhafua HI. Perinatal mortality and cesarean section in Jos University Teaching Hospital, Nigeria. Int J Gynaecol Obstet. 1991;35(4):299-304.
305. Urrio TF. Maternal Deaths at Songea Regional Hospital, Southern Tanzania. East African Medical Journal. 1991;68(2):81-7.
306. Wirakusumah FF. Maternal and perinatal mortality/morbidity associated with cesarean section in Indonesia. J Obstet Gynaecol. 1995;21(5):475-81.
307. Gomathy E, Swamy MN, Seema BR, Gomathy E, Swamy MN, Seema BR. Pattern of Maternal Mortality in a Rural Referral Hospital: A Six Year Retrospective Study. Indian Journal of Public Health Research & Development. 2013;4(4):5-10.
308. Pereira C, Bugalho A, Bergstrom S, Vaz F, Cotiro M. A comparative study of caesarean deliveries by assistant medical officers and obstetricians in Mozambique. British Journal of Obstetrics and Gynaecology. 1996;103(6):508-12.
309. Tadesse E, Adane M, Abiyou M. Caesarean section deliveries at Tikur Anbessa Teaching Hospital, Ethiopia. East African Medical Journal. 1996;73(9):619-22.
310. Njokanma F, Egri-Okwaji M, Nwokoro C, Orebamjo TO, Okeke G. Birth asphyxia, perinatal and maternal mortality associated with caesarean section. Tropical Journal of Obstetrics and Gynaecology. 2002;19(1):25-8.
311. Kumari S, Jain S, Jain RK, Goyal A, Shendrunikar N, Kanodia K. Neonatal outcome following cesarean birth: a prospective study. Indian Pediatrics. 1990;27(4):353-8.
312. Longombe AO, Wood PB, Dix R. Cesarean section--indications and risks in rural Zaire. International Journal of Gynaecology and Obstetrics. 1990;33(3):199-202.

313. Picaud A, Nlome-Nze AR, Kouvahe V, Faye A, Ondo-mve R. Indications for Cesarean Section and Their Outcome at the Hospital Center in Libreville. Rev Fr Gynecol Obstet. 1990;85(6):393-8.
314. Dey N, Hatai SK. A study of caesarean section cases with special reference to maternal and neonatal outcome. Journal of the Indian Medical Association. 1992;90(6):149-51.
315. Yaïch P, Ouattara A, Koffi N, Chiaké A, Sanou J, Itéké F, et al. Césariennes en urgence : pronostic materno-foetal au CHU de Cocody D'Abidjan. Revue Africaine d'Anesthésiologie et de Médecine d'Urgence. 2012;17(1).
316. Burshan NM, Abusnena O, Alhamdi MR, Oommen S, El Heggiagi AM. Emergency Caesarian Section among Libyan Women at Khaddar Hospital, Tripoli, Libya. IOSR Journal of Dental and Medical Sciences. 2015;14(1):20-2.
317. Gessessew A, Barnabas GA, Prata N, Weidert K. Task shifting and sharing in Tigray, Ethiopia, to achieve comprehensive emergency obstetric care. International journal of gynaecology and obstetrics. 2011;113(1):28-31.
318. OMAMALIN NG, . INDICATIONS FOR EMERGENCY CESAREAN SECTION AND ASSOCIATED CLINICAL MATERNAL ANDNEONATAL OUTCOMES AT WVSU-MC: A THREE-YEAR RETROSPECTIVE STUDY
.
319. McCord C, Mbaruku G, Pereira C, Nzabuhakwa C, Bergstrom S. The quality of emergency obstetrical surgery by assistant medical officers in Tanzanian district hospitals. Health Affairs. 2009;28(5):w876-w85.
320. Basak S, Kanungo S, Majhi C. Symphysiotomy: Is it obsolete? The Journal of Obstetrics and Gynaecology Research. 2011;37(7):770-4.
321. Begum KS, Khan NU, Akter F. Factors Affecting the Pregnancy Outcome in Patients with Previous One Caesarean Section. Medicine Today. 2014;26(1):1-3.
322. Briand V, Dumont A, Abrahamowicz M, Sow A, Traore M, Rozenberg P, et al. Maternal and Perinatal Outcomes by Mode of Delivery in Senegal and Mali: A Cross-Sectional Epidemiological Survey. PloS one. 2012;7(10).
