Exploring Interventions To Reduce Blood Loss During And After Caesarean Delivery In Africa

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This thesis is dedicated to Shirley Georgina Cullen (1935 – 2011) and to women in Africa who lack access to safe and affordable caesarean delivery.

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Contents

Figures

Tables

Abstract

Background

Women in Africa are fifty times more likely to die following caesarean delivery compared to high-income settings and blood loss during and after caesarean delivery is independently associated with mortality. We aimed to (i) identify interventions, and (ii) identify which interventions African clinicians and researchers recommend as feasible and effective to reduce blood loss during and after caesarean delivery.

Methods

(i) We conducted a systematic review and network meta-analysis to identify non-pharmacological interventions. We conducted a comprehensive search from database inception to 31st December 2019, with no language restrictions. We included studies of women undergoing caesarean delivery, which assess non-pharmacological interventions, and report one of the study co-primary outcomes (blood loss [ml] or risk of post-partum haemorrhage [>1,000 ml]). We excluded retrospective studies, and study cohorts not representative of the general caesarean delivery population.

(ii) We conducted a Delphi Consensus study, including obstetrics and anaesthesia providers from across Africa. Rounds one to three were online surveys, and round four formed a live online discussion.

Findings

(i) We included 51 studies in the network-meta-analysis, forming 13 distinct intervention groups. Thirty studies were not included in the meta-analysis and were synthesised narratively. On random effects model analysis, only three interventions had clinically significant findings, of which one had statistical significance.

(ii) Twenty-eight interventions were considered highly effective and highly feasible. These interventions covered broad domains including community based; antenatal; perioperative; and health system strengthening interventions.

Interpretation

The published trials on the effect of non-pharmacological interventions on blood loss associated with caesarean delivery are inconclusive. There is a need for collaborative pragmatic trials to identify effective and generalisable interventions. The broad range of recommended interventions highlights the importance of a multifaceted systems strengthening approach to reduce morbidity and mortality associated with blood loss during and after caesarean delivery in Africa.

Chapter 1: Background

1.1.1 Maternal Mortality

Over 800 mothers die each day. Over two thirds of these deaths occur in Africa.[1] In 2017, the World Health Organisation (WHO) estimated a global maternal morality ratio (MMR) of 211 maternal deaths per 100,000 live births.[1] The MMR for the same period in Sub-Saharan Africa was 542 per 100,000 live births - over 50 times higher than the ratio in Europe. Between 2000 and 2017 the global MMR fell from 342 per 100,000 to 211 per 100,000 – a reduction of 38.4%. In Sub-Saharan Africa the overall percentage change for the same period was similar, yet the total annual maternal deaths fell by only 16% from 234,000 to 196,000.[1] This is likely due to the increasing birth rate across the region.[2] Indeed, the population of African is rising at the fastest rate worldwide.[2] There are significant country-level variations in MMR across Africa, ranging from an MMR of 1,150 per 100,000 live births in South Sudan, to 43 per 100,000 in Tunisia. Despite significant variation, the overall MMR across the region remains high. Of the 19 countries with the highest MMR worldwide, 18 are in Africa.[1]

The Sustainable Development Goals (SDGs), set in 2015, aim to *'reduce the global maternal mortality ratio to less than 70 per 100,000 live births"* by 2030 *(SDG target 3.1).*[3] Given the majority of maternal deaths occur in Africa, a colossal reduction in MMR across Africa is needed to achieve this goal, where the MMR is currently eight times higher than the SDG target. The SDGs replace the Millennium Development Goals (MDGs), which called for a 75% reduction in MMR from 1990 to 2015. Though significant progress was made by an estimated reduction of 45% by 2013, and the global MMR reduced from 380 to 210 per 100,000 live births, the reduction fell 30% short of the target.[4]

The large variation in global maternal morality indicates that the majority of maternal deaths are preventable or treatable.

Obstetric haemorrhage is the most common direct cause of maternal death across Africa, accounting for 36.9% of maternal deaths in Northern Africa and 24.5% of maternal deaths in Sub-Saharan Africa.[5]

1.1.2 Caesarean Delivery

The WHO have made reducing maternal mortality a key priority. As stated in 'Strategies toward ending preventable maternal mortality (EPMM)', the WHO aims to work with nations to achieve five key objectives; one being to ensure '*Universal Health Coverage (UHC) for comprehensive sexual, reproductive, maternal and newborn health care'*. EPMM highlights the need for safe use of surgical interventions, including caesarean delivery. The role of surgery, not limited to caesarean delivery, has been formally recognised as an essential component of UHC through the passing of the World Health Assembly Resolution 68.15. on strengthening emergency and essential surgical care and anaesthesia.[6]

Caesarean delivery is defined as:

> *'the delivery of a foetus(es) through surgical incisions made through the anterior abdominal wall and the anterior uterine wall.'* [7]

Caesarean delivery is recognised as a core 'Bellwether Procedure' by the Lancet Commission on Global surgery.[8] Caesarean delivery is the most common surgical procedure performed worldwide,[9] and when appropriately indicated is a life-saving

procedure for both mother and baby. However, the procedure contributes to a significant proportion of obstetric haemorrhage related deaths.[10]

1.1.3 Access

Access to caesarean delivery is a vital component of comprehensive obstetric care. The number of caesarean deliveries performed each year are increasing at a steady rate worldwide.[11] Globally, the percentage of births by caesarean section - caesarean section rate (CSR) - increased from 6.7% to 19.1% between 1990 and 2014.[11] In Africa this increase was less marked, and rose from 2.9% to 7.4%.[11] Low CSR is a marker of poor access to caesarean delivery. There is large variation in CSR worldwide. Caesarean section rate in North America is estimated to be 40.5%, while the estimate for Africa sits well below at 7.3%.[11] There is significant variation across the African continent: Western Africa 3%; Eastern Africa 3.9% Middle Africa 5.8%; Northern Africa 27.8% *(there was insufficient coverage from Southern Africa to provide estimates).*[11] Significant within country inequality in CSR also exists. An observational study of 72 low- and middle-income countries (LMICs) showed that CSR were lowest in the poorest quintile of the population, and highest in the richest quintile.[12]

There is debate regarding the optimum CSR. Since 1985 WHO recommended that CSR should not exceed 10-15% for optimal maternal and perinatal outcomes.[13] Data from an international observational study published since, corroborate this recommendation - although there was no data from Africa and only 19 countries were included.[14] A recent and comprehensive analysis of 172 countries estimated that increasing CSR to 7.2% is associated with a dramatic reduction in maternal mortality.[15] The reduction in maternal mortality continues between a CSR of 7.2% to 19.1% at a steady rate.[15] A CSR above 19.1% is not associated with a reduction in maternal mortality.[15] This data shows that the CSR of Africa

(7.3%) and in particular Sub-Saharan Africa (3.7%),[11] is well below the level needed for safe and comprehensive obstetric care.

1.1.4 Surgical Volume and Case-Mix

The volume of surgical procedures taking place across Africa falls well below optimum levels. A secondary analysis of data from Surgical Outcomes Studies[16,17] showed that surgical volume in low human development index countries (HDI), many of which are in Africa, is considerably lower than in high HDI countries.[18]

Despite the low overall caesarean section rate across Africa, caesarean delivery is the most common surgical procedure performed in the region. According to the landmark African Surgical Outcomes Study (ASOS), caesarean delivery account for one third of all operations.[17] This reflects the overall low volume of surgery performed in the region. Despite data from ASOS being the most robust continental estimate to date, the true African surgical case-mix is relatively unknown, especially given that almost half of the hospitals in ASOS were tertiary or university affiliated sites. Therefore, data from ASOS may not accurately reflect the picture in rural and district hospitals.

1.1.5 Perioperative Mortality

The 'Lancet Global Health Commission - High Quality Health Systems in the SDG Era' estimated that the majority of treatable deaths in LMICs are a result of poor-quality care rather than poor access to care.[19] The commission advocated that a key component of UHC should be improving the quality of care within health systems. In Africa, excess mortality

due to low quality health care is particularly high[19] For those who reach caesarean delivery in Africa, peri-operative outcomes are poor.[20] In ASOS, which included 3,782 women undergoing caesarean delivery - the maternal mortality was 543 per 100,000 caesarean deliveries. This indicated that women in Africa are 50 times more likely to die following caesarean delivery, compared to women in high-income regions.[20] In ASOS, low access to caesarean delivery across Africa manifested in women presenting for caesarean delivery with high perioperative risk. The majority (78.2%) were emergency procedures. The perioperative complications independently associated with mortality were severe obstetric haemorrhage and anaesthesia complications. The presence of major bleeding risk (placenta praevia, placenta abruption, ruptured uterus, and antepartum haemorrhage) pre-operatively was also associated with mortality.[20] A meta-analysis of complications and outcomes associated with caesarean delivery in LMICs found that women in LMICs are 100-times more likely to die compared to women in the United Kingdom. The majority of studies included in the pooled analysis were from Sub-Saharan Africa, where the maternal mortality rate was highest.[21] The study found that around a quarter of all maternal deaths were during or after caesarean delivery.[21] The meta-analysis also identified haemorrhage as the most common complication associated with after caesarean delivery.[21]

There is currently a lack of prospectively collected data on maternal outcomes associated with caesarean delivery across Africa. Establishing a surgical data registry was identified as a top priority for peri-operative researchers in Africa, and will allow for better surveillance of interventions aimed at reducing perioperative morbidity and mortality.[22] The Commission on Global Surgery recommend data is collected on proposed global surgery indicators.[8] Though internationally comparable data may be of great use, locally designed datasets identifying key contextually important variables may allow for greater ownership and utilisation in low resourced settings.

1.1.6 Workforce

The specialist workforce capable of providing caesarean delivery is distributed with considerable inequity across the world, and in African is particularly low.[23] It is estimated that between 20 and 40 specialist surgeons, anaesthetists and obstetrics providers per 100,000 population are required to produce the necessary surgical volume for more equitable access to surgical care.[8] Below 20 providers per 100,000 is associated with a sharp increase in maternal mortality.[8] In ASOS, the specialist workforce was found to be scarce, at below 1 specialist provider per 100,000 population. This may have been a key driver in the high maternal morality following caesarean delivery observed in ASOS.[20] Data from the World Federation of Societies of Anaesthesiologists (WFSA) Global Anaesthesia Workforce Survey shows the majority of Africa to have less than 1 specialist anaesthesia provider per 100,000 population, corroborating data from ASOS.[24] A study combining data from the WFSA workforce survey and MMR data from the World Bank, found a strong association between increased physician anaesthesia providers and decreasing maternal mortality ratio, when controlling for HDI.[25] In order to reduce the large gap in workforce capable of providing caesarean delivery across Africa, there is a role for task-shifting and task sharing among non-specialist providers. A meta-analysis comparing caesarean delivery outcomes between clinical officers and physician providers found no significant difference between the two groups. However, the findings must be interpreted with caution given the limited number of included studies, high levels of heterogeneity and generally low methodological quality of included texts.[26] There was no difference in maternal mortality between physician and non-physician anaesthesia provider in the ASOS cohort.[20] A systematic review and meta-analysis of anaesthesia related maternal mortality in LMICs found maternal death was lower with physician anaesthesia providers compared to non-physician providers.[27] Studies comparing outcomes between physician and non-physician providers must be interpreted with caution

given the multitude of confounding factors associated with available resources across different clinical environments.[28]

1.1.7 Economics

Surgery has traditionally been viewed as too expensive and too complex to implement in low-resource environments.[8] The Lancet Commission on Global Surgery advocates for investment in surgical services, including caesarean delivery, suggesting that investing in surgery is affordable and economically viable.[8] A systematic review of the cost effectiveness of surgical interventions in low- and middle-income countries found caesarean delivery for obstructed labour to be '*very cost effective*'.[29] The study estimated the cost per disability adjusted life years (DALY) of caesarean delivery for obstructed labour was lower than the cost/DALY for other public health interventions such as antiretroviral therapy for HIV/AIDS.[29] Studies from both Zambia and Democratic Republic of Congo have demonstrated the cost-effectiveness of caesarean delivery in low-resource settings.[30,31]

Though investing in caesarean delivery across Africa may be cost effective up-stream, women undergoing caesarean delivery may be left with catastrophic expenditure and impoverishment.[8] A study in Mali found that caesarean delivery cost families up to one quarter of their annual income, and led to almost half of mothers and their families incurring catastrophic expenditure, and a reduction in food consumption.[32] A study from Madagascar found out-of-pocket costs for caesarean delivery to exceed the annual income of mothers from lower socio-economic groups.[33] Interviews of women in Burkina Faso show caesarean delivery is considered unaffordable and that many fear the cost may lead to *'social calamity'*.[34] In order to reduce the financial burden on mothers and their families, appropriate financial risk protection mechanisms should be implemented.

1.1.8 Aims

Given the unacceptably high mortality and morbidity associated with caesarean delivery across Africa, urgent action is needed. The African Perioperative Research Group identify '*Early identification and management of mothers at risk from peripartum haemorrhage in the peri-operative period'* as a top priority on the perioperative research agenda.[22]

The aims of this thesis are to:

(i) Identify interventions to reduce blood loss during and after caesarean delivery.

(ii) Identify which interventions African researchers and clinicians recommend as the most effective and feasible to implement.

Chapter 2: A Systematic Review and Network Meta-analysis on the Effect of Non-pharmacological Interventions on Blood Loss During and After Caesarean Delivery

2.1 Introduction

2.1.1 Rationale

Caesarean delivery is a life-saving procedure, and is the most common surgical procedure performed worldwide.[9] Caesarean deliveries account for two thirds of surgery performed in Africa.[17] To achieve the Sustainable Development Goal of reducing the global maternal mortality ratio to less than 70 per 100,000 live births by 2030, universal access to timely and safe caesarean delivery is critical.[3] Access to caesarean delivery across Africa remains low compared to the global average.[11] Women in low- and middle-income countries have disproportionately high caesarean delivery related mortality and morbidity.[21] Women in Africa have the highest burden of caesarean delivery related mortality, and are 50-times more likely to die during and after caesarean delivery compared to women in high-income countries according to the African Surgical Outcomes Study. The unacceptably high caesarean delivery related mortality in Africa is likely related to multiple factors within complex health systems.[35] The complication most strongly associated with mortality is haemorrhage.[20,21] There is an urgent need to identify interventions to reduce blood loss during and after caesarean delivery in low-resource settings. There is a strong evidence base regarding the most effective pharmacological agents to manage peripartum haemorrhage. A

recently updated Cochrane Review and network meta-analysis provides evidence regarding the most effective uterotonic agents for preventing postpartum haemorrhage.[36] The WOMAN trial provides high quality evidence regarding the use of tranexamic acid to reduce mortality due to post-partum haemorrhage.[37] There is an urgent need to identify both pharmacological and non-pharmacological interventions which reduce morbidity and mortality from blood loss associated with caesarean delivery. Though previous systematic reviews and meta-analyses have explored specific types and categories of non-pharmacological interventions, to our knowledge there has been no recent study investigating non-pharmacological interventions in their entirety, with regard to their effectiveness in the prevention and treatment of blood loss during and after caesarean delivery.

2.1.2 Objectives

We conducted a systematic review and network meta-analysis to determine which non-pharmacological interventions are most effective at reducing blood loss during and after caesarean delivery.

2.2 Methods

We adhered to the PRISMA reporting guidelines for systematic reviews and network meta-analysis of healthcare interventions.[38]

2.2.1 Protocol and registration

A protocol was prospectively registered with PROSPERO CRD42018116268.

2.2.2 Eligibility criteria

POPULATION:	women undergoing caesarean delivery
INTERVENTION:	any non-pharmacological interventions
COMPARATOR:	as defined by the authors of included studies
OUTCOME:	the primary outcome of interest is blood loss, defined as either (i) continuous outcome - blood loss measured in millilitres (ml), or (ii) dichotomous outcome - post-partum haemorrhage in the context of caesarean delivery - blood loss >1,000 ml
STUDY DESIGN:	any prospective study design

Table 1: PICOS

We included prospective studies of interventions, reporting at least one of the primary outcomes of interest; including randomised, pseudo-randomised and non-randomised study designs. Quality improvement, implementation studies and programme evaluations were also eligible for inclusion if the primary outcome of interest of this review was identified by study investigators *a priori*.

We excluded systematic reviews, meta-analyses, trials investigating the efficacy of pharmacological interventions, studies not reporting at least one of the primary outcomes of interest, and studies in which the populations were selectively restricted and therefore not representative of the general caesarean delivery population, for example: studies recruiting only those with caesarean hysterectomy; placenta accreta spectrum disorder; caesarean myomectomy; or impacted foetal head.

2.2.3 Information sources

We conducted a comprehensive electronic database search of MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Global Index Medicus – World Health Organisation. Databases were searched from inception to 31st December 2019. No language restrictions were applied.

2.2.4 Search

The search strategy was based on three additive concepts (caesarean delivery, haemorrhage, and study designs of interest). The search strategy was developed with assistance from specialist librarians at the University of Oxford and the University of Cape Town. The full search strategy can be found in Appendix 1. An example of the search strategy is found below:

2.2.4.1 Example search strategy

[1] CESAREAN SECTION [MeSH] OR Caesarean section OR Cesarean section* OR Caesarean deliver* OR Cesarean deliver* OR C-section* OR Abdominal deliver**

[2] HEMORRHAGE [MeSH] OR blood loss OR bleeding OR haemorrhag OR hemorrhag

[3] trial OR comparative stud* controlled OR evaluation stud* OR follow up stud* OR longitudinal stud* OR non randomised OR non randomized OR program* evaluation* OR prospective stud* OR randomised OR randomized quantitative stud* OR quasi experimental OR cohort*

2.2.5 Study selection

All retrieved titles and abstracts were exported into Mendeley, and duplicates were removed. The titles and abstracts were screened independently by two reviewers based on pre-defined inclusion and exclusion criteria. Conflicts were resolved by consensus, or by a third reviewer. Eligible full-text articles were screened independently by two reviewers based on pre-defined inclusion and exclusion criteria. Conflicts were resolved by mutual agreement, or by a senior third reviewer where consensus could not be reached. The above study selection was undertaken independently by both the thesis author (ET) and a team of second reviewers (SM, LdT, RD, KS, KvdS, SS, NV, CJEC, AO, DB). To ensure consistency in study selection, the thesis author conducted instructional sessions via ZOOM Video Communications Version: 5.0.5, an online video conferencing platform.

2.2.6 Data collection process

Data extraction and risk of bias assessment were conducted on a piloted Excel form. Data extraction and risk of bias assessment of each study was completed independently by at least two reviewers. Conflicts were resolved by mutual agreement, or by a senior third reviewer where consensus could not be reached. To maintain consistency, reviewers watched a detailed instructional video (created by the thesis author) on use of the data extraction and risk of bias assessment forms. At the time of writing, the data from some articles was extracted only by the thesis author – these articles are marked accordingly in the summary table of included texts.

2.2.7 Data items

The following data items were sought: location; funding sources and reported conflicts of interest; study design; recruitment dates; number of participants; a description of the interventions and comparators assessed; individual study inclusion and exclusion criteria; population baseline characteristics: age, BMI, percentage first time caesarean delivery, percentage general anaesthetic, ASA grade, percentage emergency cases.

The reviews primary outcomes were both: risk of postpartum haemorrhage (blood loss >1,000 ml) and volume of blood loss (ml). Secondary outcomes of interest were: maternal death and maternal near miss. Additional outcomes of interest were: blood transfusion; number of emergency hysterectomies performed; other haemostatic interventions used; unanticipated critical care or higher care admission; maternal adverse events; breastfeeding at discharge; APGAR; cord blood gas; neonatal intensive care admissions; neonatal adverse events. Outcomes were selected based on a Delphi consensus study which determined core outcomes for reporting on the prevention and treatment of postpartum haemorrhage.[39]

2.2.8 Determinants of Network Geometry

During a joint work session, we merged study groups (intervention and comparison groups) into nodes based on their similarity. This process took place after data extraction, but before data-analysis. We aimed to consolidate the intervention and comparison/ 'usual care' groups across studies into the fewest number of network nodes. 'Usual care' was defined as the study group in which the intervention of interest was not implemented – as defined by individual study authors. Study groups were dealt with as separate nodes if there was insufficient evidence that groups in different studies were selected and treated similarly. This was necessary to uphold the transitivity assumption underpinning the planned network meta-

analysis. For this reason, 'usual care' groups were treated as separate nodes when there was insufficient evidence to consider them equivalent. The similarity of interventions and 'usual care' assessed defined the network structure. Where a network contained only one pairwise comparison it was treated and reported as a simple pairwise meta-analysis.

2.2.9 Risk of bias within individual studies

We assessed risk of bias within individual studies using both the Cochrane risk of bias assessment tools for randomised (RoB 2)[40] and non-randomised (ROBINS-I)[41] studies of interventions. The RoB 2 tool assessed 5 domains: bias arising from the randomisation process; bias due to deviations from the intended interventions; missing outcome data; bias in measurement of the outcome; bias in selection of the reported result.[40] In the RoB 2 assessment, a component of domain 2 - the blinding of participants and healthcare providers - was not considered in the overall scoring of studies. This is due to the difficulty in blinding surgical interventions, as this may favour interventions where participant or healthcare providers are more easily blinded. The ROBINS-I tool assessed 7 domains: confounding; selection of participants into the study, classification of interventions; deviations from intended interventions; missing data; measurement of outcomes; and selection of the reported result.[41]

Each study was given an overall risk of bias judgement, which is based on the poorest score in any given domain. Risk of bias assessment was conducted independently by two reviewers. Conflicts were resolved by mutual agreement, or by a third reviewers when consensus was not reached. At the time of writing, the risk of bias of some articles was assessed only by the thesis author – these articles are marked accordingly in the summary table of included texts.

2.2.10 Summary measures

Aggregate participant data was used for network meta-analysis if included studies were sufficiently homogenous to allow for sensible grouping of comparators. We used the pooled relative risk to summarise the relative effectiveness of interventions for reducing the risk of post-partum haemorrhage and the pooled mean difference (ml) to summarise the effect of interventions on estimated blood loss during and after caesarean delivery.

2.2.11 Planned methods of analysis

Network meta-analysis was conducted using the graph-theoretical method described by Rucker.[42] The method is akin to the frequentist approach based on weighted least squares regression. The analysis was conducted in Rstudio[43] utilising the 'netmeta' package.[44] Estimates of effect from singles studies not incorporated into any networks were calculated using MedCalc free online calculator.[45]

2.2.12 Assessment of inconsistency

We aimed to conduct network meta-analyses that combine direct and indirect comparisons of interventions as our primary analysis method. We assessed and report both consistency and heterogeneity in the proposed network meta-analysis. For each analysis we reported pooled estimates for both fixed and random-effects models. We report the random effects models as our primary results and the fixed effect models for comparison (e.g. to assess the magnitude of small study effects). Variance (τ^2) in random effects models is derived with an adaptation of the DerSimonian-Laird estimator.[46] We assess the τ^2, I^2 and Q statistics as measures of statistical inconsistency and heterogeneity. We considered an I^2 <25% - minimal heterogeneity; I^2 25-50% - moderate heterogeneity; I^2 >50% - significant heterogeneity. The Q statistic is partitioned into within-design (heterogeneity) and between-design

(inconsistency) variance components. Where applicable, we evaluated the difference between each direct and indirect estimate to identify pairwise comparisons within a network that produce inconsistent estimates.

2.2.13 Risk of bias across studies

Publication bias was investigated with funnel plots and Egger's tests for meta-analysis groups with ≥10 studies.