323. Daniel CN, Singh S. Caesarean delivery: An experience from a tertiary institution in north western Nigeria. Nigerian Journal of Clinical Practice. 2016;19(1):18-24.
324. Abebe FE, Gebeyehu AW, Kidane AN, Eyassu GA. Factors leading to cesarean section delivery at Felegehiwot referral hospital, Northwest Ethiopia: a retrospective record review. Reproductive Health. 2016;13(6).
325. Jabir M, Abdul-Salam I, Suheil DM, Al-Hilli W, Abul-Hassan S, Al-Zuheiri A, et al. Maternal near miss and quality of maternal health care in Baghdad, Iraq. BMC Pregnancy Childbirth. 2013;13(11).
326. Kim YM, Tappis H, Zainullah P, Ansari N, Evans C, Bartlett L, et al. Quality of caesarean delivery services and documentation in first-line referral facilities in Afghanistan: a chart review. BMC Pregnancy Childbirth. 2012;12(14).
327. Litorp H, Kidanto HL, Roost M, Abeid M, Nystrom L, Essen B. Maternal near-miss and death and their association with caesarean section complications: a cross-sectional study at a university hospital and a regional hospital in Tanzania. BMC Pregnancy Childbirth. 2014;14:244.
328. Maaloe N, Bygbjerg IC, Onesmo R, Secher NJ, Sorensen BL. Disclosing doubtful indications for emergency cesarean sections in rural hospitals in Tanzania: a retrospective criterion-based audit. Acta obstetricia et gynecologica Scandinavica. 2012;91(9):1069-76.

329. Madoue GB, Madoue KB, Mahamat HA, Abbo MD, Hassan M, Sakine M. Caesarean Section in the Context of Exemption Fees for Emergency Care. Sudan Medical Journal. 2015;51(3):18-23.
330. Okonta PI, Otoide VO, Okogbenin SA. Caesarean Section at the University of Benin Teaching Hospital Revisited. Tropical Journal of Obstetrics and Gynaecology. 2003;20(1):63-6.
331. Rahlenbeck S, Hakizimana C. Deliveries at a district hospital in Rwanda, 1997-2000. International Journal of Gynaecology and Obstetrics. 2002;76(3):325-8.
332. Sebhatu B. Profile of Caesarian Section in Orotta Maternity Hospital. Journal of Eritrean Medical Association.6-7.
333. Sekirime WK, Lule JC. Outcome of cesarean section in asymptomatic HIV-1 infection in Kampala, Uganda. Journal of Obstetrics and Gynaecology Research. 2009;35(4):679-88.
334. Utoo B, Utoo P. Primary Caesarean Section And Fetal Outcome Amongst Nulliparous Women At A Health Facility In Southern Nigeria. The Internet Journal of Gynecology and Obstetrics. 2013;17(1).
335. Berhan Y, Abdela A. Emergency obstetric performance with emphasis on operative delivery outcome: Does it reflect the quality of care? Ethiopian Journal of Health Development. 2004;18(2):96-106.
336. Hounton SH, Newlands D, Meda N, De Brouwere V. A cost-effectiveness study of caesarean-section deliveries by clinical officers, general practitioners and obstetricians in Burkina Faso. Human Resources for Health. 2009;7(1):34.
337. Landry E, Pett C, Fiorentino R, Ruminjo J, Mattison C. Assessing the quality of record keeping for cesarean deliveries: results from a multicenter retrospective record review in five low-income countries. BMC Pregnancy Childbirth. 2014;14:139.
338. Asicioglu O, Gungorduk K, Yildirim G, Asicioglu BB, Gungorduk OC, Ark C, et al. Second-stage vs first-stage caesarean delivery: comparison of maternal and perinatal outcomes. Journal of Obstetrics and Gynaecology. 2014;34(7):598-604.
339. Kor-Anantakul O, Suwanrath C, Lim A, Chongsuviwatwong V. Comparing complications in intended vaginal and caesarean deliveries. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2008;28(1):64-8.
340. Seal SL, Kamilya G, Mukherji J, Bhattacharyya SK, De A, Hazra A. Outcome in second- versus first-stage cesarean delivery in a teaching institution in eastern India. American journal of perinatology. 2010;27(6):507-12.
341. Teguete I, Traore Y, Sissoko A, Djire MY, Thera A, Dolo T, et al. Determining Factors of Cesarean Delivery Trends in Developing Countries: Lessons from Trends in Developing Countries: Lessons from Trends in Developing Countries: Lessons from Point G National Hospital (Bamako – Mali). Cesarean Delivery: InTech; 2012. p. 161-200.