2.3 Results

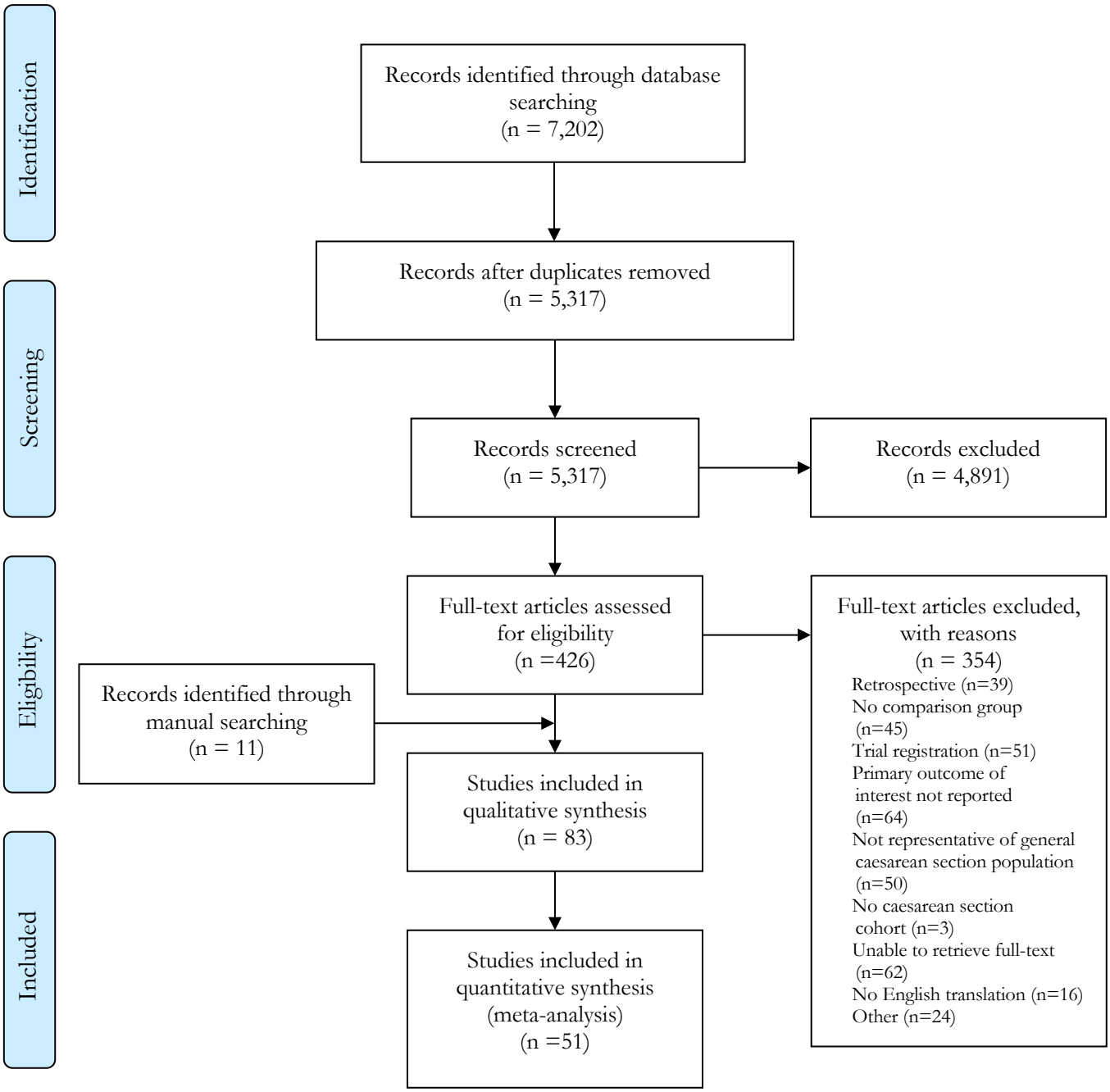
2.3.1 Study selection

The database search yielded 7,202 titles and abstracts. Following the removal of duplicates, 5,317 were screened for eligibility based on pre-defined inclusion and exclusion criteria. The full-texts of 426 articles were screened. Eleven additional texts were identified through searching the references of included texts. In total 83 studies were included in the review. Please refer to Figure 1: PRISMA Flow Diagram.

We assessed 51 studies through meta-analysis, forming 13 separate intervention groups, which include 13,521 women. We were unable to incorporate 32 studies in the network meta-analysis, data extracted from these studies were synthesised narratively.

Refer to appendix 4, for a summary table of included study characteristics.

Figure 1: PRISMA Flow Diagram



2.3.2 Network Meta-Analysis of the Effectiveness of Interventions to Prevent Blood Loss.

The 13 intervention types evaluated in meta-analysis were: figure of 8 suture with or without cervical inversion for bleeding placental bed; caesarean delivery surgical techniques; blunt and sharp expansion of the uterine incision; normal saline irrigation of the abdominal cavity; staple uterine incision; anaesthesia technique; uterine closure material; cervical dilatation; early and delayed umbilical cord clamping; fluid and mattress warming; abdominal binder; and extra-abdominal and intra-abdominal uterine repair.

2.3.2.1 Figure of 8 suture with or without cervical inversion

Two studies[47,48] reported the effectiveness of figure of eight sutures with or without cervical inversion for the management of intraoperative bleeding from the placental bed. Both studies were randomised controlled trials and reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing figure of eight sutures with or without cervical inversion versus usual care. Figure 2 reports the network structure. The network reports two direct comparisons including 350 randomised participants. There was insufficient data to assess network heterogeneity and consistency. Compared to usual care, cervical inversion with figure of eight suture resulted in a reduction of estimated blood loss of 616.33 ml (95% CI for the random effects model -717.44; -515.22;); figure of eight sutures alone resulted in a reduction of 136.36 ml (95% CI for the random effects model-235.98; -36.74). Refer to the overall meta-analysis forest plot (figure 38). The fixed effects model yielded the same estimates (appendix 2: group 1). The risk of bias of studies within this network is reported in figure 3.

One study[48] (also included in the estimated blood loss network meta-analysis), reported the effect of the figure of eight suture compared to usual care on the risk of postpartum

haemorrhage (PPH; > 1000 ml): four of 55 women in the figure 8 suture group, and seven of 55 women in the usual care group experienced PPH; Relative Risk (RR; 95% CI) 0.57 (0.18 to 1.84). This study was judged to have high overall risk of on RoB 2 assessment.

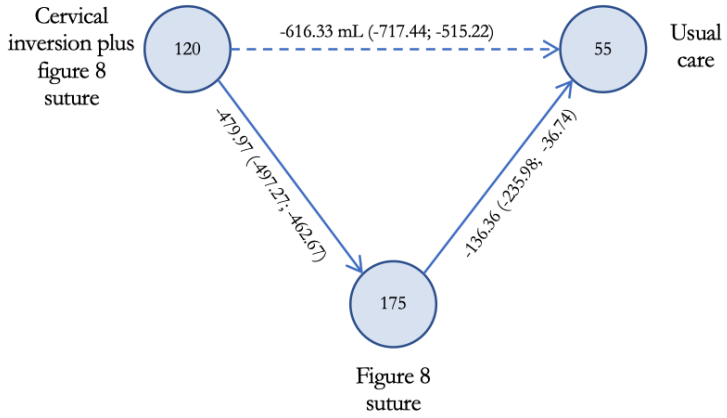


Figure 2: Network graph – Figure of 8 suture with or without cervical inversion for management of the bleeding placental bed.

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

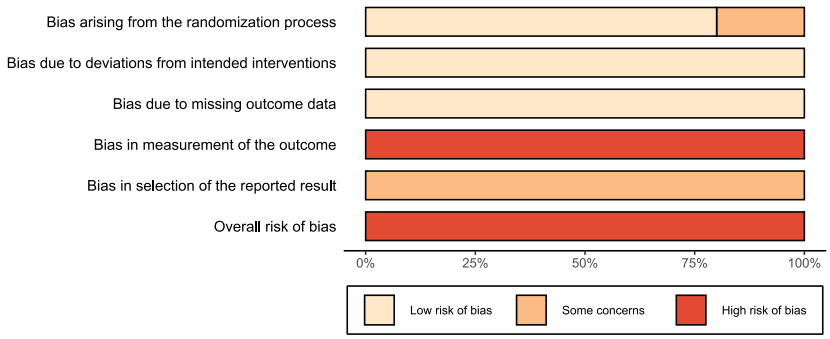


Figure 3: Weighted RoB 2 assessment for the estimated blood loss network meta-analysis- Figure of 8 suture with or without cervical inversion for management of the bleeding placental bed – 2 randomised studies assessed.

2.3.2.2 Caesarean delivery surgical technique

Seven studies[49,50,51,52,53,54,55] reported the effectiveness of various caesarean delivery surgical techniques on estimated blood loss (ml). All were randomised controlled trials, and all studies reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing lower-midline incision, Joel Cohen, Misgav-Ladach, Modified Joel Cohen, Modified Misgav-Ladach, and Pfannenstiel technique. Figure 4 reports the network structure. The network reports six direct comparisons including 1,362 randomised participants. The network has significant heterogeneity I^2=73.9% (95% CI 27.0%; 90.7%). The heterogeneity is explained by differences between designs (inconsistency). Compared to Pfannenstiel, Joel Cohen resulted in a reduction in estimated blood loss of 22.60 ml (95% CI for the random effects mode --134.30;89.10). Compared to Pfannenstiel, Misgav-Ladach resulted in a reduction in estimated blood loss of 134.33 ml (95% CI for the random effects model -199.52; -69.14). Compared to Pfannenstiel, Modified Joel Cohen technique resulted in a reduction in estimated blood loss of 155.00 ml (95% CI for the random effects model -314.05; 4.05). Compared to Pfannenstiel, Modified Misgav-Ladach resulted in a reduction in estimated blood loss of 137.40 ml (95% CI for the random effects model -207.37; -67.44). Compared to Pfannenstiel, Modified Misgav-Ladach resulted in a reduction in estimated blood loss of 137.40 ml (95% CI for the random effects model -207.37; -67.44). Compared to Pfannenstiel, lower midline incision resulted in a reduction in estimated blood loss of 41.33 ml (95% CI for the random effects model -162.57; 79.91). Refer to the overall meta-analysis forest plot (figure 38). The pooled estimate for the random effects model varied by up to 16 ml compared to pooled estimated for the fixed effects model (appendix 2: group 2). The risk of bias of studies within this network is reported in figure 5.

None of the included studies reported on the risk of postpartum haemorrhage.

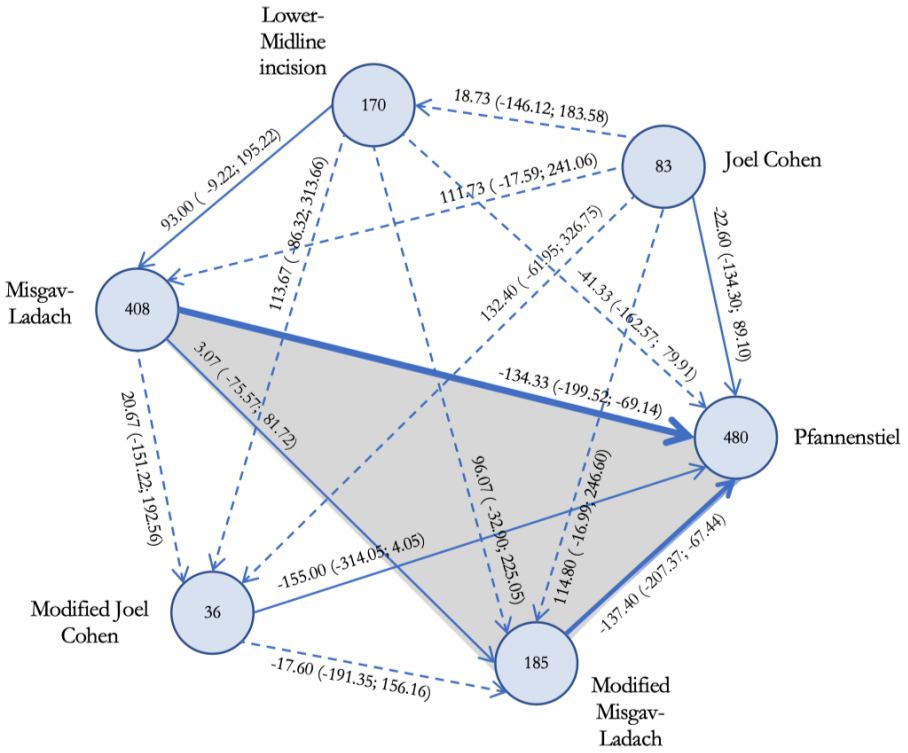


Figure 4: Network graph - Caesarean delivery surgical technique

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

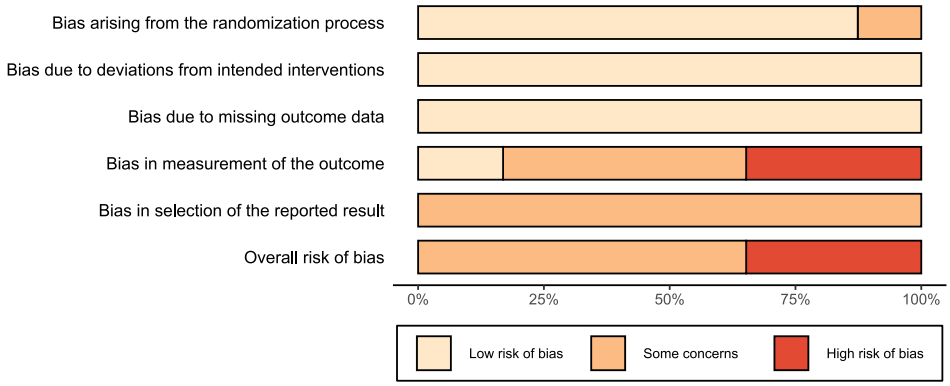


Figure 5: Weighted RoB 2 assessment for the estimated blood loss network meta-analysis - Caesarean delivery surgical technique – 7 randomised studies assessed.

2.3.2.3 Blunt versus sharp expansion of the uterine incision

Four studies[56,57,58,59] reported the effectiveness of blunt versus sharp expansion of the uterine incision for the prevention of blood loss. Three[56,57,58] were randomised controlled trials and one was a non-randomised controlled trial.[59] All four studies reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a simple pairwise meta-analysis comparing blunt expansion of the uterine incision versus sharp expansion of the uterine incision. Figure 6 reports the components of the pairwise comparison. The pairwise meta-analysis includes 2,321 participants. The network has significant heterogeneity I^2=98.8% (95% CI 98.1%: 99.2%). Compared to sharp expansion of the uterine incision, blunt expansion of the uterine incision resulted in a reduction in estimated blood loss of 69.53 ml (95% CI for the random effects model -167.60; 28.54. Refer to the overall meta-analysis forest plot (figure 38). The pooled estimate for the random effects model varied by 109 ml compared to pooled estimated for the fixed effects model (appendix 2: group 3). The risk of bias of studies in the pairwise meta-analysis is reported in figures 7 and 8.

One study[56] (also included in the estimated blood loss meta-analysis) reported the effect of blunt versus sharp expansion of the uterine incision on the risk of postpartum haemorrhage (PPH; > 1000 ml): 37 of 541 women in the blunt uterine expansion group, and 61 of 535 women in the sharp group experienced PPH; Relative Risk (RR; 95% CI) 0.59 (0.41 to 0.89). The study had 'low' overall risk of bias on RoB 2 assessment.

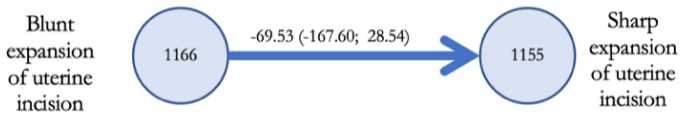


Figure 6: Pairwise comparison - Blunt versus sharp expansion of the uterine incision

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside

arrows indicate the meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

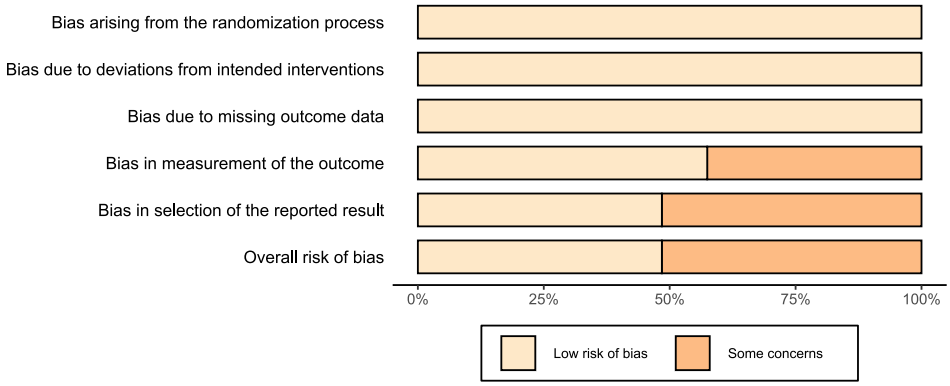


Figure 7: Weighted RoB 2 assessment for the estimated blood loss meta-analysis - Blunt versus sharp expansion of the uterine incision – 3 randomised studies assessed

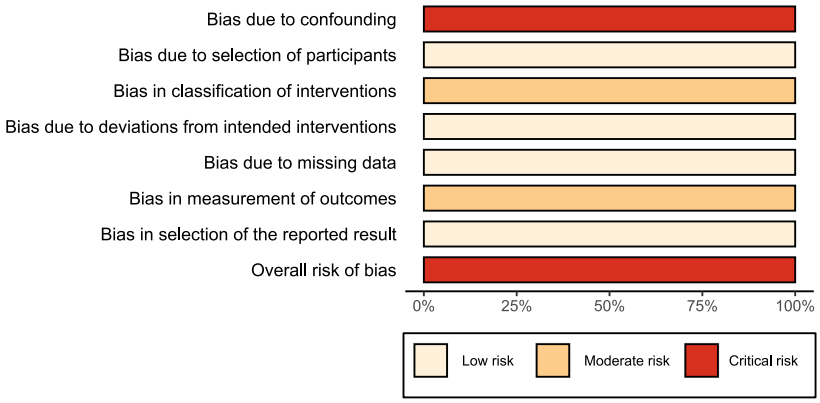


Figure 8: Weighted ROBINS-I assessment for the estimated blood loss meta-analysis - Blunt versus sharp expansion of the uterine incision – 1 non-randomised study assessed

2.3.2.4 Normal saline irrigation of the abdominal cavity

Two studies[60,61] reported the effectiveness of normal saline irrigation of the abdominal cavity for the prevention of blood loss. Both were randomised controlled trials, and both reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a simple pairwise meta-analysis comparing normal saline irrigation of the abdominal cavity versus usual care. Figure 9 reports the components of the pairwise meta-analysis. The meta-analysis reports two direct comparisons including 432 randomised participants. There was insufficient data to assess network heterogeneity. Compared to usual care, normal saline irrigation of the abdominal cavity resulted in a reduction in estimated blood loss of 17.92 ml (95% CI for the random effects model -59.35; 23.52). Refer to the overall meta-analysis forest plot (figure 38). The fixed effects model yielded the same estimates (appendix 2: group 4). The risk of bias of studies within this network is reported in figure 10.

One study [60] (also included in the estimated blood loss meta-analysis) reported the effect of normal saline irrigation of the abdominal cavity compared to usual care on the risk of postpartum haemorrhage (PPH; > 1000 ml): one of 97 women in the normal saline irrigation of the abdominal cavity group, and two of 99 women in the usual care group experienced PPH; Relative Risk (RR; 95% CI) 0.51 (0.05 to 5.54). The study had 'some concerns' on overall risk of bias on RoB 2 assessment.

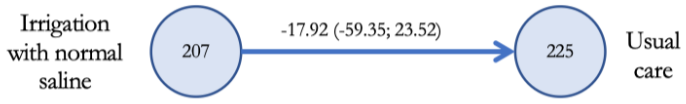


Figure 9: Pairwise Comparison – Normal saline irrigation of the abdominal cavity

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

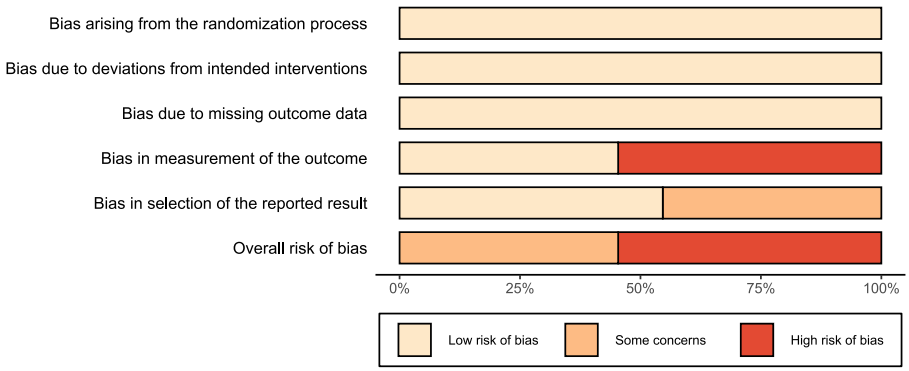


Figure 10: Weighted RoB 2 assessment for the estimated blood loss meta-analysis- Normal saline irrigation of the abdominal cavity – 2 randomised studies assessed

2.3.2.5 Staple uterine incision

Two studies[62,63] reported the effectiveness of a staple uterine incision for the prevention of blood loss. One study was a non-randomised trial,[62] and one was a randomised controlled trial.[63] Both studies reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a simple pairwise meta-analysis comparing staple uterine incision versus usual care. Figure 11 reports the components of the pairwise meta-analysis. The meta-analysis reports two direct comparisons including 488 randomised participants. There was insufficient data to assess meta-analysis heterogeneity. Compared to usual care, stable uterine incision resulted in a reduction in estimated blood loss of 86.60 ml (95% CI for the random effects model -77.89; -95.32). Refer to the overall meta-analysis forest plot (figure 38). The fixed effects model yielded the same estimates (appendix 2: group 5). The risk of bias of studies within this meta-analysis is reported in figure 12 and 13.

None of the included studies reported on the risk of postpartum haemorrhage.

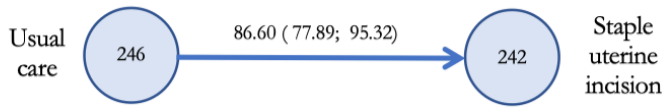


Figure 11: Pairwise Comparison - Staple uterine incision

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

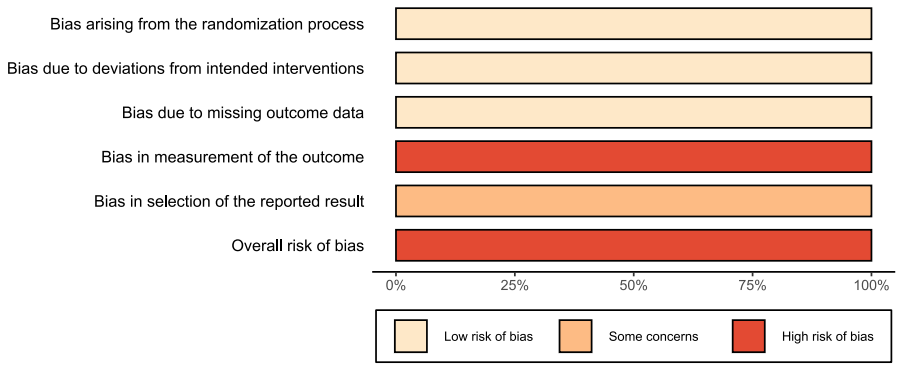


Figure 12: Weighted RoB 2 assessment for the estimated blood loss meta-analysis- Staple uterine incision – one randomised study assessed

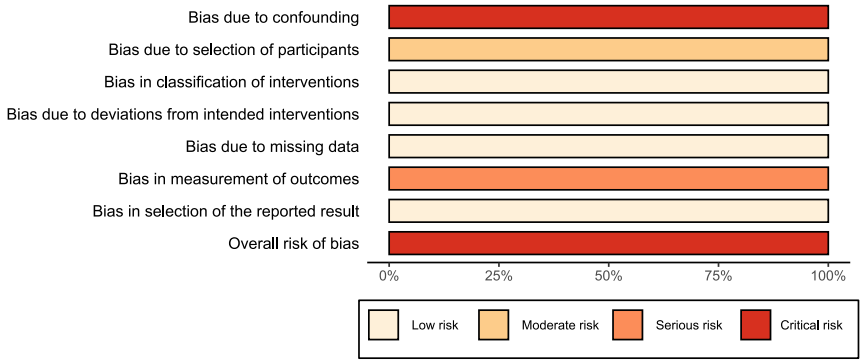


Figure 13: Weighted ROBINS-I assessment for the estimated blood loss meta-analysis- Staple uterine incision – one non-randomised study assessed

2.3.2.6 Anaesthesia technique

Three studies[64,65,66] reported the effect of anaesthesia techniques on estimated blood loss (ml). Two were randomised controlled trials,[65,66] and one was a non-randomised controlled trial.[64] All three studies reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing epidural anaesthesia, spinal anaesthesia and general anaesthesia techniques. Figure 14 reports the network structure. The network reports two direct comparisons including 183 participants. There was insufficient data to assess network heterogeneity and consistency. Compared to spinal anaesthesia, epidural anaesthesia resulted in a reduction in estimated blood loss of 42.09 ml (95% CI for the random effects model -747.75; 663.58). Compared to spinal anaesthesia, general anaesthesia resulted in an increase in estimated blood loss of 162.91 ml (95% CI for the random effects model 50.87; 274.94). Refer to the overall meta-analysis forest plot (figure 38). The fixed effects model yielded the same estimates (appendix 2: group 6). The risk of bias of studies within this network is reported in figures 15 and 16.

None of the included studies reported on the risk of postpartum haemorrhage.

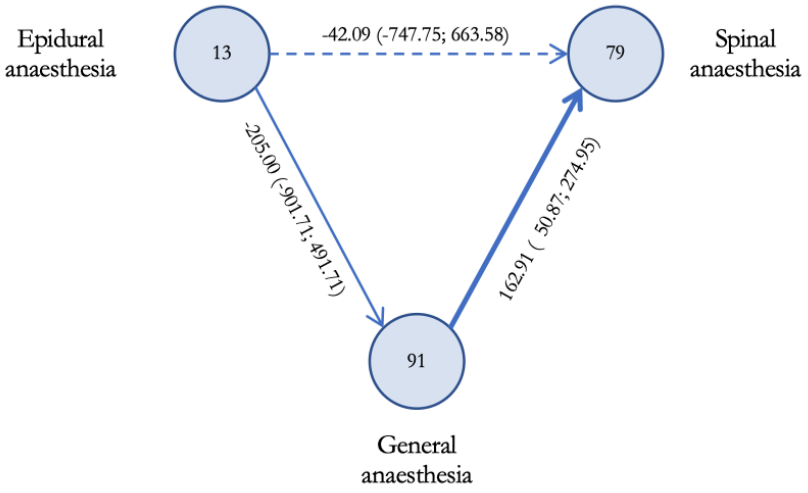


Figure 14: Network 6 – Anaesthesia technique

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

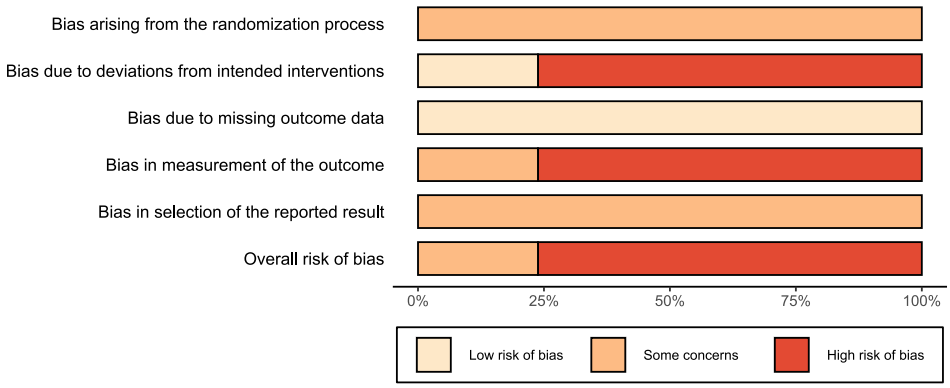


Figure 15:Weighted RoB 2 assessment for the estimated blood loss network meta-analysis- Anaesthesia technique – 2 randomised studies assessed

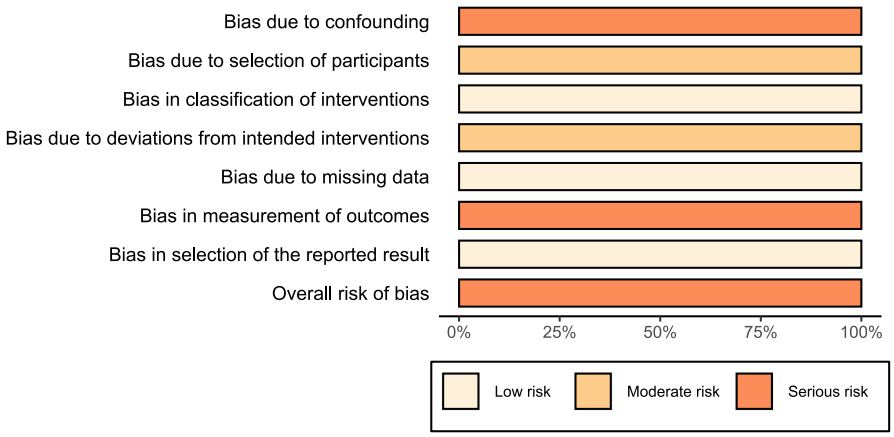


Figure 16: Weighted ROBINS-I assessment for the estimated blood loss network meta-analysis- Anaesthesia technique – 1 non-randomised study assessed

2.3.2.7 Material for uterine closure

Three studies[67,68,69] reported the effectiveness of various materials for uterine incision closure on estimated blood loss (ml). All were randomised controlled trials. These three studies all reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing absorbable staples, polyglactin suture, and knotless barbed suture. Figure 17 reports the network structure. The network reports two direct comparisons including 261 randomised participants. The network has significant heterogeneity I^2=79.4% (95% CI 11.0%; 95.2%). The heterogeneity is explained by differences within designs, and there was no inconsistency within the network. Compared to polyglactin suture, knotless barbed suture resulted in a reduction in estimated blood loss of 40.57 ml (95% CI for the random effects model -168.40; 87.25). Compared to polyglactin suture, absorbable staples resulted in a reduction in estimated blood loss of 174.00 ml (95% CI for the random effects model (-382.81; 34.81). Refer to the overall meta-analysis forest plot (figure 38). The pooled estimate for the random effects model varied by 23 ml compared to pooled estimated for the fixed effects model yielded (appendix 2: group 7). The risk of bias of studies within this network is reported in figure 18.

None of the included studies reported on the risk of postpartum haemorrhage.

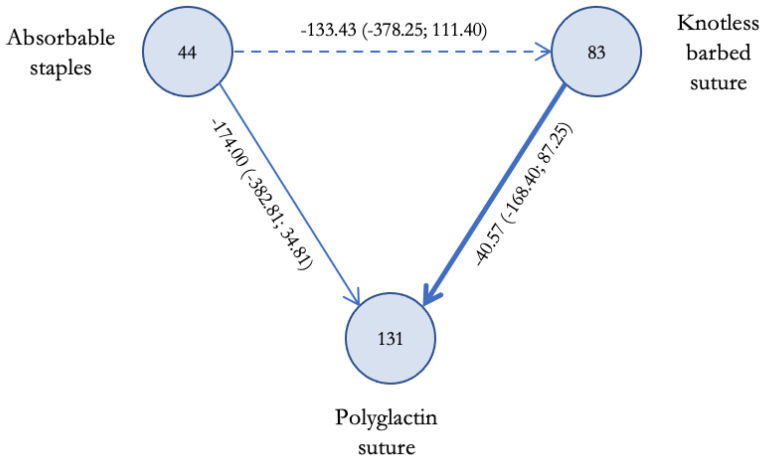


Figure 17: Network Graph – Material for uterine closure

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

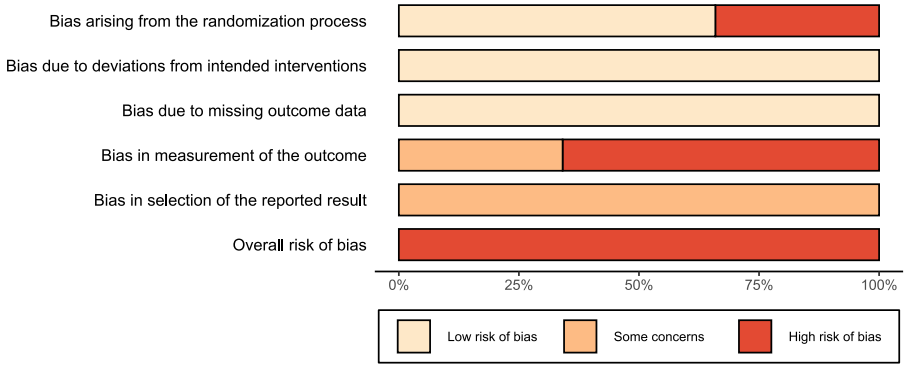


Figure 18: Weighted RoB 2 assessment for the estimated blood loss network meta-analysis -Material for uterine closure – 3 randomised studies assessed

2.3.2.8 Cervical dilatation

Five studies reported the effectiveness of cervical dilatation for the prevention of blood loss.[70,71,72,73,74] Four were randomised controlled trials,[70,71,72,73] and one was a case-control study.[74] Four of these studies[70,71,72,74] reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a simple pairwise meta-analysis comparing cervical dilatation versus usual care. Figure 19 reports components of the meta-analysis. The meta-analysis reports one direct comparison including 2,503 participants. There was moderate heterogeneity, I^2= 27.3% (95% CI 0.0%; 72.7%). Compared to usual care, cervical dilatation resulted in a reduction in estimated blood loss of 43.90 ml (95% CI for the random effects model -64.45; -23.34). Refer to the overall meta-analysis forest plot (figure 38). The pooled estimate for the random effects model varied by up to 2 ml compared to pooled estimates for the fixed effects model yielded (appendix 2: group 8). The risk of bias of studies within this meta-analysis is reported in figure 20 and 21.

Two studies,[73, 71] (of which one[73] was not included in the estimated blood loss meta-analysis) reported the effect of cervical dilatation compared to usual care on the risk of postpartum haemorrhage (PPH; > 1000 ml). These were synthesised as a simple pairwise meta-analysis. Figure 22 reports the meta-analysis components. Compared to usual care, the relative risk of PPH in the cervical dilatation group was (RR;95%CI) 0.92 (0.21;3.94). There was significant heterogeneity, I^2= 54.8% (95% CI 0%; 89%). Of the two studies included in the PPH meta-analysis, one study had 'some concerns', and one had 'high' overall risk of bias on the RoB 2 tool.

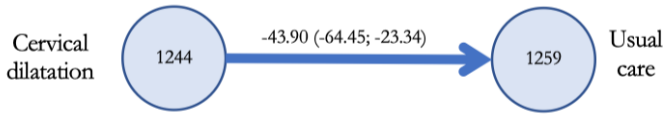


Figure 19: Pairwise Comparison – Cervical dilatation – estimated blood loss

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

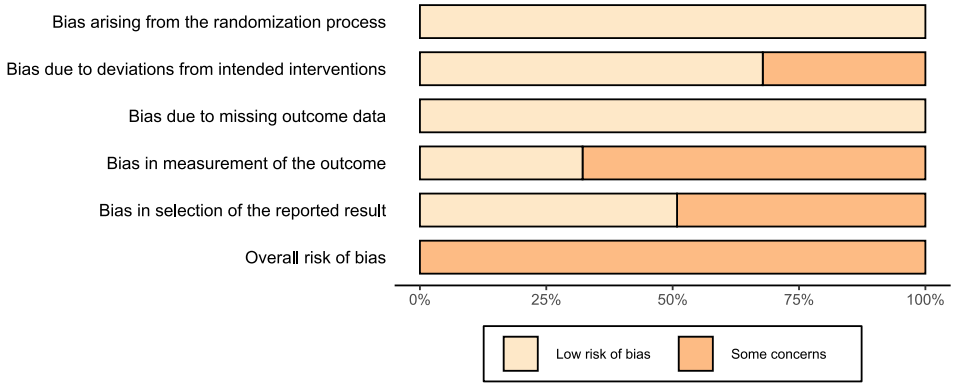


Figure 20: Weighted RoB 2 assessment for the estimated blood loss meta-analysis - Cervical dilatation – 3 randomised studies assessed

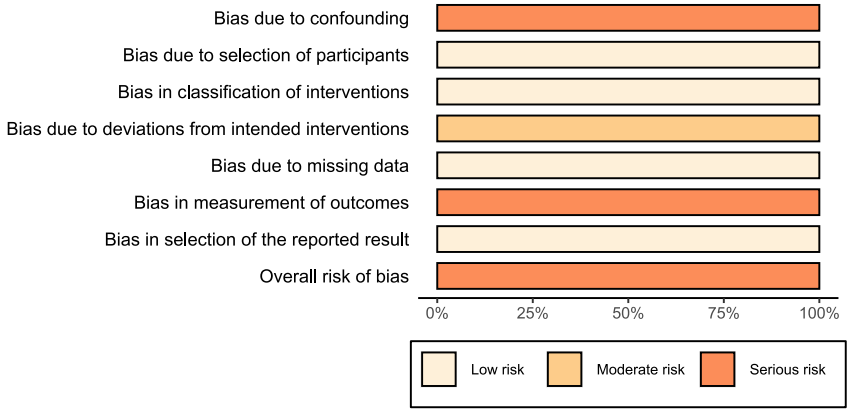


Figure 21: Weighted ROBINS-I assessment for the estimated blood loss meta-analysis - Cervical dilatation – 1 non-randomised study assessed

Figure 22: Pairwise Comparison – Cervical dilatation - PPH

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the relative risk of PPH; value greater than 1.0 favours the group at the arrowhead, while a value less than 1.0 favours the group at the arrow tail.

2.3.2.9 Early versus delayed umbilical cord clamping

Four studies[75,76,77,78] reported the effectiveness of early versus delayed umbilical cord clamping on estimated blood loss (ml). All were randomised controlled trials. Three of these studies[75,76,78] reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing early cord clamping <60 seconds, delayed cord clamping >60 seconds and delayed cord clamping >120 seconds. Figure 23 reports the network structure. The network reports three direct comparisons including 687 randomised participants. The network has significant heterogeneity I^2=82.8% (95% CI 47.6%; 94.4%). The heterogeneity is explained by differences between designs (inconsistency). Compared to early cord clamping <60 seconds, delayed cord clamping >60 seconds resulted in a reduction in estimated blood loss of 31.19 ml (95% CI for the random effects model -111.69; 49.31). Compared to early cord clamping <60 seconds, delayed cord clamping >120 seconds resulted in a reduction in estimated blood loss of 29.47 ml (95% CI for the random effects model -147.89; 88.95). The pooled estimate for the random effects model varied by up to 4 ml compared to pooled estimated for the fixed effects model (appendix 2: group 9). The risk of bias of studies within this network is reported in figure 24.

One study,[77] (not included in the estimated blood loss meta-analysis), reported on the effect of early cord clamping <15 seconds compared to delayed cord clamping at 60 seconds on the risk of postpartum haemorrhage (PPH; > 1000 ml): five of 57 women in the delayed cord clamping group, and four of 56 women in the early cord clamping group experienced PPH; Relative Risk (RR; 95% CI) 1.23 (0.35 to 4.34). The study had 'low' overall risk of bias judgement on RoB 2 assessment.

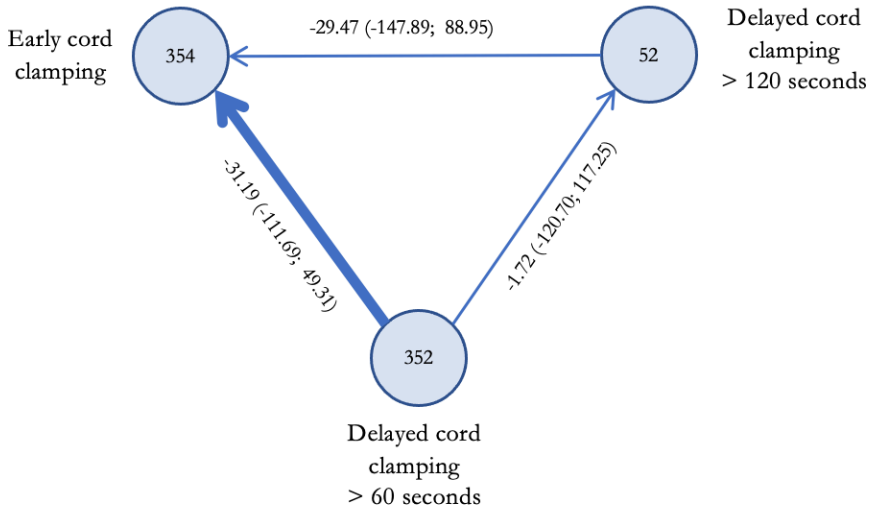


Figure 23: Network Graph – Early versus delayed umbilical cord clamping

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

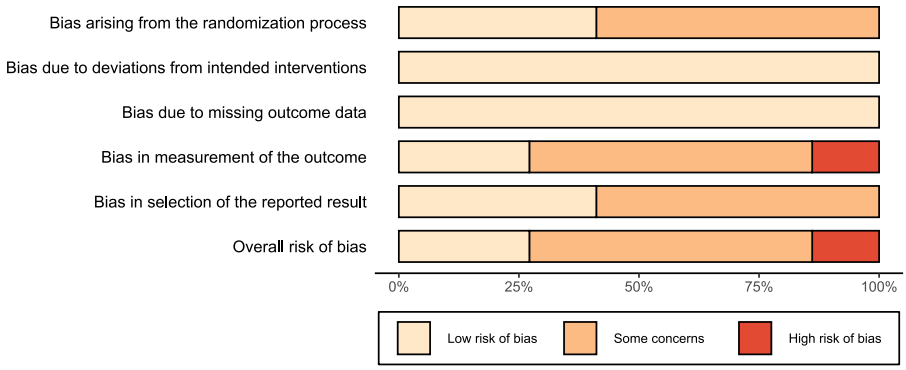


Figure 24:Weighted RoB 2 assessment for the estimated blood loss network meta-analysis - Early versus delayed umbilical cord clamping – 3 randomised studies assessed

2.3.2.10 Fluid and mattress warming

Three studies[79,80,81] reported the effectiveness of fluid and/or mattress warming on estimated blood loss (ml). All were randomised controlled trials, and all studies reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing conductive air mattress and fluid warming, forced air warming and fluid warming, hot cabinet fluid warming, in-line fluid warming, resistive warming mattress, and usual care. Figure 25 reports the network structure. The network reports seven direct comparisons including 323 randomised participants. There was insufficient data to assess network heterogeneity and consistency. Compared to usual care, resistive warming mattress resulted in a reduction in estimated blood loss of 567.00 ml (95% CI for the random effects model (-1446.31; 312.31). Compared to usual care, In-line fluid warmer resulted in an increase in estimated blood loss of 187.50 ml (95% CI for the random effects model 23.22; 351.78). Compared to usual care, hot cabinet fluid warmer resulted in an increase in estimated blood loss of 87.50 ml (95% CI for the random effects model -37.31; 212.31). Compared to usual care, forced air warming with fluid warming resulted in a reduction in estimated blood loss of 30.00 ml (95% CI for the random effects model -111.51; 51.51). Compared to usual care, Conductive air mattress with fluid warming resulted in a reduction in estimated blood loss of -10.00 ml (95% CI for the random effects model -102.31; 82.31). The fixed effects model yielded the same estimates as the random effects model (appendix 2: group 10). The risk of bias of studies within this network is reported in figure 26.

None of the included studies reported on the risk of postpartum haemorrhage.

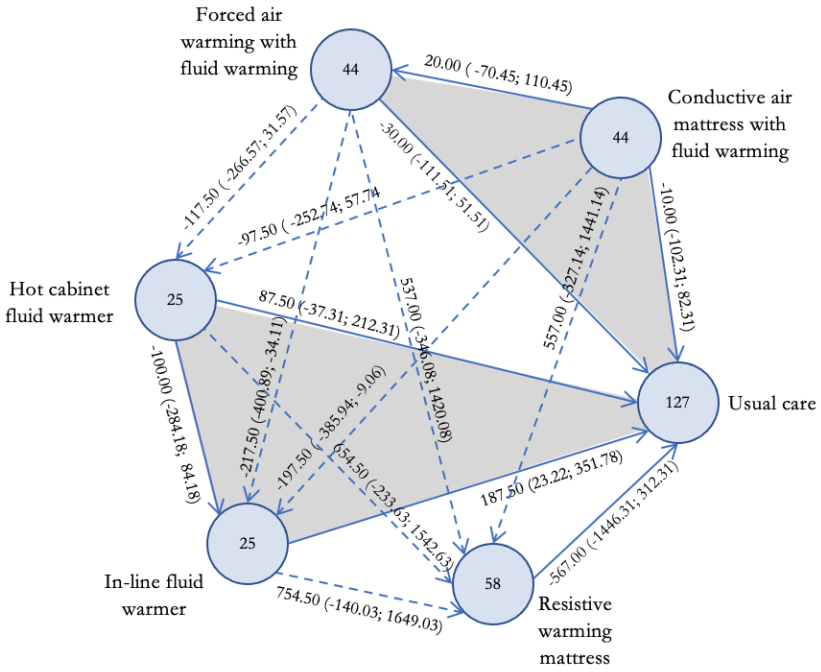


Figure 25: Network Graph – Fluid and mattress warming

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

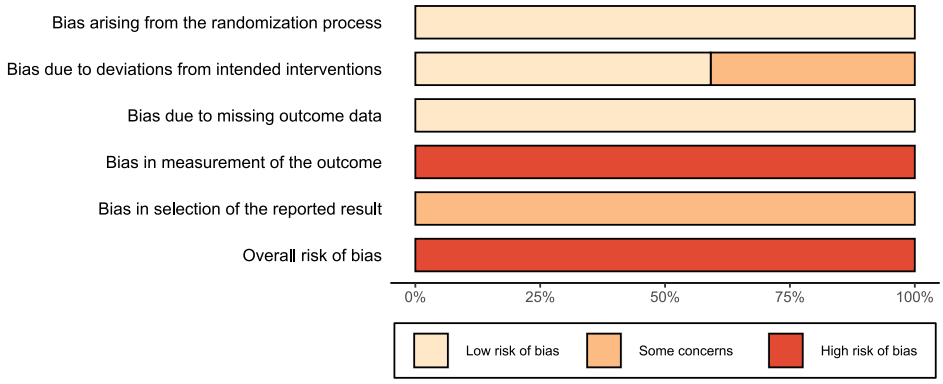


Figure 26:Weighted RoB 2 assessment for the estimated blood loss network meta-analysis- Fluid and mattress warming – three randomised studies assessed

2.3.2.11 Abdominal binder

Two studies[82,83] reported the effectiveness of an abdominal binder for the prevention of blood loss. Both were randomised controlled trials, and both reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a simple pairwise meta-analysis comparing abdominal binder versus usual care. Figure 27 reports the meta-analysis components. The meta-analysis reports two direct comparisons including 234 randomised participants. The meta-analysis has significant heterogeneity I^2 =97.9% (95% CI 95.0%; 99.1%). Compared to usual care, the abdominal binder resulted in a reduction in estimated blood loss of 221.00 ml (95% CI for the random effects model -627.05; 185.06). Refer to the overall meta-analysis forest plot (figure 38). The pooled estimate for the random effects model varied by up to 22 ml compared to pooled estimated for the fixed effects model (appendix 2: group 11). The risk of bias of studies within this network is reported in figure 28.

None of the included studies reported on the risk of postpartum haemorrhage.

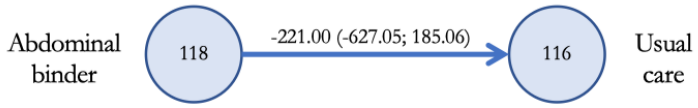


Figure 27: Pairwise Comparison - Abdominal binder

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

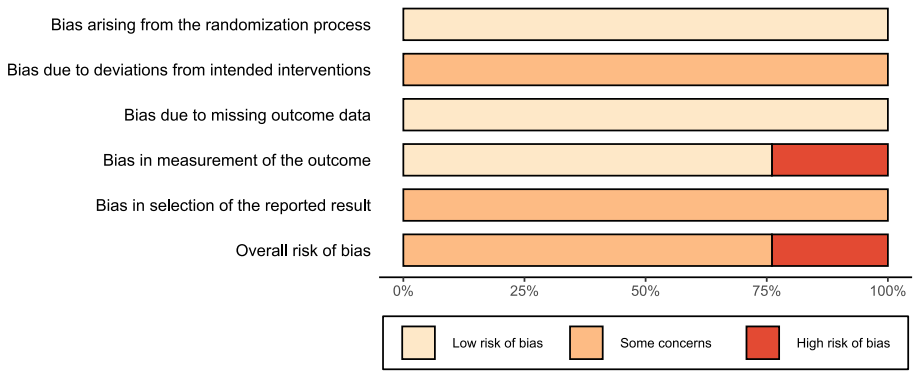


Figure 28: Weighted RoB 2 assessment for the estimated blood loss meta-analysis- Abdominal binder – 2 randomised studies assessed

2.3.2.12 Extra-abdominal versus intra-abdominal uterine repair

Nine studies[84,85,86,87,88,89,90,91,92] reported the effectiveness of extra-abdominal versus intra-abdominal uterine repair for the prevention of blood loss. All were randomised controlled trials. Seven[86,87,88,89,90,91,92] of these studies reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a simple pairwise meta-analysis comparing extra-abdominal uterine incision versus intra-abdominal uterine incision. Figure 29 reports the meta-analysis components. The meta-analysis reports one direct comparisons including 1,932 randomised participants. There is significant heterogeneity I^2 =94.7% (95% CI 91.9%; 96.5%). Compared to intra-abdominal repair, extra-abdominal repair resulted in a reduction in estimated blood loss of 34.53 ml (95% CI for the random effects model -92.01; 22.96). Refer to the overall meta-analysis forest plot (figure 38). The pooled estimate for the random effects model varied by up to 31 ml compared to pooled estimated for the fixed effects model (appendix 2: group 12). The risk of bias of studies within this meta-analysis is reported in figure 30.