342. Diawara A, Sangho H, Tangara I, Cisse MO, Traore MN, Konate S. Complications post cesarienne et gratuite de la cesarienne au Mali = cas d'un centre de sante de district. Mali Medical. 2014;29(1):40-3.
343. Ngowa JDK, Ngassam A, Fouogue JT, Metogo J, Medou A, Kasia JM. Complications maternelles précoces de la césarienne: à propos de 460 cas dans deux hôpitaux universitaires de Yaoundé, Cameroun. The Pan African Medical Journal. 2015;21:265.

344. Diallo FB, Diallo MS, Bangoura S, Diallo AB, Camara Y. Cesarienne = Facteur de Reduction de Morbidite et de Mortalite Foetao-Maternelle au Centre Hospitalier Universitaire Ignace Deen de Conakry (Guinee). Medecine d'Afrique Noire. 1998;45(6):359-64.
345. Sucak A, Çelen Ş, Akbaba E, Soysal S, Moraloglu O, Danışman N. Comparison of Nulliparas Undergoing Cesarean Section in First and Second Stages of Labour: A Prospective Study in a Tertiary Teaching Hospital. Obstetrics and Gynecology International. 2011;2011.
346. Geelhoed DW, Visser LE, Asare K, Schagen van Leeuwen JH, van Roosmalen J. Trends in maternal mortality: a 13-year hospital-based study in rural Ghana. European journal of obstetrics, gynecology, and reproductive biology. 2003;107(2):135-9.
347. Gonzales GF, Tapia VL, Fort AL, Betran AP. Pregnancy outcomes associated with Cesarean deliveries in Peruvian public health facilities. International Journal of Women's Health. 2013;5:637-45.
348. van Dillen J, Meguid T, Petrova V, van Roosmalen J. Caesarean section in a semi-rural hospital in Northern Namibia. BMC Pregnancy Childbirth. 2007;7:2.
349. Nelissen EJT, Mduma E, Ersdal HL, Evjen-Olsen B, van Roosmalen JJM, Stekelenburg J. Maternal near miss and mortality in a rural referral hospital in northern Tanzania: a cross-sectional study. BMC Pregnancy and Childbirth. 2013;13(1):141.
350. Nahar K. Indications of Caesarean Section - Study of 100 cases in Mymensingh Medical College Hospital. Journal of Shaheed Suhrawardy Medical College. 2009;1(1):6-10.
351. Ozumba BC, Nwogu-Ikojo EE. Avoidable maternal mortality in Enugu, Nigeria. Public Health. 2008;122(4):354-60.
352. Kwawukume EY. Caesarean section in developing countries. Best Practice & Research Clinical Obstetrics & Gynaecology. 2001;15(1):165-78.
353. Chilopora G, Pereira C, Kamwendo F, Chimbiri A, Malunga E, Bergström S. Postoperative outcome of caesarean sections and other major emergency obstetric surgery by clinical officers and medical officers in Malawi. Human Resources for Health. 2007;5(1):17.
354. Garba NA, Muhammad Z. Caesarean Morbidity and Mortality at Aminu Kano Teaching Hospital, Kano- A Two- Year Review. Borno Medical Journal Online. 2011;8(1):10-4.
355. Wu WL. Cesarean delivery in Shantou, China: a retrospective analysis of 1922 women. Birth. 2000;27(2):86-90.
356. Fesseha N, Getachew A, Hiluf M, Gebrehiwot Y, Bailey P. A national review of cesarean delivery in Ethiopia. International Journal of Gynecology and Obstetrics. 2011;115(1):106-11.
357. Adekanle DA, Adeyemi AS, Fasanu AO. Caesarean section at a tertiary institution in Southwestern Nigeria—A 6-year audit. Open Journal of Obstetrics and Gynecology. 2013;03(03):357-61.
358. Chu K, Cortier H, Maldonado F, Mashant T, Ford N, Trelles M. Cesarean section rates and indications in sub-Saharan Africa: a multi-country study from Medecins sans Frontieres. PLoS One. 2012;7(9):e44484.
359. Davies JF, Lenglet A, van Wijhe M, Ariti C. Perioperative mortality: Analysis of 3 years of operative data across 7 general surgical projects of Medecins Sans Frontieres in Democratic Republic of Congo, Central African Republic, and South Sudan. Surgery. 2016;159(5):1269-78.