Two studies[84,85] (not included in the estimated blood loss meta-analysis) reported on the effect of extra-abdominal versus intra-abdominal uterine repair on the risk of postpartum haemorrhage (PPH; > 1000 ml). These were synthesised as a simple pairwise meta-analysis. Figure 31 reports the meta-analysis components. Compared to intra-abdominal repair, the relative risk of PPH in the extra-abdominal uterine repair group was (RR;95%CI) 0.99 (0.91;1.07). There is insufficient data to assess meta-analysis heterogeneity. Both studies included in the PPH meta-analysis, had 'some concerns' on overall risk of bias judgement for the RoB 2 tool.

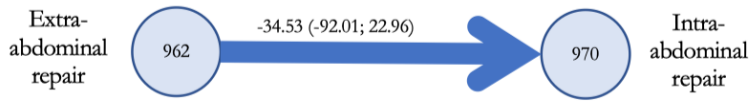


Figure 29: Pairwise Comparison – Extra-abdominal versus intra-abdominal uterine repair – estimated blood loss

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

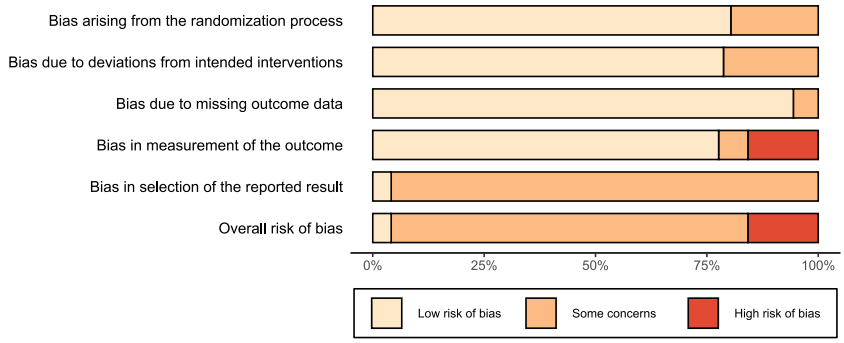


Figure 30: Weighted RoB 2 assessment for the estimated blood loss meta-analysis - Extra-abdominal versus intra-abdominal uterine repair – 7 randomised studies assessed

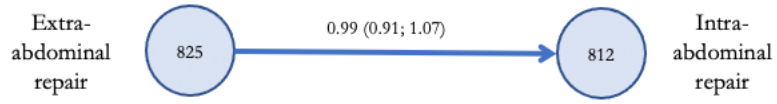


Figure 31: *Figure 32: Pairwise Comparison – Extra-abdominal versus intra-abdominal uterine repair - PPH*

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the relative risk of PPH; value greater than 1.0 favours the group at the arrowhead, while a value less than 1.0 favours the group at the arrow tail.

2.3.2.13 Placenta removal technique

Nine studies [93,94,95,96,97,98, 99,91,92] reported the effectiveness of placenta removal technique on estimated blood loss (ml). All were randomised controlled trials. Eight studies[93,94,95,96,97,98,91,92] reported the relative effectiveness of the intervention as a mean difference in estimated blood loss (ml). These were synthesised as a network comparing cord traction with massage, spontaneous separation with and without gentle traction, and manual removal. Figure 33 reports the network structure. The network reports two direct comparisons including 2,445 randomised participants. The network has significant heterogeneity I^2=92% (95% CI 87.1%; 95.1%). The heterogeneity is explained by differences within designs and there was no inconsistency within the network. Compared to spontaneous separation with and without gentle traction, cord traction and external massage resulted in an increase in estimated blood loss of 275.03 ml (95% CI for the random effects model -2.61; 550.68). Compared to spontaneous separation with and without gentle traction, manual removal resulted in an increase in estimated blood loss of 174.03 ml (95% CI for the random effects model 81.11; 266.96). The pooled estimate for the random effects model varied by up to 91 ml compared to pooled estimated for the fixed effects model (appendix 2: group 13). The risk of bias of studies within this network is reported in figure 34.

Four studies[93, 99, 94,95] (of which one[99] was not included in the estimated blood loss meta-analysis) reported on the effect of cord traction with massage, spontaneous separation with and without gentle traction, and manual removal on the risk of postpartum haemorrhage (PPH; > 1000 ml). These were synthesised into a network meta-analysis. Figure 35 reports the network structure. Compared to spontaneous placental separation with and without gentle traction, the relative risk of PPH in manual removal of the placenta group was (RR;95%CI) 1.33 (0.76;2.32). Compared to spontaneous placental separation with and without gentle traction, the relative risk of PPH in cord traction and external massage

group was (RR;95%CI) 2.74 (0.21; 35.44). The network has significant heterogeneity I^2=55.3% (95% CI 0%; 87.2%). The heterogeneity is explained by differences within designs and there was no statistical evidence of inconsistency within the network. Two studies included in the PPH meta-analysis, had 'some concerns', while two had 'high' overall risk of bias on RoB 2 assessment.

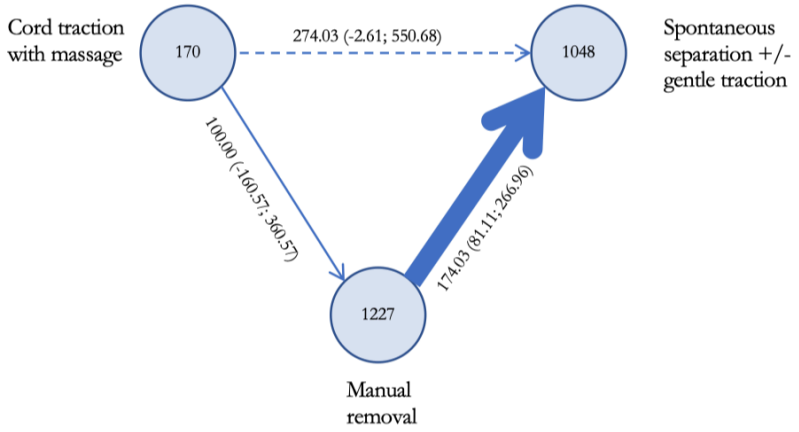


Figure 33: Network Graph - Placenta removal technique – estimated blood loss

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the network. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the network meta-analysis estimate for the mean difference in estimated blood loss (ml); a positive value favours the group at the arrowhead, while a negative value favours the group at the arrow tail.

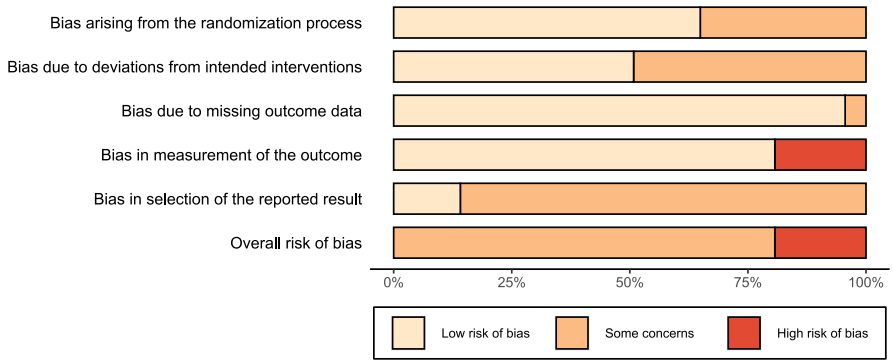


Figure 34: Weighted RoB 2 assessment for the estimated blood loss network meta-analysis - Placenta removal technique – 8 randomised studies assessed

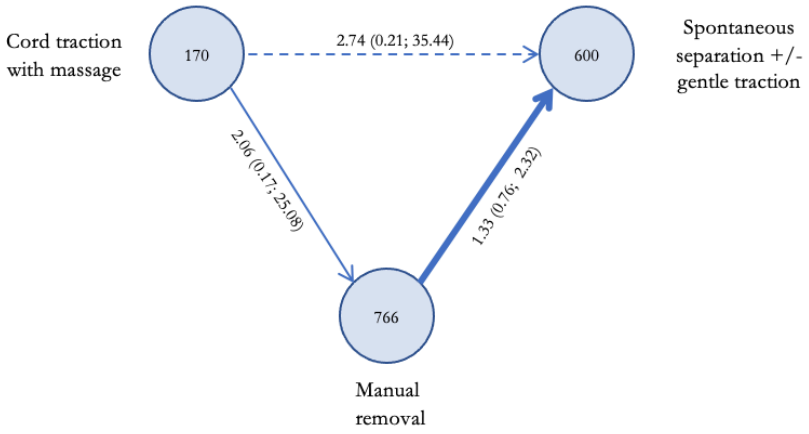


Figure 35: Network Graph - Placenta removal technique – PPH

Each node represents an intervention. The number printed inside each node is the number of participants randomised to that intervention within the meta-analysis. Solid line arrows represent network estimates that include direct comparisons, while dashed line arrows represent estimates comprised of indirect comparisons only. The thickness of solid arrows is proportional to the number of trials investigating each direct comparison. Values alongside arrows indicate the meta-analysis estimate for the relative risk of PPH; value greater than 1.0 favours the group at the arrowhead, while a value less than 1.0 favours the group at the arrow tail.

2.3.3 Publication bias

Only the network meta-analysis comparing the effectiveness of different placenta removal techniques on estimated blood loss (ml) had a sufficient number of included studies to generate a funnel plot (figure 40) assessing publication bias. The funnel plot indicates publication bias towards studies with a positive mean difference, however, the plot contains limited information, the Egger's test is not statistically significant and the estimates are widely distributed.

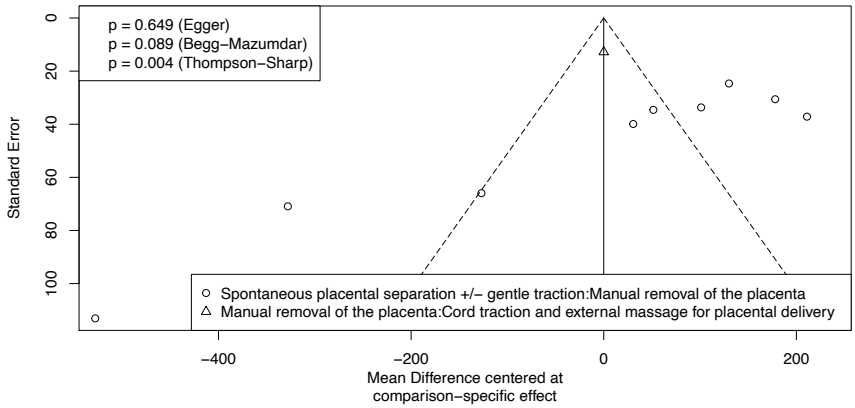


Figure 36: Funnel plot assessment of publication bias - placenta removal techniques

2.3.3.1 Overall meta-analysis risk of bias

Figure 36 reports the overall weighed risk of bias judgement for all randomised controlled trials included in the estimated blood loss meta-analyses. Figure 37 reports the overall weighted risk of bias judgement for all non-randomised studies included in the estimated blood loss meta-analyses.

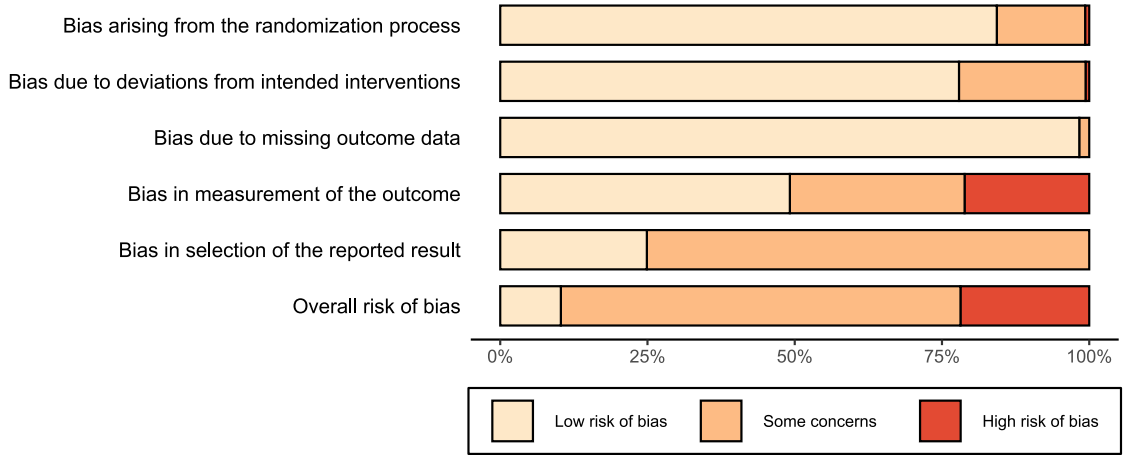


Figure 37: Overall weighted RoB 2 assessment for all estimated blood loss network meta-analyses

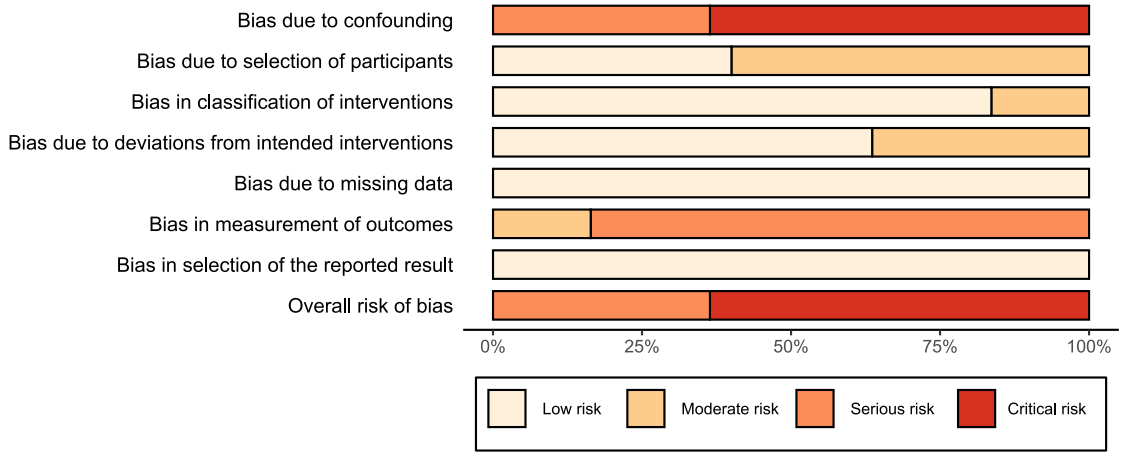


Figure 38: Overall weighted ROBINS-I assessment for all estimated blood loss network meta-analyses

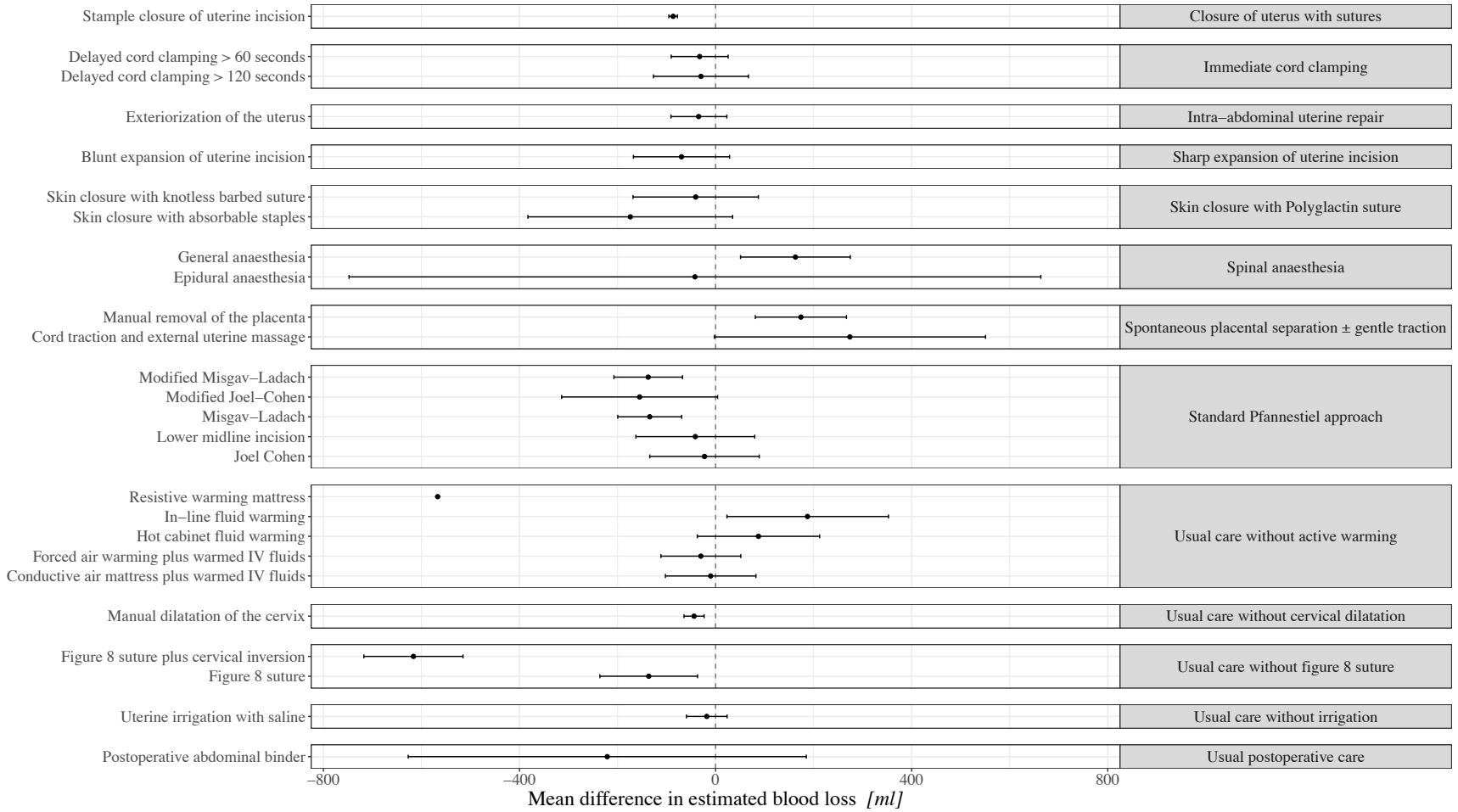


Figure 39: Overall forest plot of mean difference in estimated blood loss - random effects model

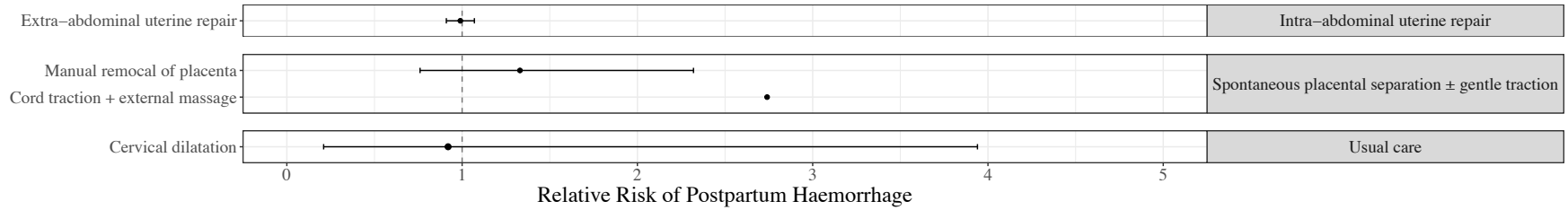


Figure 40: Overall forest plot of relative risk of postpartum haemorrhage - random effects model

Please note: for point estimates without confidence intervals, the confidence intervals have been omitted as they exceed the x-axis scale

2.3.4 Miscellaneous interventions for the prevention of blood loss

There were 23 miscellaneous studies reporting the effectiveness of preventative interventions on estimated blood loss and/or the risk of post-partum haemorrhage that could not be grouped into meta-analyses. Refer to appendix 4 for a summary table of study characteristics.

A randomised controlled trial[100] compared closure of the peritoneum versus non-closure of the peritoneum. Compared to closure, non-closure of the peritoneum resulted in a reduction in estimated blood loss of 83.30 ml (95% CI -177.73; 11.14). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A non-randomised trial[101] compared open visceral peritoneum versus sutured visceral peritoneum. Compared to open visceral peritoneum, sutured visceral peritoneum resulted in an increase in estimated blood loss of 24 ml (95% CI 16.95; 31.05). The overall risk of bias judgement for this study was 'critical' on ROBINS-I assessment.

A randomised controlled trial[102] compared closure of parietal peritoneal layer versus non-closure of parietal peritoneal layer. Compared to closure of parietal peritoneal layer, non-closure of parietal peritoneal layer resulted in an increase in estimated blood loss of 56.97 ml (95% CI -29.06; 143.00). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[103] compared non-dissection of the rectus sheath inferiorly from the underlying muscle versus dissection of the rectus sheath inferiorly from the underlying muscle. Compared to non-dissection of the rectus sheath inferiorly, dissection of the rectus sheath inferiorly resulted in an increase in estimated blood loss of 37.60 ml (95%

CI -69.54; 144.74). The overall risk of bias judgement for this study was 'some concerns' on RoB 2 assessment.

A randomised controlled trial[104] compared single-layer closure of the uterine incision versus double-layer closure of the uterine incision. Compared to single layer closure, double layer closure resulted in a reduction in estimated blood loss of 7 ml (95% CI -101.80; 87.80). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A non-randomised trial[105] compared a 3D MRI model for uterine incision versus usual care. Compared to 3D MRI model for uterine incision, usual care resulted in an increase in estimated blood loss of 255.31 ml (95% CI 9.14; 501.48). The study also reported on the risk of postpartum haemorrhage (PPH; > 1000 ml). 11 of 45 women in the 3D MRI model group and 25 of 89 women in the usual care group experienced PPH; Relative Risk (RR; 95% CI) 0.87 (0.47 to 1.60). The overall risk of bias judgement for this study was 'critical' on ROBINS-I assessment.

A randomised controlled trial[106] compared the use of an Alexis retractor versus a standard retractor. Compared to the Alexis retractor, the standard retractor resulted in an increase in estimated blood loss of 2.40 ml (95% CI -21.53; 26.33). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[107] compared uterine cleaning versus no uterine cleaning. Compared to uterine cleaning, no uterine cleaning resulted in an decrease in estimated blood loss of 1.00 ml (95% CI -79.89; 77.89). The study also reported on the risk of postpartum haemorrhage (PPH; > 1000 ml). 6 of 103 women in the uterine cleaning group and 8 of 103 women in the no uterine cleaning group experienced PPH; Relative Risk (RR; 95% CI) 0.75

(2.27 to 2.09). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[108] compared Continuous non-invasive arterial pressure (CNAP) monitor used by anaesthesia provider versus non-invasive blood pressure (NIBP) monitor used by anaesthesia provider. Compared to CNAP, NIBP resulted in an increase in estimated blood loss of 140.80 ml (95% CI 4.86; 276.74). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[109] compared Controlled hypotension at 80% of basal blood pressure (BP) after delivery of foetus versus Controlled hypotension at 70% of Basal BP after delivery of foetus versus BP maintained in normal range after delivery of foetus. Compared to controlled hypotension at 70%, normal range resulted in an increase in estimated blood loss of 618.10 ml (95% CI 237.28; 998.92). Compared to controlled hypotension at 80%, normal range resulted in an increase in estimated blood loss of 390.70 ml (95% CI -12.79; 794.19). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[110] compared cephalad-caudad expansion of uterine incision versus transverse extension of uterine incision. Compared to cephalad-caudad expansion, transverse extension resulted in an increase in estimated blood loss of 5 ml (95% CI -8.56; 18.56). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[111] compared prophylactic Bakri balloon following placenta delivery versus usual care. Compared to prophylactic Bakri balloon, usual care resulted in a reduction in estimated blood loss of 148.00 ml (95% CI -461.11; 165.11). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[112] compared internal iliac artery balloon occlusion versus usual care. Compared to internal iliac artery balloon occlusion, usual care resulted in a reduction in estimated blood loss of 73.67 ml (95% CI -782.71; 635.37). The study also reported on the risk of postpartum haemorrhage (PPH; > 1000 ml). 15 of 20 women in the internal iliac artery balloon occlusion group and 15 of 20 women in the usual care group experienced PPH; Relative Risk (RR; 95% CI) 1.00 (0.70 to 1.43). The overall risk of bias judgement for this study was 'some concerns' on RoB 2 assessment.

A randomised controlled trial[113] compared Balloon Uterine Artery Ligation (BUAL) versus no BUAL. Compared to BUAL, no BUAL, resulted in an increase in estimated blood loss of 175.20 ml (95% CI 169.69; 180.71). The overall risk of bias judgement for this study was 'some concerns' on RoB 2 assessment.

A randomised controlled trial[114] compared uterine artery ligation versus usual care. Compared to uterine artery ligation, usual care resulted in an increase in estimated blood loss of 235.80 ml (95% CI 149.23; 322.37). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[115] compared creation of a bladder flap versus no bladder flap. Compared to creation of a bladder flap, no bladder flap resulted in a reduction in estimated blood loss of 533.34 ml (95% CI -994.87; -71.81). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[116] compared closure of the peritoneum versus non-closure of the peritoneum. The study reported on the risk of postpartum haemorrhage (PPH; > 1000 ml). 4 of 70 women in the closure of the peritoneum group group and 3 of 54 women in the

non-closure of the peritoneum group experienced PPH; Relative Risk (RR; 95% CI) 1.03 (0.24 to 4.40). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[117] compared high uterine incision versus usual care. Compared to high uterine incision, usual care resulted in an increase in estimated blood loss of 132.10 ml (95% CI 119.43;144.77). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[118] compared blunt expansion of uterine incision versus sharp expansion of uterine incision. Compared to blunt expansion of uterine incision, sharp expansion of uterine incision resulted in an increase in estimated blood loss of 41.90 ml (95% CI 24.64; 59.16). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment on RoB 2 assessment.

A randomised controlled trial[119] compared warmed IV fluids versus warmed under body pad versus usual care. Compared to warmed IV fluids, usual care resulted in a reduction in estimated blood loss of 42.67 ml (95% CI-100.87;15.53). Compared to warmed under body pad, usual care resulted in a reduction in estimated blood loss of 5.09 ml (95% CI -75.80; 65.62). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[120] compared extra-abdominal removal of the placenta versus intra-abdominal removal of the placenta. Compared to extra-abdominal removal, intra-abdominal removal of the placenta resulted in a reduction in estimated blood loss of 38.00 ml (95% CI -71.94; -4.06). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[121] compared placental drainage versus cord traction. Compared to placental drainage, cord traction resulted in an increase in estimated blood loss of 6.67 ml (95% CI -156.58; 169.92). The overall risk of bias judgement for this study was 'some concerns' on RoB 2 assessment.

A randomised controlled trial[122] compared Spontaneous placental detachment with in situ uterine repair versus Spontaneous placental detachment with exteriorized uterine repair versus Manual placental removal with in situ uterine repair versus Manual placental removal with exteriorized uterine repair. Compared to spontaneous placental detachment with in situ uterine repair, manual placental removal with in situ uterine repair resulted in an increase in estimated blood loss of 694.40 ml (95% CI 255.45; 733.35). Compared to spontaneous placental detachment with in situ uterine repair, manual placental removal with exteriorized uterine repair resulted in an increase in estimated blood loss of 507.40 ml (95% CI 362.64; 652.16). Compared to spontaneous placental detachment with in situ uterine repair, spontaneous placental detachment with exteriorized uterine repair resulted in an increase in estimated blood loss of 3.60 ml (95% CI -128.91;136.11). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

2.3.5 Interventions for the treatment of blood loss

There were seven trials investigating the effectiveness of interventions for the treatment of blood loss and/or post-partum haemorrhage, none of which could not be grouped for meta-analysis. Refer to appendix 4 for a summary table of study characteristics.

A non-randomised trial[123] compared a combined strategy of haemorrhage management versus usual management. Compared to the combined strategy, the usual management resulted in an increase in estimated blood loss of 666.00 ml (95% CI 608.12; 723.88). The overall risk of bias judgement for this study was 'high' on ROBINS-I assessment.

A randomised controlled trial[124] compared modified B-lynch suture technique versus classic B-lynch suture technique. Compared to the modified technique, the classic technique resulted in an increase in estimated blood loss of 244.00 ml (95% CI 192.35; 295.65). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[125] compared endouterine square haemostatic sutures versus Bakri balloon. Compared to endouterine square haemostatic sutures, Bakri balloon resulted in a reduction in estimated blood loss of 426 ml (95% CI -642.42; -209.58). The overall risk of bias judgement for this study was 'some concerns' on RoB 2 assessment.

A prospective cohort study[126] compared Bakri balloon versus a non-balloon protocol. Compared to the Bakri balloon, the non-balloon protocol resulted in an increase in estimated blood loss of 320.90 ml (95% CI 165.80; 476.00). The overall risk of bias judgement for this study was 'serious' on ROBINS-I assessment.

A randomised controlled trial[127] compared Bakri Ballon with a traction stitch versus Bakri balloon without traction stitch. Compared to Bakri Ballon with a traction stitch, Bakri balloon without traction stitch resulted in an increase in estimated blood loss of 766.67 ml (95% CI -392.67; 1926.01). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[128] compared balloon catheter versus gauze. Compared to balloon catheter use, gauze use resulted in an increase in estimated blood loss of 229.00 ml (95% CI 98.06; 359.94). The study also reported on the risk of postpartum haemorrhage (PPH; > 1000 ml). 43 of 102 women in the balloon catheter group and 65 of 102 women in the gauze group experienced PPH; Relative Risk (RR; 95% CI) 0.66 (0.50 to 0.87). The overall risk of bias judgement for this study was 'high' on RoB 2 assessment.

A randomised controlled trial[129] compared early uterine suction tamponade versus delayed uterine suction tamponade. Compared to early uterine suction tamponade, delayed uterine suction tamponade resulted in a reduction in estimated blood loss of 5.33 ml (95% CI -218.01; 207.35). The overall risk of bias judgement for this study was 'some concerns' on RoB 2 assessment.

2.4 Discussion

2.4.1 Summary of evidence

This study forms a comprehensive analysis of the effectiveness of non-pharmacological interventions on blood loss associated with caesarean delivery. 13,521 women from 51 studies were included in the network meta-analyses, evaluating 13 types of interventions. A variety of interventions were assessed: figure of 8 suture with or without cervical inversion for bleeding placental bed; caesarean delivery surgical techniques; blunt and sharp expansion of the uterine incision; normal saline irrigation of the abdominal cavity; staple uterine incision, anaesthesia technique; uterine closure material; cervical dilatation; early and delayed umbilical cord clamping; fluid and mattress warming; abdominal binder; and extra-abdominal and intra-abdominal uterine repair. Apart from warming strategies and use of an abdominal binder, all types of interventions focused on variations of the surgical procedure. None of the included studies evaluated broader perioperative management strategies such as early warning systems, checklists, and haemorrhage prevention and management algorithms.

To interpret the effectiveness of an intervention measured in terms of a mean difference in estimated blood loss, we considered which absolute amount of blood loss increase or decrease is likely to affect patient important outcomes. We decided *post hoc* to define a clinically significant difference in blood loss as a difference of more than 250 ml. The reasons for this are twofold: (i) we believe a difference of than 250 ml is unlikely to translate to a difference in patient important outcomes in the general caesarean delivery population included in our review, and (ii) given the challenges in accurately measuring blood loss during caesarean delivery and the variation in methods used,[130] we cannot be certain that differences of less than 250 ml are true differences.

Three interventions had a pooled estimated that exceeded this definition of a clinically significant effect size. Figure of 8 suture plus cervical inversion resulted in a reduction in blood loss of 616.33 ml when compared to usual care (95% CI for the random effects model -717.44; -515.22). Resistive warming mattress resulted in a reduction in blood loss of 567.00 ml when compared to usual care without active warming (95% CI for the random effects model -1446.31; 312.31). Spontaneous placental separation with or without gentle traction resulted in a clinically significant reduction in blood loss of 274.03 ml when compared to cord traction and external uterine massage (95% CI for the random effects model -2.61; 550.68). Though these three interventions had a clinically significant point estimate, only the figure of 8 suture plus cervical inversion resulted in a statistically significant point estimate. Overall, the relative effect sizes yielded from network meta-analysis are imprecise. This is largely due to the small number of participants within each network, resulting in wide confidence intervals around the point estimates.

We were able to form three meta-analyses assessing the effect of interventions on the risk of postpartum haemorrhage (>1,000 ml). Two were simple pairwise meta-analyses, and one was a network meta-analysis. We assessed the effect of cervical dilatation compared to usual care; extra-abdominal versus intra-abdominal uterine repair; and cord traction with massage versus spontaneous separation with and without gentle traction versus manual removal, on the relative risk of postpartum haemorrhage. The estimated treatment effects were not considered clinically relevant (relative risk reduction or increase <0.25) for the intervention of cervical dilatation or exteriorisation of the uterus. The method of placenta removal had a notable effect on the risk of post-partum haemorrhage; spontaneous placental separation with or without gentle traction performed notably superior to the alternative strategies.

The majority of studies included in the network meta-analysis had 'some concerns' or 'high' overall risk of bias. Across all groups the quality of evidence was low. Moving forward, small

single centre studies should be discouraged in favour of larger multinational studies; which have been associated with lower risk of bias in perioperative literature.[131]

Statistical heterogeneity was concerning in most of the meta-analyses. For the blood loss (ml) outcome - seven networks had significant heterogeneity, one network had moderate heterogeneity, and in five networks there was insufficient data to quantify heterogeneity by I^2. For the PPH outcome – two networks had significant heterogeneity, and in one network there was insufficient data to quantify heterogeneity by I^2. Due to the limited number of studies within each network, and the relatively small sample sizes, we were unable to carry out pre-planned sub-group analyses, which may have provided an indication of the sources of heterogeneity. We consider the following to be potential sources of heterogeneity: population elements - the baseline risk of haemorrhage or whether procedures were predominantly elective or emergency; intervention elements – the dose and timing of the intervention; comparator elements – what constituted 'usual care'; outcome elements – the risk of bias associated with the method of quantifying blood loss; study design – whether participants were randomised or not; quality – measured as the overall risk of bias judgement, as determined by the RoB2 (randomised) or ROBINS-I (non-randomised) assessment tools; context elements – World Bank country income level classification at the time of study recruitment, and hospital service level (primary, secondary or tertiary). Due to the limited information size, and that very few studies reported such outcomes, we were unable to analyse the pre-stated secondary outcomes of interest for this study.

2.4.2 Limitations

The information size supporting each intervention is small. A limited number of studies were included in each network, median (range): 3 (2 – 8). The number of participants included in each network was also limited median (range): 488 (183 – 2,503).

We aimed to identify and assess interventions which had been assessed prospectively in clinical trials. This approach biases towards the inclusion of interventions that are easily assessed in randomised controlled trials and against the inclusion of research evaluating systems interventions, education, and quality improvement projects which are less likely to be evaluated in a prospective experiment. Randomised controlled trials are considered the most reliable source of evidence when assessing the effectiveness of an intervention. The 'gold standard' is a double-blind placebo-controlled trial. There are inherent challenges with blinding participants and investigators in surgical trials. There are also barriers in creating a placebo intervention or sham treatment. The challenges associated with conducting randomised controlled trials of surgical interventions, have been well described.[132,133,134]

The lack of available evidence and challenges in conducting prospective randomised trials of surgical interventions is not to say that pragmatic randomised controlled trials relating to surgical procedures cannot be conducted. However, complex interventions in health systems may be more appropriately evaluated in large collaborative trials employing stepped wedge and cluster randomisation techniques. An iterative process of program development paired with a formal approach to monitoring and evaluation may have the greatest impact, but methods of synthesis that combine both the output of such real-world data with that of mainstream scientific methods are lacking. Future studies designed to assess complex interventions to improve outcomes from caesarean delivery may also look to the IDEAL framework as a guideline on how to assess interventions and evaluate their long term impact.[135] However, adaptation of the IDEAL framework may be necessary when assessing interventions in low resourced settings.

We chose to assess both the volume of blood loss in millilitres, and the risk of post-partum haemorrhage in the context of caesarean delivery (>1,000 ml) as our primary outcomes of interest. Objectively and accurately measuring blood loss in surgery is a challenge, and is

particularly difficult in caesarean delivery due to the presence of amniotic fluid. This challenge is reflected by the range of techniques used to quantify blood loss across the included studies. We did not include studies that exclusively determined blood loss through a surrogate marker such as change in haemoglobin or haematocrit, due to the poor correlation between these surrogate markers and actual blood loss.[136] Though estimated blood loss using the visual and gravimetric method is correlate with a reduced haemoglobin pre- and post-operatively,[137,138] the correlation is likely not strong enough, and too inaccurate to compare interventions in a clinical trial.

Studies which only assessed risk of blood transfusion as a measure of blood loss, were also excluded. Though transfusion rate is an easily measured objective outcome variable, transfusion protocols and practices vary significantly between countries and within countries. In countries where blood is a scarce resource, the clinical threshold for blood transfusion is higher. Therefore, there would likely be too much heterogeneity within this outcome to allow for synthesis of findings.

A further limitation is the exclusion of texts in language other than English. Though we endeavoured to find relevant translations, we may have missed additional studies and interventions. The segregation of medical literature by language may lead to distinct approaches to bleeding during and after caesarean delivery in different language regions. Any such approach that is particular to a language region would have been excluded in our review.

2.4.3 Findings in context

There is high quality evidence that pharmacological interventions are effective at reducing post-partum haemorrhage. A Cochrane network meta-analysis found several uterotonic agents to be effective at reducing the risk of PPH, and that the effects were similar for women

giving birth vaginally and by caesarean delivery.[36] The volume and quality of evidence investigating the effectiveness of pharmacological agents appears much greater than that of non-pharmacological interventions.

The CORONIS trial[139] – an international multicentre pragmatic randomised controlled trial including almost 16,000 from 19 centres, assessed the effectiveness of various caesarean delivery techniques on maternal and neonatal outcomes. The following interventions were assessed: "*(1) blunt versus sharp abdominal entry; (2) exteriorisation of the uterus for repair versus intra-abdominal repair; (3) single-layer versus double-layer closure of the uterus; (4) closure versus non-closure of the peritoneum (pelvic and parietal); and (5) chromic catgut versus polyglactin-910 for uterine repair".* Using a composite primary outcome of *"death, maternal infectious morbidity, further operative procedures, or blood transfusion of more than 1 unit of whole blood or packed cells up to the 6-week follow-up visit",* the study found no significant difference between any of the assessed interventions with regard to the primary outcome. The CORONIS trial did not assess any of the primary outcomes of this review, and thus was not eligible for inclusion. However, there is overlap in the interventions assessed in CORONIS with those assessed in this network meta-analysis: blunt versus sharp abdominal entry; and exteriorisation of the uterus for repair versus intra-abdominal repair. We too found no statistically or clinically significant effect for these comparisons.

The CORONIS trial is evidence that large scale international pragmatic trials in obstetrics are indeed possible. CORONIS was conducted across seven low- and middle-income countries (Argentina, Chile, Ghana, India, Kenya, Pakistan, and Sudan). Given that the burden of caesarean delivery mortality is far greater in low- and middle-income countries, compared to high-income countries[21], it is essential that future studies follow in the footsteps of CORONIS, to produce findings generalisable to where the burden is greatest.

2.5 Conclusion

The published trials of the effect of non-pharmacological interventions on blood loss associated with caesarean delivery are inconclusive, due to generally small sample sizes, high risk of bias across studies, and significant heterogeneity. There is an urgent need for collaborative pragmatic trials to identify interventions to reduce the mortality and morbidity associated with blood loss during and after caesarean delivery. The number of women worldwide undergoing caesarean delivery annually is estimated to be 29.7 million and rising.[9] Given the large number of women undergoing caesarean delivery, identifying interventions that reliably have a beneficial effect on blood loss have the potential to reduce the mortality and morbidity for a large number of women worldwide.

Chapter 3: Identifying Interventions to Reduce Blood Loss During and After Caesarean Delivery Across Africa: a Delphi Consensus Study

3.1 Introduction

The population of Africa is growing at the world's fastest rate,[2] with the population of sub-Saharan Africa expected to double by 2050.[140] In sub-Saharan Africa one in 36 women die during childbirth, which is five times the global average. This equates to 545 maternal deaths per 100,000 live births – accounting for two thirds of all maternal deaths globally.[141] This. unacceptably high maternal mortality is substantially higher than the Sustainable Development Goal for 2030, which aim to reduce the maternal mortality ratio to less than 70 per 100,000 live births.[3] Caesarean delivery is considered a Bellwether Procedure by the Lancet Commission on Global Surgery.[8] Access to caesarean delivery across Africa varies, though generally the caesarean delivery rate remains low across the continent. Caesarean delivery rates below 19% of live births are associated with increased maternal mortality.[15] It is estimated that in Africa 7.3% of live births are by caesarean delivery, while in sub-Saharan Africa the rate is as low as 3.5%.[11]

Though the caesarean delivery rate remains low, the African Surgical Outcomes Study (ASOS) found that caesarean delivery is the most common surgical procedure, accounting for one third of surgical procedures performed across the continent.[17] Women undergoing caesarean delivery in Africa are 50 times more likely to die compared to women in high-income settings. In ASOS, haemorrhage accounted for 70% of perioperative complications

and was independently associated with mortality.[20] A meta-analysis of studies reporting maternal outcomes after caesarean delivery in low- and middle-income countries found sub-Saharan Africa to have the highest burden of caesarean delivery related maternal mortality. This study also identified haemorrhage as the most common cause.[21]

The African Peri-operative Research Group consider the 'early identification and management of mothers at risk from peripartum haemorrhage in the peri-operative period' as a vital research priority.[22] There is an urgent need to develop pragmatic solutions to address blood loss during and after caesarean delivery.

We aimed to gain consensus on which interventions are recommended by African researchers and clinicians to reduce blood loss during and after caesarean delivery.

3.2 Methods

The Delphi technique is a widely used and accepted method for generating data and forming consensus among subject matter experts.[142] We conducted a Delphi study to identify interventions and reach consensus on which are considered the most effective and feasible to implement across Africa.

3.2.1 Ethics and consent

Ethical approval was provided by the Human Research Ethics Committee of the University of Cape Town, South Africa (HREC 187/2020), and by the Oxford Tropical Research Ethics Committee (524-20). Participants were provided with an information sheet and online consent was obtained at the beginning of each round.

3.2.2 Data collection

The study was conducted in both English and French. Study data from rounds one to three were collected and managed using REDCap, a web-based data capture software.[143] Round four was held via ZOOM Video Communications Version: 5.0.5, an online video conferencing platform.

3.2.3 Participant selection

Country leads from the African Surgical Outcomes Study and/or the African Surgical OutcomeS-2 Trial were asked to nominate one lead obstetrician or surgeon providing obstetric care and one lead anaesthetist providing obstetric anaesthesia care within their country. We encouraged the participation of two obstetric and anaesthesia providers from each country.

3.2.4 The Delphi Process

3.2.4.1 Round one

In round one, participants were asked to propose at least six key interventions for consideration. Participants were asked to identify interventions across three broad categories: prevention, early identification, and management of peripartum haemorrhage in the perioperative period. Participants were encouraged to provide justifications and references for the inclusion of recommended interventions. The list of interventions was amalgamated and grouped according to common themes. The accuracy of the amalgamation was verified by members of the study steering committee. We collected demographic data on participants' speciality and the level of healthcare facility in which they primarily work

3.2.4.2 Round two

In round two, all recommended interventions were distributed to participants. Participants were asked to score each intervention on a 9-point Likert scale for (i) effectiveness – '*how effective do you predict the intervention would be at reducing peripartum haemorrhage in the perioperative period, within your local context'*, and (ii) feasibility – *'how feasible do you predict it would be to implement the intervention within your local context'*. A score of 1-3 was considered low effectiveness/feasibility (not recommended); 4-6 was considered moderate effectiveness/feasibility (possibly recommended); and 7-9 was considered high effectiveness/feasibility (recommended). Participants were given the option to provide justifications or references to support their scoring. The group scores for each intervention were summarised by the median and inter-quartile range (IQR).

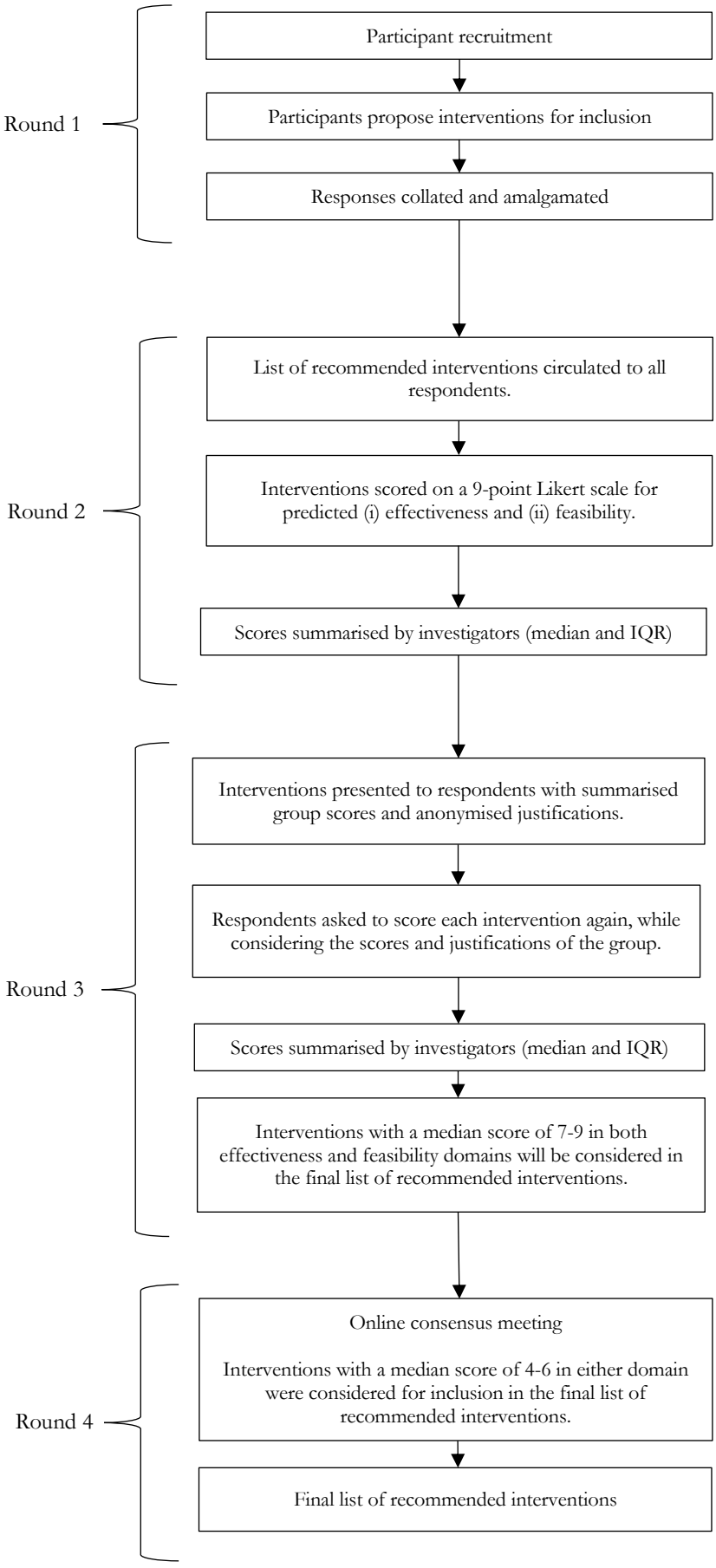
3.2.4.3 Round three

In round three participants were presented with the same list of recommended interventions, alongside summarised group scores (median and IQR) and anonymised justifications or references from round two. Participants were asked to re-score each intervention on the same 9-point Likert scale for effectiveness and feasibility, while considering the summarised group scores from the previous round. Participants were again given the option to provide justifications and/or references for their score. The group scores for each intervention were again summarised by the median and IQR.