360. Festin MR, Laopaiboon M, Pattanittum P, Ewens MR, Henderson-Smart DJ, Crowther CA. Caesarean section in four South East Asian countries: reasons for, rates, associated care practices and health outcomes. BMC pregnancy and childbirth. 2009;9:17.
361. Akasheh HF, Amarin V. Caesarean sections at Queen Alia Military Hospital, Jordan: a six-year review. Eastern Mediterranean Health Journal. 2000;6(1):41-5.
362. Richard F, Ouedraogo C, De Brouwere V. Quality cesarean delivery in Ouagadougou, Burkina Faso: a comprehensive approach. International Journal of Gynecology and Obstetrics. 2008;103(3):283-90.
363. Nana PN, Fomulu JN, Djenabou A, Mbu RE, Tonye R, Wandji JC, et al. Epidemio-Clinical Factors Associated with Caesarean Section in Two Referral Hospitals (Public/Faith-Based), Far-North Region, Cameroon. Clinics in Mother and Child Health. 2011;8.
364. Moges A, Ademe BW, Akessa GM. Prevalence and Outcome of Caesarean Section in Attat Hospital, Gurage Zone, SNNPR, Ethiopia. Archives of Medicine. 2015;7(4):8.
365. Akinola OI, Fabamwo AO, Tayo AO, Rabiu KA, Oshodi YA, Onyekwere CA. Evaluation of blood reservation and use for caesarean sections in a tertiary maternity unit in south western Nigeria. BMC Pregnancy Childbirth. 2010;10:57.
366. Abbassi H, Aboulfalah A, Morsad F, Matar N, Himmi A, El Mansouri A. Maternal complications of cesarean section: retrospective analysis of 3,231 interventions at the Casablanca University Hospital (Morocco). Cahiers d'études et de recherches francophones / Santé. 2000;10(6):419-23.
367. Abiodun OM, Balogun OR. A review of caesarean sections associated with perinatal mortality at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. Nigerian Journal of Clinical Practice. 2009;12(3):248-51.
368. Onoh RC, Eze JN, Ezeonu PO, Lawani LO, Iyoke CA, Nkwo PO. A 10-year appraisal of cesarean delivery and the associated fetal and maternal outcomes at a teaching hospital in southeast Nigeria. International Journal of Women's Health. 2015;7:531-8.
369. Ali Y. Analysis of caesarean delivery in Jimma Hospital, south-western Ethiopia. East African Medical Journal. 1995;72(1):60-3.
370. Feresu SA, Harlow SD, Welch K, Gillespie BW. Incidence of stillbirth and perinatal mortality and their associated factors among women delivering at Harare Maternity Hospital, Zimbabwe: a cross-sectional retrospective analysis. BMC Pregnancy and Childbirth. 2005;5(1):9.
371. Swende TZ. Emergency caesarean section in a Nigerian tertiary health centre. Nigerian Journal of Medicine. 2008;17(4):396-8.
372. Wanyonyi S, Sequeira E, Obura T. Caesarian section rates and perinatal outcome at the Aga Khan University Hospital, Nairobi. East African Medical Journal. 2006;83(12):651-8.
373. Ezechi OC, Loto OM, Ndububa VI, Okogbo FO, Ezeobi PM, Nwokoro CA. Caesarean Section and Perinatal Mortality in South Western Nigeria. Nepal Journal of Obstetrics and Gynaecology. 2009;4(1):46-8.
374. Moodliar S, Moodley J, Esterhuizen TM. Complications associated with caesarean delivery in a setting with high HIV prevalence rates. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2007;131(2):138-45.

375. Ijaiya MA, Aboyeji PA. Caesarean Delivery: The Trend Over a Ten-Year Period at Ilorin, Nigeria. The Nigerian Journal of Surgical Research. 2001;3(1):11-8.
376. Ekoundzola JR, Buambo S, Nkihouabonga G, Mayanda FH. Enfants nés par césarienne au centre hospitalier universitaire de Brazzaville. Archives de pédiatrie. 2001;8(11):1265-73.
377. Foumsou L, Saleh AS, Choua O, Oumar G, Dangar GD, Denakpo J, et al. Maternal and Fetal Prognosis of Emergency Caesarean Section in Mother and Child Hospital of N'djamena. African Journal of Integrated Health. 2014;5(1):59-62.
378. Khan A, Ghani T, Rahim A, Rahman MM. Changing trends in incidence and indications of caesarean section. Mymensingh medical journal : MMJ. 2014;23(1):52-5.
379. Rasoarimahandry ACL, Andrianarivony MO, Ranjalahy RJ. Indications and prognosis of cesarean section at Befelatanana maternity unit--Central University Hospital of Antananarivo (apropos of 529 cases, during the year 1998). Gynecologie, Obstetrique & Fertilite. 2001;29(12):900-4.
380. Akar ME, Eyi EG, Yilmaz ES, Yuksel B, Yilmaz Z. Maternal deaths and their causes in Ankara, Turkey, 1982-2001. Journal of Health, Population, and Nutrition. 2004;22(4):420-8.
381. Johnson AN, Buchmann EJ. Puerperal infection after caesarean section at Chris Hani Baragwanath Academic Hospital, Johannesburg. South African Journal of Obstetrics and Gynaecology. 2012;18(3):90-1.
382. Beltman J, T VDA, L VANL, Schmidt A, Chidakwani R, J VANR. Beyond maternal mortality: obstetric hemorrhage in a Malawian district. Acta Obstetricia et Gynecologica Scandinavica. 2011;90(12):1423-7.
383. Zongo A, Dumont A, Fournier P, Traore M, Kouanda S, Sondo B. Effect of maternal death reviews and training on maternal mortality among cesarean delivery: post-hoc analysis of a cluster-randomized controlled trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2015;185:174-80.
384. Govender V, Panday M, Moodley J. Second stage caesarean section at a tertiary hospital in South Africa. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2010;23(10):1151-5.
385. Belay T, Yusuf L, Negash S. A comparative study on first stage versus second stage caesarean section on maternal and perinatal outcome. Ethiopian medical journal. 2014;52(1):1-8.
386. Moodley J, Devjee J, Khedun SM, Esterhuizen T. Second-stage primary Caesarean deliveries: Are maternal complications increased? South African Family Practice. 2014;51(4):328-31.
387. Rabiu KA, Adewunmi AA, Akinola OI, Eti AE, Tayo AO. Comparison of maternal and neonatal outcomes following caesarean section in second versus first stage of labour in a Tertiary Hospital in Nigeria. The Nigerian postgraduate medical journal. 2011;18(3):165-71.
388. Suwal A, Shrivastava VR, Giri A. Maternal and fetal outcome in elective versus emergency cesarean section. JNMA; journal of the Nepal Medical Association. 2013;52(192):563-6.
389. Bokossa M NK, Doumbia Y. cesariennes prophylactiques et d'urgence. medecine d'afriques noire. 2008;55(11):593-601.

390. kizonde K. La cesarienne en milieu africain. medecine d'afriques noire. 2006;53(5):293-8.
391. Ugwa E, Ashimi A, Abubakar MY. Caesarean section and perinatal outcomes in a sub-urban tertiary hospital in North-West Nigeria. Nigerian medical journal : journal of the Nigeria Medical Association. 2015;56(3):180-4.
392. Urbani G, de Vries MM, Cronje HS, Niemand I, Bam RH, Beyer E. Complications associated with cesarean section in HIV-infected patients. International Journal of Gynecology & Obstetrics. 2001;74(1):9-15.
393. Nakimuli A, Nakubulwa S, Kakaire O, Osinde MO, Mbalinda SN, Nabirye RC, et al. Incidence and determinants of neonatal morbidity after elective caesarean section at the national referral hospital in Kampala, Uganda. BMC Research Notes. 2015;8:624.
394. van den Boogaard W, Manzi M, De Plecker E, Caluwaerts S, Nanan-N'zeth K, Duchenne B, et al. Caesarean sections in rural Burundi: how well are mothers doing two years on? Public Health Action. 2016;6(2):72-6.
395. Ouedraogo CM, Ouedraogo A, Ouattara A, Lankoande J. Cesarean deliveries in a district hospital in Ouagadougou. Epidemiological, clinical, and prognostic study of 3381 cases. Medicine et Sante Tropicales. 2015;25(2):194-9.
396. Nyamtema A, Mwakatundu N, Dominico S, Mohamed H, Shayo A, Rumanyika R, et al. Increasing the availability and quality of caesarean section in Tanzania. BJOG : an international journal of obstetrics and gynaecology. 2016;123(10):1676-82.