3.2.4.4 Round four

Round four took place as a live online discussion. Interventions were presented to participants based on the summarised group scores from round three. Interventions with a median score of 1-3 in either effectiveness or feasibility domain were excluded; interventions with a median score of 7-9 in either domain were recommended and included in the final list of interventions. The aim of round four was to gain consensus on whether to upgrade any of the 'borderline' interventions with a median score of 4-6 to the final list of recommended interventions.

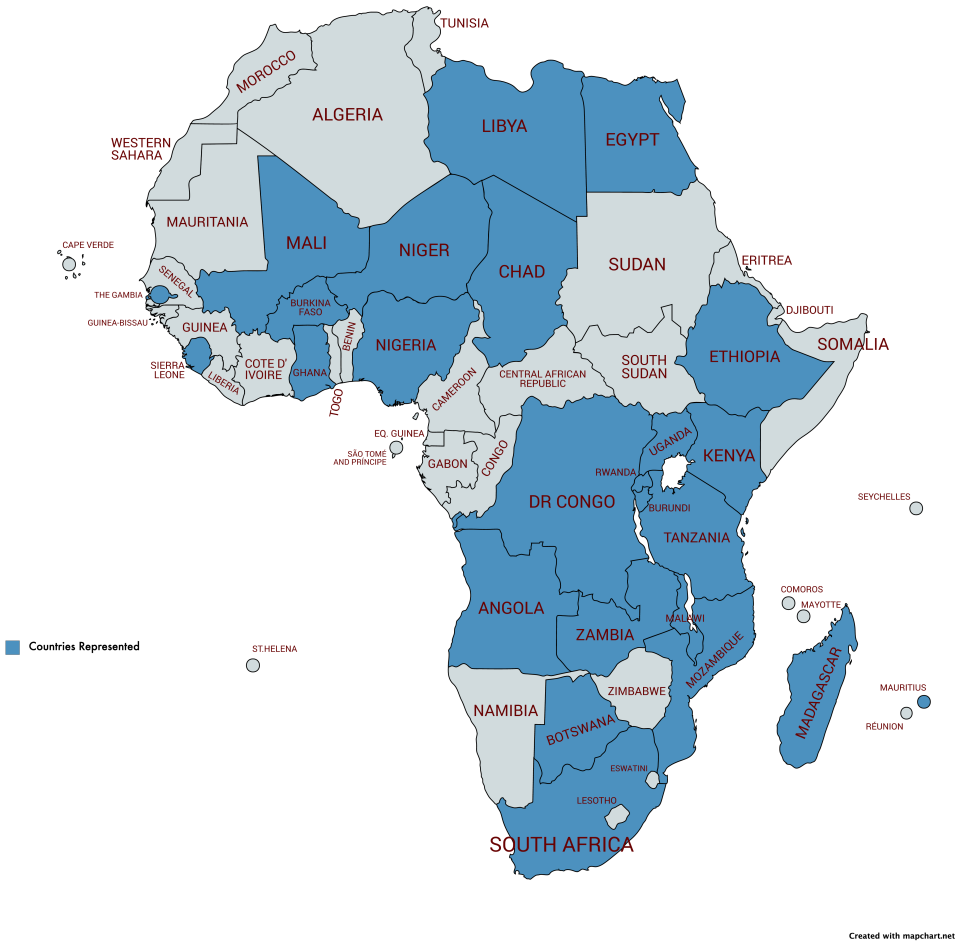
Figure 41: Study Flow Diagram



3.3 Results

The Delphi process was conducted between August and November 2020. Overall, 55 experts from 24 African countries participated: Angola; Botswana; Burkina Faso; Burundi; Democratic Republic of Congo; Egypt; Ethiopia; Gambia; Ghana; Kenya; Libya; Madagascar; Malawi; Mali; Mauritius; Mozambique; Niger; Nigeria; Rwanda; Sierra Leone; South Africa; Tanzania; Uganda; Zambia.

Figure 42: Map of representation.



In round one 44 experts participated. Forty-five percent were obstetrics providers and 55% were anaesthesia providers. 78% of participants work at a tertiary facility, 17% at a regional facility and 4% at a district / rural facility. Participants recommended 195 potential interventions. The interventions were de-duplicated and amalgamated to form 39 unique interventions across 4 broad categories of interventions: community based; antenatal care and assessment; peri-operative and health system strengthening interventions.

In round two 41 participants scored each intervention twice on the 9-point Likert scale for effectiveness and feasibility, the results of which can be found in appendix 6. In round three, 40 participants re-scored the interventions, while considering the group scores (median and IQR) from round two. Following round three, 24 interventions were considered to be of high effectiveness and high feasibility and were recommended in the final list of interventions. One intervention was considered to be of low effectiveness or feasibility and was not included in the final list of recommended interventions. There were 14 borderline interventions considered to have moderate effectiveness or feasibility. The borderline interventions were taken forward for consideration in round four. Through a live online consensus meeting, four borderline interventions were upgraded to the final list of recommended interventions. The final recommendations include 28 interventions, listed in table two. These interventions cover a broad range of fields including: community and maternal education; availability of contraception and family planning pre-operative risk assessment and screening; checklists and protocols; monitoring and surveillance; availability of resources; ability to perform technical skills; minimum training standards; referral patterns and delays; advocacy to key stakeholders; simulation and team training; and 24-hour access to caesarean delivery.

Table 2: Recommended interventions.

Community based interventions
Community information, education and communication regarding reproductive health (e.g. knowledge on risks, the early recognition of danger signs in pregnancy, and the advantages of seeking healthcare at an early stage).
Availability of contraception and family planning.
Antenatal care and assessment interventions
Routine pre-operative risk assessment and risk stratification for peripartum haemorrhage
Routine screening for anaemia and patient blood management programme
Routine antenatal assessment by the anaesthesia provider for all women for planned caesarean delivery.
Maternal education on the early self-recognition of signs and symptoms of peri-partum haemorrhage.
Peri-operative interventions
Routine use of a Surgical Safety Checklist modified for caesarean delivery use.
Implementation of a standardised peri-partum haemorrhage protocol.
Intrapartum monitoring: routine, close monitoring of mother and foetus during intrapartum period.
Early and increased surveillance of vital signs in the postpartum period, possibly in a dedicated environment.
Routine use of modified early obstetric warning score in the postoperative period, or routine active monitoring for haemorrhage e.g. shock index.
Early involvement of anaesthesia providers in the management of patients at risk.
Availability of a peri-partum haemorrhage 'package' containing all items required to manage post-partum haemorrhage.
Availability of emergency blood products.
Availability of first line uterotonic agents
Availability of alternative/second line uterotonic agents.
Availability of tranexamic acid.
Ability to perform active management of the third stage of labour.
Ability to perform uterine massage and bimanual compression.
Ability to perform hysterectomy and uterine artery ligation.
Ability to perform B-lynch and compression sutures.
Ability to perform balloon tamponade.
Health System Strengthening Interventions
Ensuring a minimum training standard for healthcare providers.
Advocating to key stakeholders about the importance of reducing maternal morbidity and mortality related to peripartum haemorrhage.
Establishing smooth and timely referral patterns between levels of care.
Reducing delays in receiving care once at the healthcare facility.
Multidisciplinary simulation and team training.
Availability of resources to perform caesarean delivery 24 hours a day.

3.4 Discussion

We used a Delphi process, which is a well-established method to gain consensus among an expert group. Participants identified 39 interventions to reduce peripartum haemorrhage in the perioperative period in Africa, of which 28 were recommended and considered highly effective and feasible. The expert group represent clinicians and researchers from 24 African countries. Interventions were heterogeneous and inter-disciplinary. Interventions were divided into four inter-linked categories: community based; antenatal care and assessment; peri-operative; and health system strengthening. The Delphi group represented obstetrics and anaesthesia providers, yet the recommendations were multifaceted and varied - suggesting less emphasis on clinician focussed healthcare facility based interventions, and instead a holistic system strengthening approach, with significant attention to public health interventions based.

3.4.1 Strengths

There was a high response rate in each of the three rounds. 24 African countries were represented, and there was even mix of anaesthesia and obstetrics provider experts. Rounds one to three were conducted in French and English to increase accessibility and participation.

3.4.2 Limitations

No patients were involved in the Delphi process. There was no involvement of public health specialists, community health workers, nurses, midwives, medical officers, or family medicine specialists. Despite this, the suggested interventions cover broad health domains, though the involvement of these key stakeholders may have widened the scope of recommendations.

As the Delphi study was conducted online, the study is biased towards receiving data from those with access to email and internet. The majority of participants work predominantly in tertiary healthcare settings, the study is thus biased towards capturing the insight of those working in tertiary care settings, and may omit critical insight from those working in district and rural healthcare facilities.

3.4.3 Community Based Interventions

The expert group recommend 'Community information, education and communication regarding reproductive health'. Multiple community factors and perceptions regarding obstetric complications have been identified as barriers to utilising emergency obstetric care in Africa. Community barriers to accessing obstetric care identified in the literature include: socio-cultural factors, confidence in alternative practices, negative views of healthcare services, distrust in health care workers, stigma regarding seeking healthcare, anticipating self-improvement without seeking healthcare, fear of caesarean delivery and blood transfusion, and preference for delivery in the home environment.[144] Deciding to seek care may be impacted by perceptions of the pregnant woman, their family and the wider community, and thus information, education and communication based interventions aimed at a wider community level may reduce the 'phase one delay' in which time is spent deciding whether to seek care.[145]

Both community information and education, and access to contraception and family planning form critical components of the Sustainable Development Goal 3.7:

"Target 3.7: By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes" [146]

Modern contraceptives form a vital primary prevention strategy to reduce maternal mortality.[147] Access to family planning programmes which facilitate the use of modern contraceptives avert maternal mortality both directly and indirectly.[148] Directly – by decreasing the total fertility rate, the absolute number of maternal deaths is less.[149] Indirectly – by reducing the frequency of high-risk, high-parity pregnancies.[148] Africa has the lowest prevalence of contraceptive use, and the highest unmet need for family planning in the world.[150] Significant within country inequity with regard to contraceptive use between urban and rural areas, and by other socio-economic factors has been documented.[151,152,153,154] A universal, community based approach to improve access to and uptake of modern contraceptives and family planning services may therefore be particularly effective.

3.4.4 Antenatal Care and Assessment Interventions

Anaemia during pregnancy is associated with an increased rate of post-partum haemorrhage.[155,156,157] Severe anaemia has been associated with an increased chance of caesarean delivery.[157] The risk of maternal mortality in women with severe anaemia is 2.36 times higher, when compared to women without severe anaemia.[158] Early identification of anaemia through screening, will facilitate blood management programmes.

Routine pre-operative risk assessment and risk stratification for peripartum haemorrhage may facilitate pre-operative optimisation and/or the implementation of strategies to mitigate risks in the perioperative period. Midwives play a critical role in providing antenatal care, including the assessment of risk factors.[159] A recent modelling study projected a 39% reduction in maternal mortality in low human development index (HDI) countries, and a 43% reduction in maternal mortality in low-to-medium HDI countries by 2035 if midwife-delivered interventions were to be scaled up by a 'substantial amount' – defined as a 25% increase in coverage every five years.[160]

Comprehensive antenatal care presents an opportunity to provide maternal education on the self-recognition of signs and symptoms of peri-partum haemorrhage. Timely self-recognition of danger signs is essential to reduce delay in seeking care. An observational study in Burkina Faso, Ghana and Tanzania showed that a third of women were not counselled on any danger signs of pregnancy, and that proportion of women retaining the counselled information varied across sites, but was generally low.[161] Low educational status is consistently associated with poor awareness of danger signs.[161,162,163] Contextually sensitive and tailored methods of relaying information on the self-recognition of danger signs may be more effective than traditional health counselling approaches. Such interventions may reduce the 'phase one delay' in deciding to seek healthcare.[145]

3.4.5 Perioperative Interventions

Use of surgical safety checklists have been associated with decreased post-operative mortality and decreased surgical complication rates. The first studies to assess the World Health Organisation (WHO) Surgical Safety Checklist (SSC) found a statistically significant decrease in post-operative mortality and complications following its implementation, though only one of 18 sites included in the seminal studies were from the African continent.[164, 165] A stepped wedge cluster randomised controlled trial of hospitals in Norway indicated a significant reduction in complications and length of stay following WHO SSC implementation. Following SSC implementation, post-operative mortality was significantly reduced in one of two hospital sites, however, the reduction was not statistically significant overall.[166] A meta-analysis of randomised trials assessing the effect of the surgical safety checklist found a statistically significant reduction in post-operative mortality, yet none of the studies included a single patient from Africa.[167] A meta-analysis of predominantly observational data found a significant association between SSC use and reduced post-operative mortality and post-

operative complications.[168] The majority of the data suggesting a reduction in mortality with SSC employs before-and-after implementation study design, and given the risk of bias in such trial design, claims of causality should be interpreted with caution. Indeed, the one major randomised trial assessing the effect of the SSC did not follow an intention-to-treat analysis, and excluded those in the intervention group with 'partial-compliance' or 'non-compliance' to the SSC.[166,169] Though it is difficult to assume causality, use of the SSC is strongly associated with decreased post-operative mortality and decreased post-operative complication rates. Despite the simplistic nature of checklists, there are inherent challenges to their implementation within complex health systems.[170] An analysis of pooled data from five prospective cohort studies indicated significant variation in uptake of the WHO SSC across the world. Surgical patients in the Africa Surgical Outcomes Study were exposed to the SSC in 56.7% (95% CI 55.8, 57.6) of operations, which remains well below the pooled global average of 75.4%. The SSC was significantly less likely to be used in obstetric and gynaecological surgery compared to abdominal surgery.[171] Given that use of SSC is low in Africa, and in Obstetric surgery, a modified surgical safety checklist that is specifically adjusted to incorporate important caesarean delivery related factors, and is specific to practise in Africa may have better uptake and utilisation. A recent study in a rural Rwandan hospital implemented a modified WHO SSC, which was adapted for low resourced settings.[172] Following implementation of the checklist, there was an increase in the documentation of EBL, reduced hospital length of stay, and an increase in the administration of antibiotics prior to incision. There was a non-significant reduction in haemorrhage associated with use of the checklist, though the study was inadequately powered to detect this outcome. In the study period, the checklist was used in over 80% of procedures.[172] This indicated the importance of developing contextually sensitive implementation strategies alongside a checklist tailored for differing surgical specialties and environments.

The African Surgical Outcomes Study showed that the unacceptably high caesarean delivery related mortality rates across Africa, are likely associated with 'failure to rescue'. Failure to rescue is defined as the hospital death rate following an adverse outcome or complication in the post-operative period.[173] Women in Africa are almost three times more likely to experience a complication following caesarean delivery, but are 50 times more likely to die compared to women in high income countries.[20] For women undergoing caesarean delivery in Africa, the complication most strongly associated with mortality is haemorrhage. This indicates that the failure to rescue rate following caesarean delivery is approximately 17 times higher in Africa compared to high income healthcare settings.[20]

Delphi experts identified a range of interventions that fit into a interventions reduce failure to rescue framework (figure 43). The framework divides interventions into two groups: (i) early detection of the complication, and (ii) timely and appropriate management of complications.

For 'early detection of the complication', the expert group recommend both 'early and increased surveillance of vital signs in the perioperative period, possibly in a dedicated environment' and 'routine use of modified early obstetric warning score in the postoperative period, or routine active monitoring for haemorrhage e.g. shock index'. Given the challenges in estimating volume of blood loss, and given that blood loss is often underestimated on visual estimation, vital signs are a critical indicator of haemodynamic instability.[174] The Delphi group recommend regular surveillance of vital signs perioperatively, and emphasise the importance of a dedicated environment. The group highlighted the importance of validated objective scoring systems, enabling prompt and appropriate escalation of care. It is vital that scoring systems are applicable to patient cohorts in Africa, and are feasible to use in low-resourced settings. Due to normal physiological changes of pregnancy, women may experience a prolonged period of apparent physiological compensation, prior to rapid

deterioration.[175] General scoring systems may therefore be invalid in the obstetric population, and use of an obstetric specific modified early obstetric warning score may be more effective.[176] These scores have been developed for and embedded within clinical practice within the United Kingdom and other high-income settings. The scores are not validated on a strong evidence base, and variations in how such score are implemented exist.[175] There is a need to develop a modified early obstetric warning score specific for use in a low-resourced setting, and validated on local caesarean delivery populations. The shock index is a rudimentary tool, limited to blood pressure and heart rate measurements. Despite its simplicity, shock-index is a good predictor of blood transfusion and ICU admission following haemorrhage.[174] The Delphi group highlight the importance of 'routine' use, which emphasises the need to embed such interventions within patient safety culture, as opposed to intermittent use, at the discretion of the healthcare provider. According to the African Surgical Outcomes Study, inadequate human and physical resources are a key factor in the increased failure to rescue rate across Africa. User friendly objective surveillance scores may be utilised by a range of healthcare personnel, not limited to use by trained doctors and nurses. Given the sparse workforce density of specialist surgical, anaesthesia, nursing and midwifery providers across Africa, such tools may be impactful.[8,24]

The second component of the failure to rescue interventions framework focusses on timely and appropriate management of complications. Recommendations refer to the ability to perform clinical interventions such as: uterine massage and bimanual compression; hysterectomy and uterine artery ligation; B-lynch and compression sutures; and balloon tamponade. These are life-saving procedures which require functioning healthcare systems, including a trained and physical resources. Tranexamic acid and uterotonic agents are proven to be effective for the treatment of post-partum haemorrhage[37,36], though supply may vary in many low-resource settings. Emergency blood products are a scarce resource across Africa.[177] A systematic review estimated that 26% of obstetric haemorrhage related death in

Africa was due to lack of available blood transfusion.[178] Rapid access to emergency blood transfusion is life-saving, but relies on a complex health system for its procurement.[177] The availability of a peri-partum haemorrhage package refers to the availability of necessary emergency resources, and the logistical ease of timely access. The use of emergency packages/bags/trolleys for time critical situations is well established in resuscitation scenarios. The bag may also contain protocols. The implementation of checklist-based haemorrhage protocols are associated with a reduction in maternal morbidity.[179] Though protocols and checklists appear simplistic in design, implementation within complex health systems is not without challenge.[171] Protocols designed to be contextually and culturally sensitive will likely have increased buy-in from key stakeholders, and thus enhanced utilisation and impact. The 'early involvement of anaesthesia providers in the management of patients at risk' acknowledges the importance of the early escalation of care and the vital role of anaesthesia providers in the management of haemodynamically unstable patients.

The range of recommended interventions within the failure to rescue framework may disrupt the cascade of events that occur from complication to death, and decrease the high failure to rescue rate follow caesarean delivery in Africa.

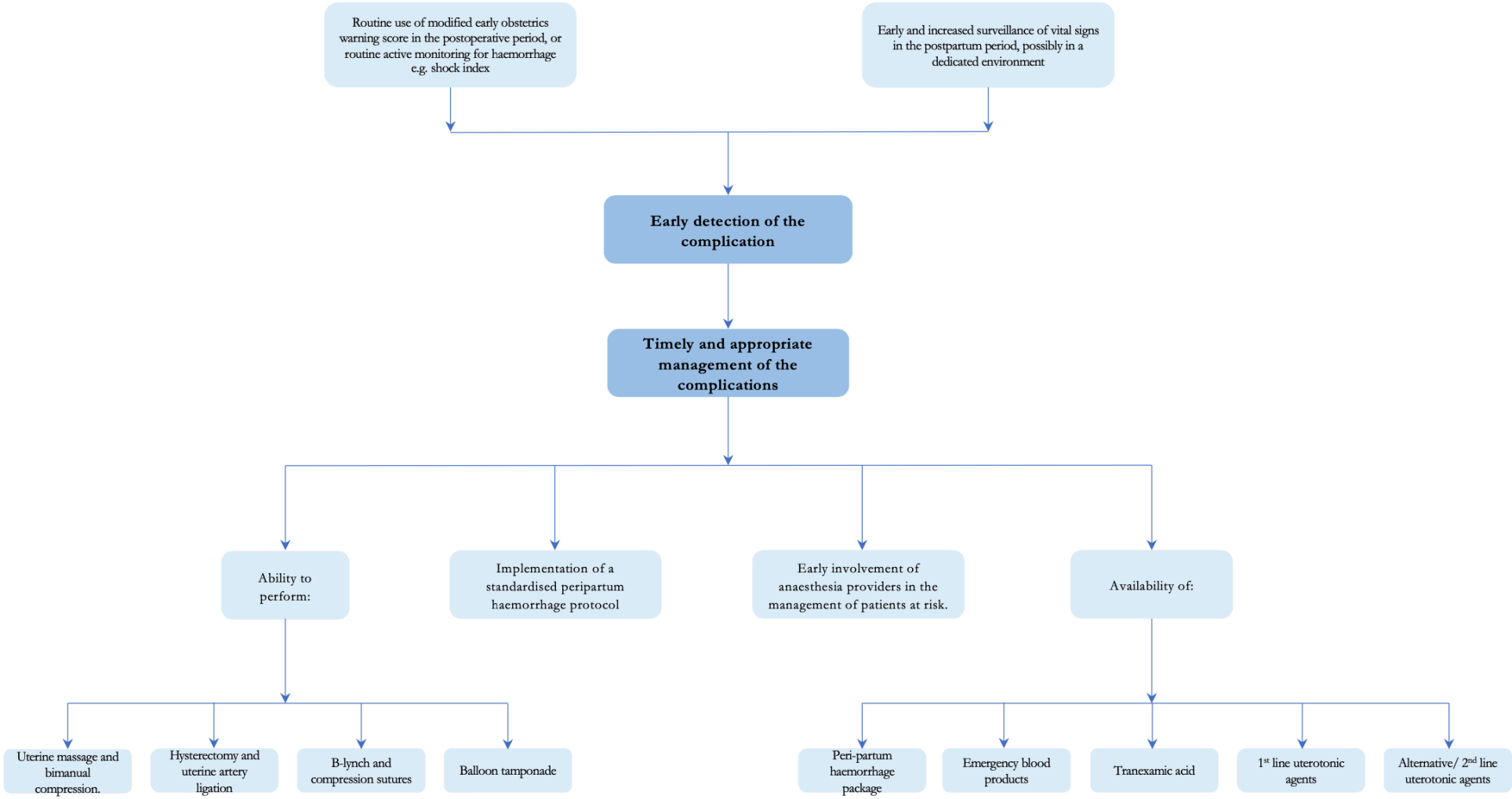


Figure 43: Failure to Rescue Intervention Framework

3.4.6 Health System Strengthening Interventions

Multidisciplinary simulation and team training, designed to optimise team performance may improve team morale, communication and utilisation of patient safety protocol. Contextually sensitive Non-Technical Skills for Surgeons (NOTSS) training, with emphasis on specific challenges faced within variable resources settings have been developed and feasibility tested in Rwanda.[180,181] Similar interventions may be developed specifically for the obstetrics setting.

Delays have been well described as a contributing factor to maternal mortality.[145] This Delphi recommends a focus on interventions which reduce delays in receiving care once at the healthcare facility, and establishing smooth and timely referral systems between levels of care. This may be reflective of the Delphi group make-up, thereby recommending attention be paid to delays which are more directly actionable from the position of obstetric and anaesthesia providers. National audit data from the Confidential Inquiries into Maternal Death in South Africa show that many women who died following caesarean delivery, died at higher levels of care, following referral from a district hospitals where the caesarean delivery took place.[10] A meta-analysis of maternal mortality after caesarean delivery found that women are more likely to die at teaching and tertiary hospitals, though there may be significant reporting bias in such findings.[21] This data emphasises the need to improve referral systems. There may be a role for technological interventions to improve communication between healthcare workers at different levels of care, an example being the model adopted by SURG-Africa - implementing Whatsapp group support networks to guide appropriate referrals between levels of care.[182]

Emergency caesarean delivery may be required at any time of day. The ability to provide a safe 24-hour caesarean delivery service reduce delays in receiving care, and may reduce unsafe referrals between healthcare facilities.