397. Benzouina S, Boubkraoui Mel M, Mrabet M, Chahid N, Kharbach A, El-Hassani A, et al. Fetal outcome in emergency versus elective cesarean sections at Souissi Maternity Hospital, Rabat, Morocco. The Pan African medical journal. 2016;23:197.
398. Soren R, Maitra N, Patel PK, Sheth T. Elective Versus Emergency Caesarean Section: Maternal Complications and Neonatal Outcomes. Journal of Nursing and Health Science. 2016;5(5):01-4.
399. El Daba AA, Amr YM, Marouf HM, Mostafa M. Retrospective study of maternal mortality in a tertiary hospital in Egypt. Anesthesia Essays and Researches. 2010;4(1):29-32.
400. Abe E, Omo-Aghoja LO. Maternal mortality at the Central Hospital, Benin City Nigeria: a ten year review. African Journal of Reproductive Health. 2008;12(3):17-26.
401. Gebhardt GS, Fawcus S, Moodley J, Farina Z. Maternal death and caesarean section in South Africa: Results from the 2011-2013 Saving Mothers Report of the National Committee for Confidential Enquiries into Maternal Deaths. South African Medical Journal. 2015;105(4):287-91.
402. Hoestermann CF, Ogbaselassie G, Wacker J, Bastert G. Maternal mortality in the main referral hospital in The Gambia, west Africa. Tropical Medicine and International Health. 1996;1(5):710-7.
403. Montgomery AL, Ram U, Kumar R, Jha P. Maternal mortality in India: causes and healthcare service use based on a nationally representative survey. PLoS One. 2014;9(1):e83331.
404. Bouvier-Colle MH, Ouedraogo C, Dumont A, Vangeenderhuysen C, Salanave B, Decam C. Maternal mortality in West Africa. Rates, causes and substandard care from a prospective survey. Acta Obstetricia et Gynecologica Scandinavica. 2001;80(2):113-9.

405. Tebeu PM, Ngassa P, Kouam L, Major AL, Fomulu JN. Maternal mortality in Maroua Provincial Hospital, Cameroon (2003-2005). The West Indian Medical Journal. 2007;56(6):502-7.
406. El-Gharib MN, Rakha SF, Awara AM, Mahfouz AE, Elhawary TS. Causes of Maternal Deaths in Tanta University Hospital. Clinical Medicine Reviews in Women's Health. 2010;2010(2):79-83.
407. Charoenweerakul P, Srisupundit K, Tongsong T. Maternal Death at Maharaj Nakorn Chiang Mai Hospital, the 17 Years Experience. Thai Journal of Obstetrics and Gynaecology. 2009;17(4):230-6.
408. Pal SJ, Mrudhula, Rao A. A Three Year Review of Maternal Mortality in a District Hospital on the West Coast in South India (April 2011-2014). International Journal of Innovative Research & Development. 2014;3(7):15-21.
409. Abdel-Hady E-S, Mashaly A-M, Sherief LS, Hassan M, Al-Gohary A, Farag MK, et al. Why do mothers die in Dakahlia, Egypt? The Journal of Obstetrics and Gynaecology Research. 2007;33(3):283-7.
410. Bashir A, Aleem M, Mustansar M. A 5-year study of maternal mortality in Faisalabad City Pakistan. International Journal of Gynecology & Obstetrics. 1995;50(2):S93-S6.
411. Mohammed AA, Elnour MH, Mohammed EE, Ahmed SA, Abdelfattah AI. Maternal mortality in Kassala State - Eastern Sudan: community-based study using Reproductive age mortality survey (RAMOS). BMC Pregnancy Childbirth. 2011;11:102.
412. Bano N, Chaudhri R, Yasmeen L, Shafi F, Ejaz L. A study of maternal mortality in 8 principal hospitals in Pakistan in 2009. International Journal of Gynecology and Obstetrics. 2011;114(3):255-9.
413. Oladapo OT, Lamina MA, Fakoya TA. Maternal deaths in Sagamu in the new millennium: a facility-based retrospective analysis. BMC Pregnancy Childbirth. 2006;6:6.
414. Bolnga JW, Hamura NN, Umbers AJ, Rogerson SJ, Unger HW. Insights into maternal mortality in Madang Province, Papua New Guinea. International Journal of Gynecology and Obstetrics. 2014;124(2):123-7.
415. Ray S, Madzimbamuto FD, Ramagola-Masire D, Phillips R, Mogobe KD, Haverkamp M, et al. Review of causes of maternal deaths in Botswana in 2010. South African Medical Journal. 2013;103(8):537-42.
416. Kane TT, el-Kady AA, Saleh S, Hage M, Stanback J, Potter L. Maternal mortality in Giza, Egypt: magnitude, causes, and prevention. Studies in Family Planning. 1992;23(1):45-57.
417. Amarin Z, Khader Y, Okour A, Jaddou H, Al-Qutob R. National maternal mortality ratio for Jordan, 2007-2008. International Journal of Gynecology and Obstetrics. 2010;111(2):152-6.
418. Wagaarachchi PT, Fernando L. Trends in maternal mortality and assessment of substandard care in a tertiary care hospital. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2002;101(1):36-40.
419. Mahbouli S, Basli M, Messaoudi F, Messaoudi I, Chibani M, Rachdi R. Maternal mortality: epidemiology, risk factors and evitability. About ten cases. Gynécologie Obstétrique & Fertilité. 2003;31(12):1018-23.
420. Kassas M, Hefni M, Hanafi A, Campbell O. The national maternal mortality study of Egypt 1992–1993. International Journal of Gynecology & Obstetrics. 1995;50(2):S101-S8.

421. Mukherjee S, Mukherjee S, Sarkar RR. A Six Year Retrospective Study of Maternal Mortality at a Tertiary Teaching Institute in Uttar Pradesh. International Journal of Medical Science and Public Health. 2014;3(11):1407-9.
422. M AA. A study of changing trends of Maternal Mortality at the tertiary care centre, MMC and RI, Mysore, India. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2015;4(1):239-42.
423. Saleh WF, Ragab WS, Aboulgheit SS. Audit of maternal mortality ratio and causes of maternal deaths in the largest maternity hospital in Cairo, Egypt (Kasr Al Aini) in 2008 and 2009: lessons learned. African journal of reproductive health. 2013;17(3):105-9.
424. Karimi-Zarchi M, Ghane-Ezabadi M, Vafaienasab M, Dehghan A, Ghasemi F, Zaidabadi M, et al. Maternal mortality in Yazd Province, Iran. Electron Physician. 2016;8(2):1949-54.
425. National committie on confidential enquiries into maternal death; Tenth interim report on Confidential Enquiries into Maternal Deaths in South Africa 2011and 2012. Department of health, Pretoria, 2014.
426. Asuquo B, Vellore AD, Walters G, Manney S, Mignini L, Kunst H. A case-control study of the risk of adverse perinatal outcomes due to tuberculosis during pregnancy. Journal of Obstetrics and Gynaecology. 2012;32(7):635-8.
427. Lin HC, Chen SF. Increased risk of low birthweight and small for gestational age infants among women with tuberculosis. Bjog-an International Journal of Obstetrics and Gynaecology. 2010;117(5):585-90.
428. Ricardo Figueroa-Damián*, , José Luis Arredondo-García*. Neonatal Outcome of Children Born to Women with Tuberculosis. 2001;32(1):66–9.
429. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. International Journal of Gynecology & Obstetrics. 1994;44(2):119-24.
430. Ali AA, Abdallah TM, Rayis DA, Adam I. Maternal and perinatal outcomes of pregnancies associated with tuberculosis in eastern Sudan. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2011;114(3):286-7.
431. Marynowski A, Ruszkowski J, Sianozecka E. Premature labor in women with tuberculosis. Revue francaise de gynecologie et d'obstetrique. 1972;67(8):479-81.
432. Kovganko PA. Outcomes of pregnancy and labor in females with tuberculosis. Rossiiskii Vestnik Perinatologii i Pediatrii. 2003;48(6):60-.
433. Kovganko PA. The course of pregnancy, labor and perinatal outcomes in females with extrapulmonary tuberculosis. Problemy tuberkuleza i boleznei legkikh. 2004(2):38-41.
434. Bjerkedal T, Bahna SL, Lehmann EH. Course and outcome of pregnancy in women with pulmonary tuberculosis. Scandinavian Journal of Respiratory Diseases. 1975;56(5):245-50.
435. Pranevicius A, Radzeviciute V, Bimba P, Praneviciute L. Course of pregnancy, delivery and newborn status in case of maternal tuberculosis. Medicina (Kaunas, Lithuania). 2003;39(4):399-402.