Minimum training standards should be enforced for healthcare providers. A lack of appropriated trained doctors and nurses continues to be the most frequently cited avoidable factor for maternal mortality in South Africa.[10]

The expert group identified the importance of 'advocating to key stakeholders about the importance of reducing maternal morbidity and mortality related to peripartum haemorrhage'. The recommended interventions are varied, inter-disciplinary and reflect a system strengthening approach, as opposed to a clinician focussed approach. Healthcare system strengthening is complex and requires buy-in from key stakeholders, with substantial upstream support at government and policy maker level. The rising number of caesarean deliveries across Africa, combined with the unacceptably high proportion of women who die following this procedure[11,20] necessitates urgency when advocating for health system strengthening interventions, to avert the avoidable death of mothers across the continent.

Conclusion

The unacceptably high maternal mortality rate following caesarean delivery in Africa necessitates urgent action. The complication most strongly associated with caesarean delivery associated mortality is severe obstetric haemorrhage. We conducted a systematic review and network meta-analysis to identify non-pharmacological intervention to reduce blood loss during and after caesarean delivery. Given the important of identifying contextually sensitive perioperative interventions, we also conducted a Delphi consensus study of clinicians and researchers from 24 Africa nations.

The comprehensive systematic review and network meta-analysis undertaken in chapter two yielded underwhelming results. The published data on non-pharmacological interventions and their effect on blood loss during and after caesarean delivery are inconclusive. This is largely due to generally small sample sizes, high risk of bias, and significant heterogeneity across the published data. The majority of studies were small scale, single centre trials from high-income settings, and thus if clinically significant results were found, the results may have had been poorly generalisable, especially in low-resource clinical environments. There is an urgent need for collaborative, pragmatic multi-centre research which aim to identify and assess the effectiveness of interventions to prevent and treat blood loss during and after caesarean delivery. Given that women are 50 times more likely to die following caesarean delivery in Africa compared to high income settings,[20] future trials must identify contextually sensitive and generalisable interventions, most likely to be impactful in low resource settings. Groups such as the African Perioperative Research Group have a central role to play in determining the future research agenda in this field.

A Delphi consensus study of clinicians and researchers from 24 African nations recommended 39 interventions to reduce blood loss during and after caesarean delivery. Twenty-eight interventions were recommended based on their perceived feasibility and effectiveness. The Delphi expert group were obstetrics and anaesthesia providers. Despite this, recommended interventions covered broad health domains including: education; contraception and family planning; comprehensive antenatal care; perioperative medicine; specialist workforce training; availability of clinical resource; reducing delays at health centres and improving referral systems between sites; simulation and team training. The recommended interventions highlight the importance of a multi-faceted, upstream system strengthening approach, and indicate that clinical interventions in isolation may be futile in resource limited environments. Delphi participants highlighted the vital role of advocating to key stakeholders. In order to bring about systems change, significant stakeholder buy-in is necessary.

To reach the Sustainable Development Goal of reducing the maternal mortality ratio to below 70 per 100,000 live births,[3] focussed attention must be paid to a system strengthening approach to reduce mortality caused by lack of access to, and unsafe caesarean delivery across Africa.

The findings of this thesis contribute to the body of evidence available to investigators of the African Perioperative Research Group (APORG). It is hoped that in future this work will aid the development of a pragmatic trial across Africa led by APORG collaborators, which aims to reduce the morbidity and mortality associated with blood loss during and after caesarean delivery.

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Appendix 1

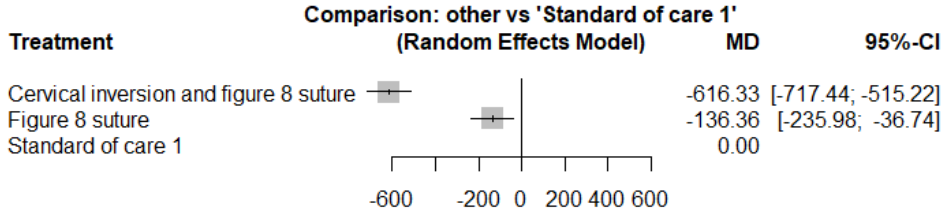
Example Search Strategy

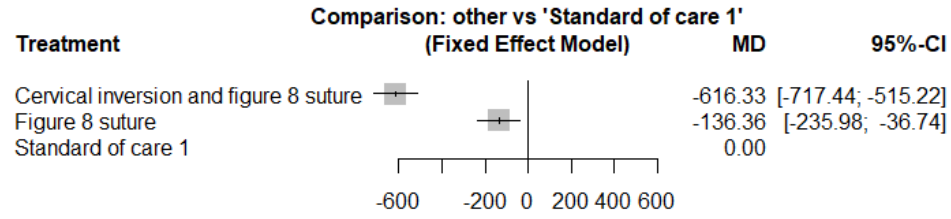
1	CESAREAN SECTION/
2	"Caesarean section* ".af.
3	"Cesarean section* ".af.
4	"Caesarean deliver* ".af.
5	"Cesarean deliver* ".af.
6	"C-section* ".af.
7	"Abdominal deliver* ".af.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	HEMORRHAGE/
10	"blood loss".af.
11	bleeding.af.
12	"haemorrhag*".af.
13	"hemorrhag*".af.
14	9 or 10 or 11 or 12 or 13
15	8 and 14
16	"trial*".af.
17	"comparative stud* ".af.
18	controlled.af.
19	"evaluation stud* ".af.
20	"follow up stud* ".af.
21	"longitudinal stud* ".af.
22	"non randomised".af.
23	"non randomized".af.
24	"program* evaluation* ".af.
25	"prospective stud* ".af.
26	randomised.af.
27	randomized.af.
28	"quantitative stud* ".af.
29	"quasi experimental".af.
30	"cohort*".af.
31	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	15 and 31
33	limit 32 to yr="1860 - 2019"

Appendix 2

Comparison of random versus fixed effects models

Group 1:





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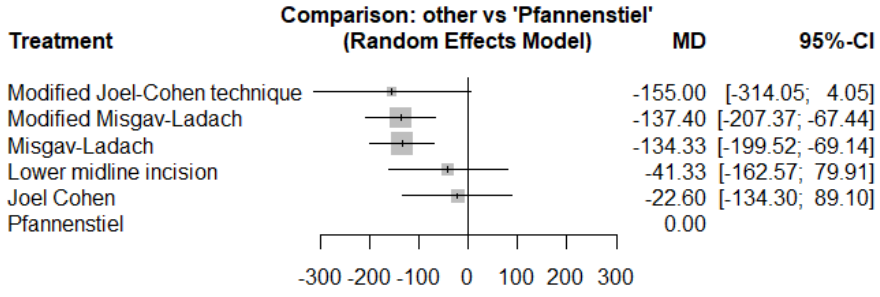

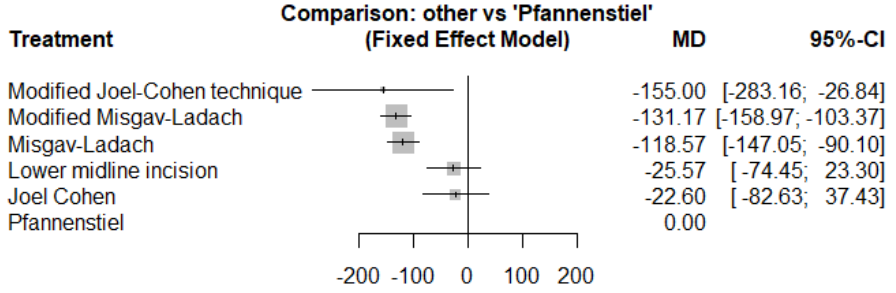

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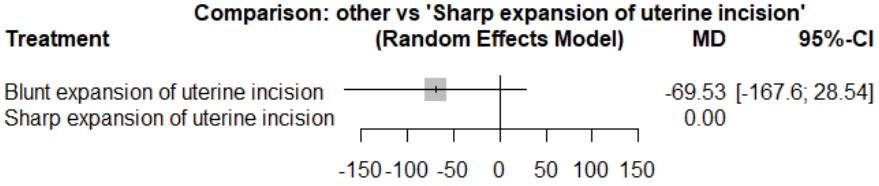

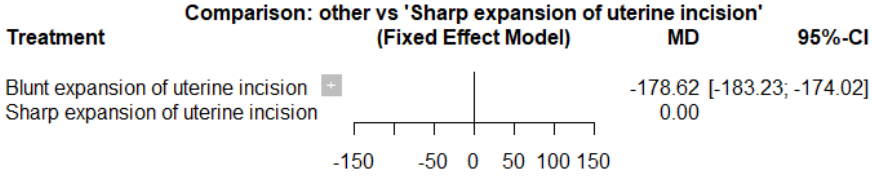

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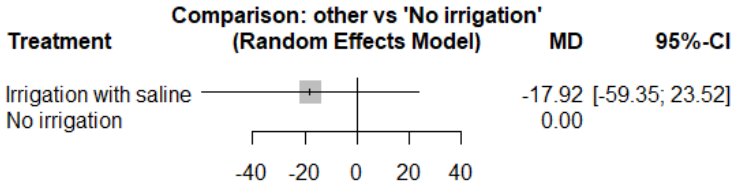

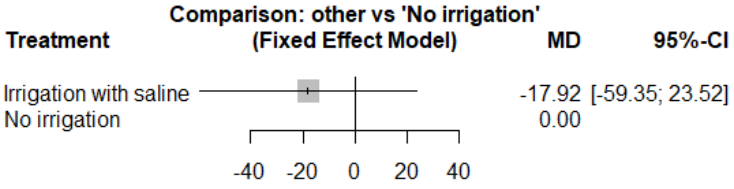

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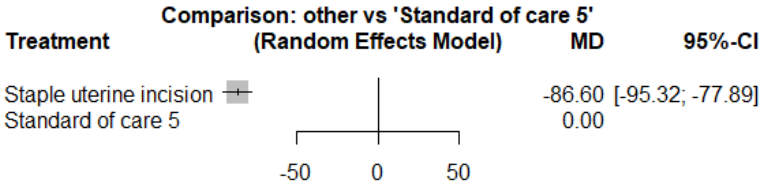

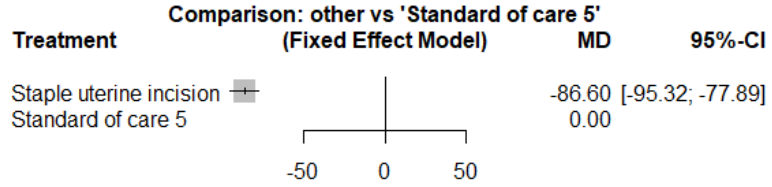

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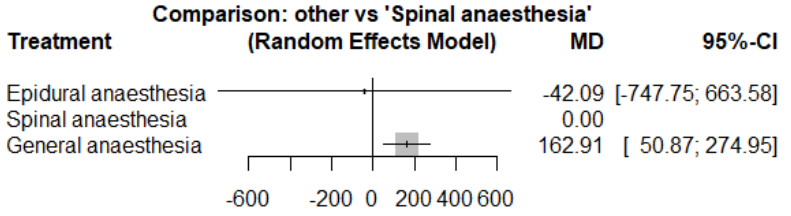
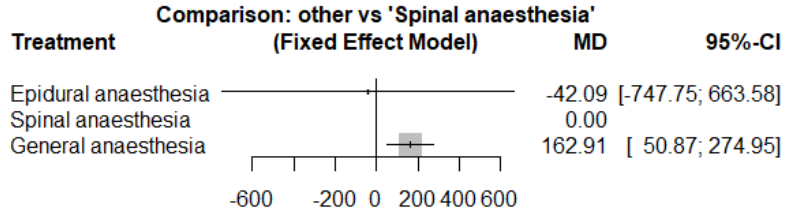
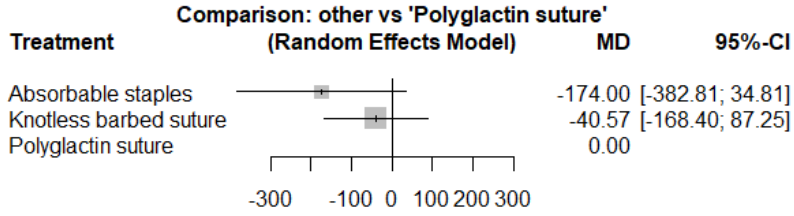
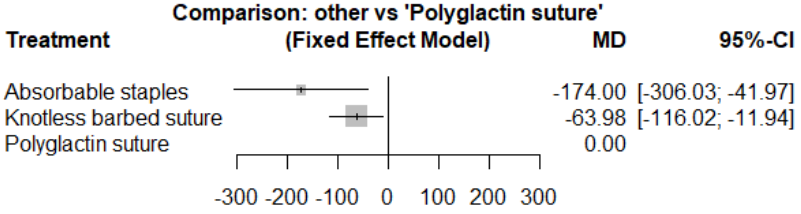




Group 7:





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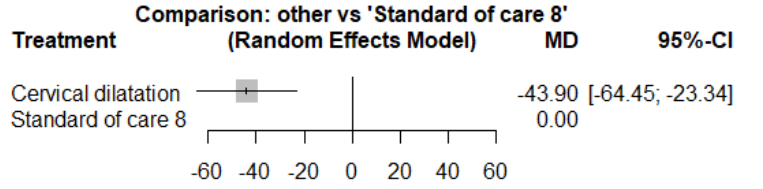

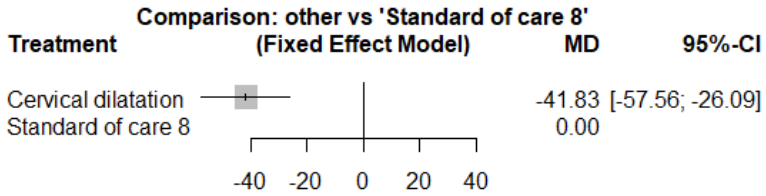

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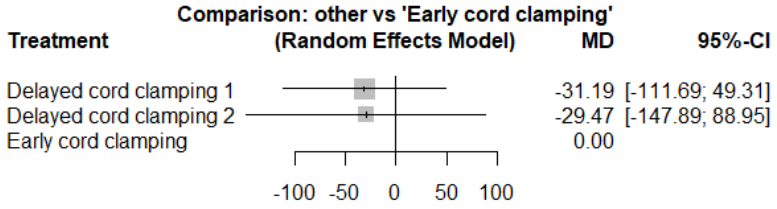

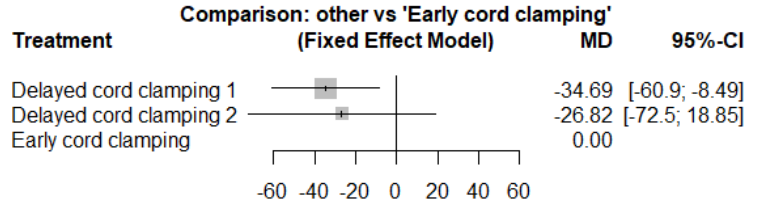

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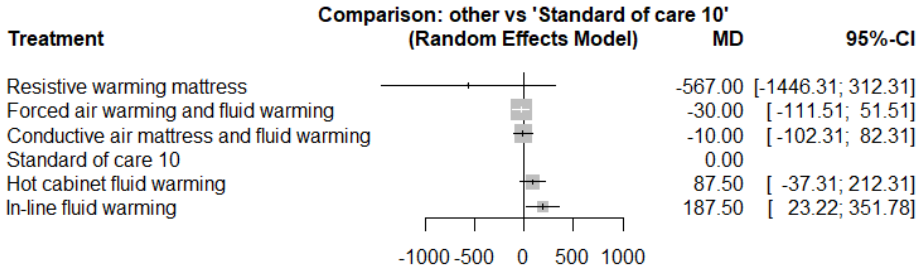

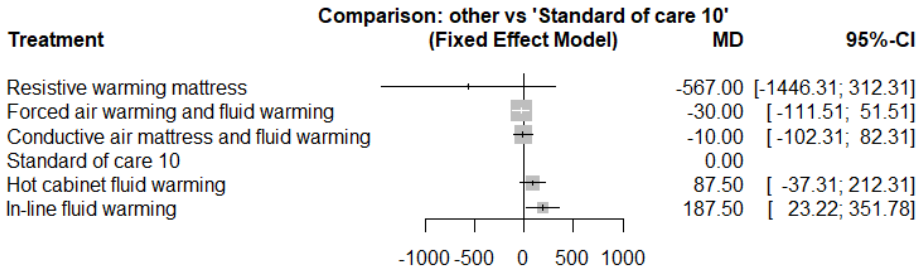

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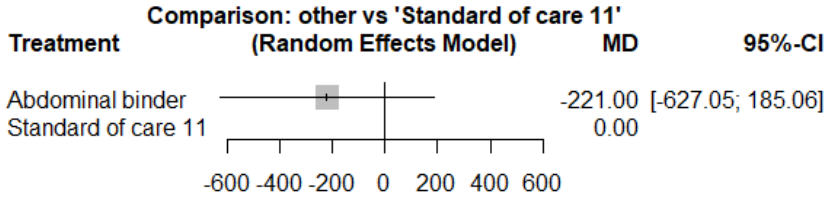

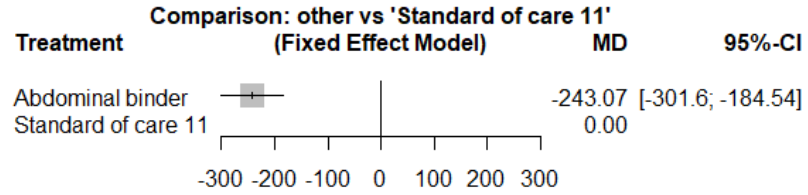

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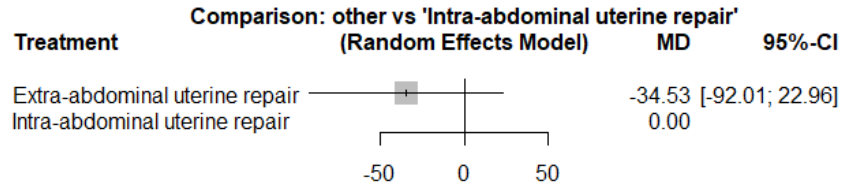

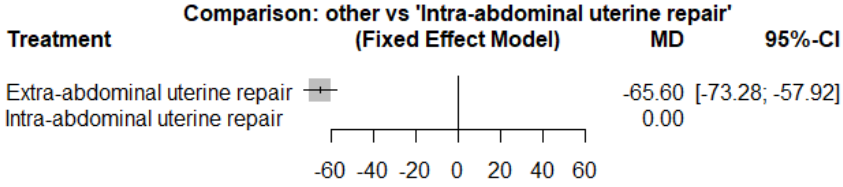

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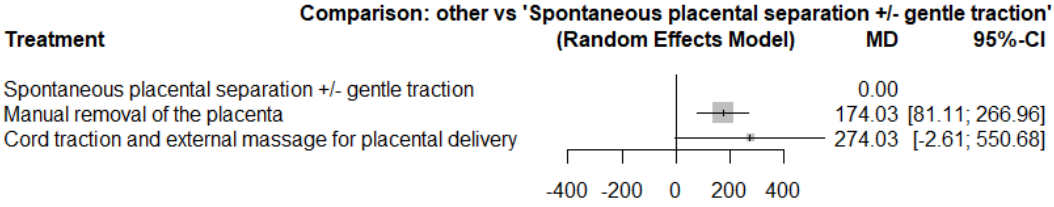
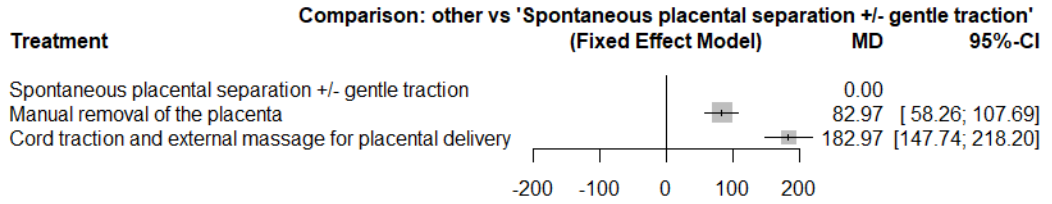

Comparison: other vs 'Spontaneous placental separation +/- gentle traction'
Treatment
(Random Effects Model)
MD
95%-CI
Spontaneous placental separation +/- gentle traction
Manual removal of the placenta
Cord traction and external massage for placental delivery
0.00
174.03 [81.11; 266.96]
274.03 [-2.61; 550.68]
-400 -200 0 200 400


Comparison: other vs 'Spontaneous placental separation +/- gentle traction'
Treatment
(Fixed Effect Model)
MD
95%-CI
Spontaneous placental separation +/- gentle traction
Manual removal of the placenta
Cord traction and external massage for placental delivery
0.00
82.97 [58.26; 107.69]
182.97 [147.74; 218.20]
-200 -100 0 100 200

Appendix 3

Meta-Analysis League Tables

Group 1:

Cervical inversion plus figure 8 suture	-479.97 (-497.27; -462.67)	
-479.97 (-497.27; -462.67)	Figure 8 suture	-136.36 (-235.98; -36.74)
-616.33 (-717.44; -515.22)	-136.36 (-235.98; -36.74)	Usual care

Group 2:

Joel Cohen	.	.	.	.	-22.60 (-134.30; 89.10)
18.73 (-146.12; 183.58)	Lower midline incision	93.00 (-9.22; 195.22)	.	.	.
111.73 (-17.59; 241.06)	93.00 (-9.22; 195.22)	Misgav-Ladach	.	14.00 (-81.33; 109.33)	-128.09 (-195.80; -60.39)
132.40 (-61.95; 326.75)	113.67 (-86.32; 313.66)	20.67 (-151.22; 192.56)	Modified Joel-Cohen technique	.	-155.00 (-314.05; 4.05)
114.80 (-16.99; 246.60)	96.07 (-32.90; 225.05)	3.07 (-75.57; 81.72)	-17.60 (-191.35; 156.16)	Modified Misgav-Ladach	-122.63 (-196.51; -48.76)
-22.60 (-134.30; 89.10)	-41.33 (-162.57; 79.91)	-134.33 (-199.52; -69.14)	-155.00 (-314.05; 4.05)	-137.40 (-207.37; -67.44)	Pfannenstiel

Group 3:

Blunt expansion of uterine incision	-69.53 (-167.60; 28.54)
-69.53 (-167.60; 28.54)	Sharp expansion of uterine incision

Group 4:

Irrigation with saline	-17.92 (-59.35; 23.52)
-17.92 (-59.35; 23.52)	Usual care

Group 5:

Usual care	86.60 (77.89; 95.32)
86.60 (77.89; 95.32)	Staple uterine incision

Group 6:

Epidural anaesthesia	-205.00 (-901.71; 491.71)	.
-205.00 (-901.71; 491.71)	General anaesthesia	162.91 (50.87; 274.95)
-42.09 (-747.75; 663.58)	162.91 (50.87; 274.95)	Spinal anaesthesia

Group 7:

Absorbable staples	.	-174.00 (-382.81; 34.81)
-133.43 (-378.25; 111.40)	Knotless barbed suture	-40.57 (-168.40; 87.25)
-174.00 (-382.81; 34.81)	-40.57 (-168.40; 87.25)	Polyglactin suture

Group 8:

Cervical dilatation	-43.90 (-64.45; -23.34)
-43.90 (-64.45; -23.34)	Usual care

Group 9:

Delayed cord clamping 1	30.00 (-99.08; 159.08)	-31.19 (-111.69; 49.31)
-1.72 (-120.70; 117.25)	Delayed cord clamping 2	1.00 (-126.82; 128.82)
-31.19 (-111.69; 49.31)	-29.47 (-147.89; 88.95)	Early cord clamping

Group 10:

Conductive air mattress and fluid warming	20.00 (-70.45; 110.45)	.	.	.	-10.00 (-102.31; 82.31)
20.00 (-70.45; 110.45)	Forced air warming and fluid warming	.	.	.	-30.00 (-111.51; 51.51)
-97.50 (-252.74; 57.74)	-117.50 (-266.57; 31.57)	Hot cabinet fluid warming	-100.00 (-284.18; 84.18)	.	87.50 (-37.31; 212.31)
-197.50 (-385.94; -9.06)	-217.50 (-400.89; -34.11)	-100.00 (-284.18; 84.18)	In-line fluid warming	.	187.50 (23.22; 351.78)

557.00 (-327.14; 1441.14)	537.00 (-346.08; 1420.08)	654.50 (-233.63; 1542.63)	754.50 (-140.03; 1649.03)	Resistive warming mattress	-567.00 (-1446.31; 312.31)
-10.00 (-102.31; 82.31)	-30.00 (-111.51; 51.51)	87.50 (-37.31; 212.31)	187.50 (23.22; 351.78)	-567.00 (-1446.31; 312.31)	Usual care

Group 11:

Abdominal binder	-221.00 (-627.05; 185.06)
-221.00 (-627.05; 185.06)	Usual care

Group 12:

Extra-abdominal uterine repair	-34.53 (-92.01; 22.96)
-34.53 (-92.01; 22.96)	Intra-abdominal uterine repair

Group 13:

Cord traction and external massage	100.00 (-160.57; 360.57)	.
100.00 (-160.57; 360.57)	Manual removal of the placenta	174.03 (81.11; 266.96)
274.03 (-2.61; 550.68)	174.03 (81.11; 266.96)	Spontaneous placental separation +/- gentle cord traction

Appendix 4

Summary table of included texts

Author, year	Location	Study design	Number of participants	Study Groups/Arms	Primary outcomes	Inclusion/ exclusion criteria	Study population characteristics	Blood loss outcomes *Mean (SD.*
**Denotes studies in which data has been extracted by the thesis author only at the time of writing*								
Group 1: Figure of 8 suture with or without cervical inversion								
Alalfy, 2019[47]	Egypt	Randomised controlled trial	240	G1) Cervical inversion G2) Control	Not stated	Inclusion: age 22-40 yr; 38 wk gestation; placenta previa; elective CS Exclusion: morbidly adherent placenta either accrete, increta, or percreta; chronic HTN; diabetes; haematological disease; heart disease; or any medical disorders with pregnancy; multifetal pregnancy	Age, mean (SD): 1) 30 (3.92) 2) 30.1 (4.72) BMI, mean (SD): not stated Emergency CS, %: 0	G1: 1252.7 (36.6) ml G2: 1732.7 (89.5) ml
Shan, 2018[48]	China	Randomised controlled trial	110	G1) Repair group G2) Control	Blood loss in the 1st 24 hours and rate of PPH	Inclusion: singleton pregnancy, GA >= 39 weeks, one previous CS Exclusion: age below 20 or above 45 years; pregnancy related complications such as intrahepatic cholestasis of pregnancy, gestational diabetes, hypertensive disorders and placental abnormalities. Vital organ dysfunctions before gestation.	Age, mean (SD): G1) 37.5 (2.6) G2) 38.5 (3.42) BMI, mean (SD): G1) 23.1 (2.3) G2) 22.4 (2.3) Emergency CS, %: 0	G1 median (IQR): 523.6 (254) ml G2: 660 (278.6) ml PPH G1: 4/55 PPH G2: 7/55
Group 2: Caesarean delivery surgical technique								
Bjorklund, 2000[50]	Tanzania	Randomised controlled trial	340	G1) Misgav Ladach G2) Lower midline incision	Not stated	Inclusion: emergency or elective CS after an estimated 37 full weeks of gestation Exclusion: repeat CS, and those with previous abdominal surgery (except for appendectomy or corresponding other lesser abdominal procedures); known severe anaemia (including sickle cell); diabetes mellitus; bleeding disorder; intrapartum febrile illness; uterine rupture; and a history of postpartum haemorrhage	Age, mean (SD): G1) 24.2 (range 15-39) G2) 23.9 (range 16-36) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 97	G1: 354 (165) ml G2: 447 (206) ml
*Darj, 1999[50]	Sweden	Randomised controlled trial	50	G1) Misgav Ladach G2) Pfannenstiel	Not stated	Inclusion: elective CS at term; 1st CS; no previous abdominal operation Exclusion: not stated	Age, mean (SD): G1) 29.6 (range 21-40) G2) 29.3 (21-37) BMI, mean (SD)	G1: 448 (range 100-1000) ml G2: 608 (300-1000) ml

							G1) not stated G2) not stated Emergency CS, %: 0	
*Ezechi,2013[51]	Nigeria	Randomised controlled trial	323	G1) Misgav Ladach G2) Pfannenstiel	Not stated	Inclusion: not stated Exclusion: antepartum hemorrhage; prolonged obstructed labor; chorioamnionitis; preoperative hemoglobin less than 10 g/dl; prolonged premature rupture of membrane and clinically palpable uterine fibroid	Age, mean (SD): G1) 27.9 (4.9) G2) 28 (5.4) BMI, mean (SD) G1) 24.5 (5.5) G2) 24.2 (4.4) Emergency CS, %: G1) 58.6% G2) 56.2%	G1: 553.6 (259.5) G2: 734.9 (333.5)
*Ferrari, 2001[52]	Italy	Randomised controlled trial	158	G1) Modified surgical technique G2) Pfannenstiel	Not stated	Inclusion: gestation age >30 weeks, no previous caesarean section, eligibility for caesarean section by the Pfannenstiel incision technique w 7 Exclusion: History of lower abdominal surgery	Age, mean (SD): G1) 31.7 (0.53) G2) 30.7 (0.56) BMI, mean (SD) G1) 22.81 (0.43) G2) 21.85 (0.45) Emergency CS, %: G1: 54.2 G2: 42.7	G1 (standard error): 348.3 (21.25) G2 standard error: 370.9 (22.06)
Min, 2001[53]	China	Randomised controlled trial	172	G1) Modified Misgav Ladach Technique G1) Misgav Ladach G3) Pfannenstiel Technique	Not stated	Inclusion: all caesarean deliveries Exclusion: not stated	Age, mean (SD): G1) not stated G2) not stated G3) not stated BMI, mean (SD) G1) not stated G2) not stated G3) not stated Emergency CS, %: not stated	G1: 128 (35) G2: 142 (45) G3: 212 (147)
*Sahin, 2016[54]	Turkey	Randomised controlled trial	252	G1) Pfannenstiel G2) Modified Misgav-Ladach	Duration of surgery (between skin incision and skin closure), extraction time (until delivery of the neonate), Apgar score, blood loss, wound complications, and number of sutures used.	Inclusion: A gestational age >36 weeks, the first C/S (the women could have delivered vaginally before) and an obstetric indication for C/S Exclusion: Presence of any additional surgical procedure, such as myomectomy, cystectomy or tubal ligation, placenta previa, placental abruption, preeclampsia, eclampsia, or HELLP syndrome.	Age, mean (SD): G1) 30.2 (5.4) G2) 31.4 (4.7) BMI, mean (SD) G1) 30.23 (5.09) G2) 29.22 (3.97) Emergency CS, %: not stated	G1: 370 (251) G2: 205 (146)
Wallin, 1999[55]	Sweden	Randomised controlled trial	72	G1) modified Joel-Cohen technique G2) Pfannenstiel technique	Operating time and blood loss during surgery	Inclusion: elective caesarean delivery Exclusion: history of lower abdominal surgery	Age, mean (SD): G1) 30.8 (4.7) G2) 29.9 (4.4) BMI, mean (SD) G1) not stated G2) not stated	Median (IQR) G1: 250 (179-500) G2: 400 (300-694)

							Emergency CS, %: 0	
Group 3: Blunt versus sharp expansion of the uterine incision								
*Asicioglu, 2014[56]	Turkey	Randomised controlled trial	1076	G1) Sharp Expansion of uterine incision G2) Blunt expansion of uterine incision	Incidence of unintended extension	Inclusion: aged 18 - 40 yrs.; elective CS; >38 weeks' gestation Exclusion: emergency surgery; planned caesarean hysterectomy; cases with high risk of bleeding (e.g., HELLP syndrome, preeclampsia, placental insertion anomalies, abnormal placentation, grand multiparity, or multiple pregnancy); women in whom either a low segment vertical uterine or classical upper segment was utilized	Age, mean (SD): G1) 28.9 (3.4) G2) 29.13 (3.1) BMI, mean (SD) G1) 28.6 (3.35) G2) 28.2 (3.11) Emergency CS, %: 0	G1: 853.67 (42) G2: 664.8 (38) PPH: G1: 61/535 G2: 37/541
Magann, 2002[57]	USA	Randomised controlled trial	945	G1) Blunt expansion of the uterine incision G2) Sharp expansion of the uterine incision	Not stated	Inclusion: primary or repeat low segment transverse uterine incision Exclusion: emergency surgery with insufficient time to counsel the patient; women in whom either a low segment vertical uterine or a classical upper segment were utilised.	Age, mean (SD): G1) 24.4 (6.2) G2) 24.7 (6.3) BMI, mean (SD) G1) 34.2 (8.7) G2) 33.7 (8.5) Emergency CS, %: not stated	G1: 843 (164) G2: 886 (197)
*Sekhavat, 2010[58]	Iran	Randomised controlled trial	200	G1) Blunt expansion of uterine incision G2) sharp expansion of the uterine incision	Not stated	Inclusion: Primiparous women undergoing elective CS, with fondal placenta and lower segment transverse incision on uterus. Exclusion: Severe medical and surgical disorders, having blood disorders and anaemia, history of thromboembolic disorders, multiple pregnancies, macrosomia, polyhydramnios, women undergoing emergency surgery, such as placenta-abruptia, placenta-previa, and pregnancy complications, such as severe preeclampsia.	Age, mean (SD): G1) 24.3 (4.5) G2) 25.1 (4.9) BMI, mean (SD) G1) 26.6 (3.9) G2) 27.4 (3.1) Emergency CS, %: 0	G1: 375 (95) G2: 443 (86)
*Shamsi, 2005[59]	Pakistan	Non-randomised controlled trial	100	G1) Sharp Expansion of Uterine Incision G2) Blunt Explansion of the uterine incision	Not stated	Inclusion: para five or less with singleton full term pregnancy; BMI <30, primary or repeat lower segment CS; preoperative haematocrit >30%. Exclusion: those at high risk for postpartum haemorrhage i.e multiple pregnancy, polyhydramnios, antepartum, haemorrhage, placenta praevia, abruptio placenta, previous history of postpartum haemorrhage, obstructed labour, and fibroid uterus	Age, mean (SD): G1) 27.62 (5.09) G2) 26.62 (5.15) BMI, mean (SD) G1) 26.64 (1.61) G2) 27.16 (1.43) Emergency CS, %: G1) 56% G2) 64%	G1: 750.4 (247.99) G2: 805.8 (326.95)
Group 4: Normal saline irrigation of the abdominal cavity								
Harrigill, 2003[60]	USA	Randomised controlled trial	196	G1) Irrigation of abdominal cavity G2) Non-rrigation	Incidence of maternal morbidity, defined as the presence of at least one of the following: postoperative infectious morbidity (endometritis, cellulitis, urinary tract	Inclusion: all women presenting with term singleton pregnancies; undergoing routine caesarean delivery for arrest of dilation, arrest of descent, fetal malpresentation, or as an elective repeat procedure Exclusion: chorioamnionitis; type I diabetes; placenta previa; placenta 113ccrete; maternal coagulopathy; multiple gestation; human immunodeficiency virus–positive status; prior severe gastrointestinal disease; or non-reassuring foetal monitoring requiring immediate delivery	Age, mean (SD): G1) 28.2 (6.1) G2) 27.5 (6.9) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 710 (178) G2: 755 (298.7) PPH: G1: 1/97 G2: 2/99

					infection, septic pelvic thrombophlebitis), postpartum haemorrhage, severe anaemia, and urinary retention			
Viney, 2012[61]	USA	Randomised controlled trial	236	G1) Irrigation of abdominal cavity G2) No irrigation	Maternal GI disturbances during CS delivery defined as nausea with or without emesis intraoperatively.	Inclusion: English speaking; ≥18 years Exclusion: Urgent or emergent clinical situations where obtaining consent will affect care	Age, mean (SD): G1) 27.13 (6.10) G2) 26.85 (5.72) BMI, mean (SD) G1) 35.59 (9.6) G2) 35.13 (9.36) Emergency CS, %: not stated	G1: 861.95 (209.9) G2: 864.37 (195.1)
Group 5: Staple uterine incision								
Gilson, 1996[62]	USA	case-control study	288	G1) Stapled closure of uterus G2) Sutured closure of the uterus (standard hysterotomy)	Not stated	Inclusion: Elective repeat caesarean deliveries and those having their surgery because of an indication arising during labour Exclusion: Emergency caesarean delivery for acute severe foetal intolerance of labour, defined as severe (fewer than 60 beats per minute) and prolonged (longer than 5 minutes) foetal bradycardia unresponsive to conservative measures.	Age, mean (SD): G1) 27.4 (5.8) G2) 27.1 (6.3) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 822 (338) G2: 879 (318)
Villeneuve, 1990[63]	Canada	Randomised controlled trial	200	G1) Staple hysterotomy G2) Standard hysterotomy	Not stated	Inclusion: All CS performed during study period Exclusion: not stated	Age, mean (SD): G1) 29.4 (0.4) G2) 29.5 (0.4) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 492 (24) G2: 579 (38)
Group 6: Anaesthesia technique								
*Afolabi, 2003[64]	Nigeria	Non-Randomised controlled trial	78	G1) General Anaesthesia G2) Spinal Anaesthesia	Not stated	Inclusion: Undergoing emergency CS. For the purpose of this study, emergency CS refers to one carried out because of a perceived risk to the life of the mother or fetus, or for any reason after the onset of labour. Exclusion: patients who had exploratory laparotomy for ruptured uterus were not included in this study, as foetal demise has already occurred in such cases. All cases of intrauterine death before commencement of the operation were excluded, as the neonatal outcome in such cases would not have depended on the type of anaesthesia used. Cases of foetal distress were also excluded from the study.	Age, mean (SD): G1) 30.3 (4.3) G2) 30.4 (4.3) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 100	G1: 539 (340.8) G2: 405 (230.5)
Hong, 2003[65]	South Korea	Randomised controlled trial	25	G1) General anaesthesia G2) Epidural anaesthesia	Not stated	Inclusion: grade 4 placenta previa without bleeding scheduled for elective CS Exclusion: not stated	Age, mean (SD): G1) 32.5 (4.2) G2) 32.4 (4.2) BMI, mean (SD) G1) not stated G2) not stated	G1: 1623 (775) G2: 1418 (996)

							Emergency CS, %: 0	
Mohamed, 2019[66]	Egypt	Randomised controlled trial	80	G1) Spinal anaesthesia G2) General Anaesthesia	Not stated	Inclusion: Placenta praevia major (Grade 3/4), CS delivery Exclusion: Placenta praevia minor (Grade 1/2), active bleeding, abruption placenta, major congenital abnormalities, severe maternal anaemia (<8g/dl), patient refusal	Age, mean (SD): G1) 28.2 (6.1) G2) 27.6 (6.3) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 1835 (477) G2: 2086 (549)
Group 7: Material for uterine closure								
Grin, 2019[67]	Isreal	Randomised controlled trial	73	G1) Bidirectional knotless barbed suture (BKBS) G2) polyglactin suture	Time required for uterine incision repair.	Inclusion: women who had no more than two previous deliveries by CS. Exclusion: lack of consent or an urgent CS not allowing time to elicit an informed consent, suspected placenta accreta, and a known blood clotting disorder.	Age, mean (SD): G1) 32.4 (5.4) G2) 32.9 (6.1) BMI, mean (SD) G1) 30.7 (5.9) G2) 32.6 (6.4) Emergency CS, %: not stated	G1: 735(248) G2: 704 (168)
Peleg, 2018[68]	Israel	Randomised controlled trial	102	G1) Knotless Barbed suture G2) Conventional suture material	Duration of uterine incision closure	Inclusion: elective CS; in labor with obstetric indication for CS; failed trial of previous CS uterine scar Exclusion: unable to consent; general anaesthesia; chorioamnionitis; maternal diabetes; preeclampsia; placental abruption; thrombophilia; maternal medications affecting coagulation; known anterior low segment myomas; placenta previa or accreta; multiple gestation; previous classical or inverted T incision; or those requesting TL	Age, mean (SD): G1) 32.2 (6.2) G2) 33.0 (5.0) BMI, mean (SD) G1) 30.07 (5.08) G2) 30.5 (5.01) Emergency CS, %: not stated	G1: 500 (168.5) G2: 600 (145.6)
Group 8: Cervical dilatation								
*Alalfy, 2019[70]	Egypt	Randomised controlled trial	1200	G1) Cervical dilatation extraction of placenta G2) Control group	Postoperative pain	Inclusion: study subjects age range from 18 to 40 years old, Gestational age at time of caesarean delivery was above 37 gestational weeks, Singleton pregnancies, free medical history (e.g., no DM, preeclampsia), nulliparous women that have undergone their first elective CS at term or multiparous ladies who were delivered by CS in their preceding gestations with no labour pain in both categories of cases. Exclusion: the onset of labour with cervical dilatation or cases that felt labour pain before their previous caesarean deliveries, prolonged premature rupture of membranes, fever on admission or ongoing infection (e.g. chorioamnionitis), current antibiotic therapy; requirement for blood transfusion or blood products during or after caesarean delivery performance, emergency caesarean delivery, and preterm CS; pre-existing maternal medical disease, e.g. DM, cases with risk factors for postpartum haemorrhage, e.g. placenta previa, cases having chronic pelvic pain.	Age, mean (SD): G1) 28.01 (4.53) G2) 28.36 (5.41) BMI, mean (SD) G1) 32.18 (3.19) G2) 32.47 (3.38) Emergency CS, %: 0	G1: 633.2 (213.46) G2: 662.85 (151.61)
*El-Sharkawy, 2019[71]	Egypt	Randomised controlled trial	774	G1) Cervical dilatation G2) No cervical dilatation	Mean volume of total blood loss during CS	Inclusion: pregnant women with a single term foetus >37 weeks of gestational age, with American Society of Anaesthesiology (ASA) physical status I or II Exclusion: women need emergency CS, those with placenta previa, rupture of membranes, chorioamnionitis,	Age, mean (SD): G1) 28.3 (2.5) G2) 28.8 (2.6) BMI, mean (SD) G1) 29.3 (2.4)	G1: 845.8 (188.9) G2: 912.6 (242.1)

						multiple gestation, polyhydramnios, anaemia, preeclampsia, diabetes mellitus, cardiac diseases, liver, renal disorders and known coagulopathy.	G2) 28.7 (2.6) Emergency CS, %: 0	PPH: G1: 5/205 G2: 3/242
Güngördük, 2009[72]	Turkey	Randomised controlled trial	400	G1) Cervical Dilatation G2) No cervical dilatation	rate of post-partum endometritis	Inclusion: elective caesarean delivery, more than 37 weeks' gestation. Exclusion: use of antibiotics during the last 24 h, pathology that should be treated with antibiotics, pre-existing maternal diseases, chorioamnionitis, fever on admission, need of transfusion before or during the CS, ruptured membranes, emergency CS and preterm CS	Age, mean (SD): G1) 26.52 (4.26) G2) 27.69 (4.14) BMI, mean (SD) G1) 31.60 (3.09) G2) 32.12 (2.67) Emergency CS, %: 0	G1: 645.58 (232.04) G2: 693.49 (174.78)
Kirscht, 2016[73]	Germany	Randomised controlled trial	447	G1) Dilatation of the cervix during CS G2) No dilatation of the cervix during CS	PPH (defined as blood loss of at least 1000 ml) within 6 weeks	Inclusion: Pregnant women for elective CS Exclusion: current antibiotic therapy, chorioamnionitis, onset of labour with	Age, mean (SD): 1) 31.7 (5.4) 2) 31.4 (5.6) BMI, mean (SD) 1) 26.6 (6.8) 2) 26.1 (6.2) Emergency CS, %: 0	G1: not stated G2: not stated PPH: G1: 5/205 G2: 3/242
*Osemwemkha, 2013[74]	Nigeria	Randomised controlled trial	142	G1) Cervical dilatation G2) Control		Inclusion: Parturient with intact membranes that had elective caesarean delivery (performed before the onset of labour) at 36 -42 weeks' gestation Exclusion: Parturient with human immunodeficiency virus infection, Diabetes complicating pregnancy, multi -foetal pregnancy, placenta praevia and suspected clinical evidence of infection. Women with history of antibiotic use during the last 24 h, packed cell volume <30% or haemoglobin concentration <10 g/dl, blood transfusion during CS were also not eligible for this study.	Age, mean (SD): G1) 32.4 (5.2) G2) 31.6 (3.4) BMI, mean (SD) G1) 31.6 (5.6) G2) 31.4 (5.0) Emergency CS, %: 0	G1: 516 (348) G2: 533 (286)
Group 9: Early versus delayed umbilical cord clamping								
Withanathantrige, 2017[75]	Sri Lanka	Randomised controlled trial	156	G1) early cord clamping under 15 secs G2) delayed cord clamping between 60-75 secs G3) delayed cord clamping between 120-135 seconds	Operative blood loss (ml), Time duration for placental delivery, Need for MRP after 5 minutes, need for additional uterotonics, Post-operative haemoglobin reduction, Post-operative haematocrit reduction, Neonatal jaundice requiring phototherapy	Inclusion: intact membranes and healthy foetuses, who underwent antepartum LSCS between 37- 39 weeks' gestation Exclusion: increased risk of feto-maternal haemorrhage or post-operative haemorrhage, rhesus negative, multiple pregnancies, estimated fetal weight >3.5 kg, polyhydramnios, blood pressure >160/110mmHg, placenta praevia, abruptio placentae, pre-labour rupture of membranes and failed induction of labour.	Age, mean (SD): G1) 32.6 (95%CI) 30.8-34.4 G2) 30.7 (95%CI)29.1-32.3 G3) 30.2 (95%CI)28.8-32.6 BMI, mean (SD) G1) 25.7 (95%CI) 24.8-26.6 G2) 24.9 (95%CI)24.1-25.7 G3) 25.5 (95%CI)24.5-26.5 Emergency CS, %: 0	G1: 492 (95%CI) 462-522 G2: 523 (95%CI)488-558 G3: 493 (95%CI)455-531
Cavallin, 2019[76]	Italy	Randomised controlled trial	80	G1) Delayed cord clamping G2) Early cord clamping	Neonatal haematocrit at day 2 of life.	Inclusion: Elective CS (no labour), greater than or equal to 39 weeks, singleton gestation, consent Exclusion: Multiple gestations and newborns with major congenital malformations and/or chromosomic abnormalities, those with intrauterine growth restriction and/or foetal hydrops, and those with cord abnormalities	Age, mean (SD): G1) not stated G2) not stated BMI, mean (SD) G1) not stated G2) not stated	G1: 469 (292) G2: 563 (415)

						(i.e., a length <20 cm, funicular prolapse, or funicular knots)	Emergency CS, %: not stated	
Purisch, 2019[77]	USA	Randomised controlled trial	113	G1) Delayed cord clamping G2) Immediate cord clamping	Change in maternal haemoglobin level from preoperative to postoperative day 1	Inclusion: Women with singleton gestations undergoing scheduled caesarean delivery at term (at or beyond 37 weeks 0 days) Exclusion: Women for whom a delay in umbilical cord clamping might adversely affect maternal or neonatal outcomes- Specifically, those with placenta previa or placenta abruption, prenatally diagnosed foetal anomalies, known foetal anaemia, or foetal growth restriction with abnormal Dopplers. Women with pre-eclampsia, significant maternal anaemia (pre-operative haemoglobin level ≤7 g/dL), bleeding disorders, planned cord blood banking, or refusal of blood products. Women with caesarean deliveries scheduled on weekends or postponed to evening hours were deemed ineligible for participation.	Age, mean (SD): G1) 31.6 (5.5) G2) 33.5 (4.9) BMI, median (IQR) G1) 27.9 (23.9-31.2) G2) 26.6 (23.8-30.4) Emergency CS, %: 0	G1: 800 IQR: [800-1000] G2: 800 IQR: [800-1000] PPH: G1: 5/57 G2: 4/56
*Sun, 2015[78]			338	G1) Delayed cord clamping <60 secs G2) Early cord clamping >60 secs		Inclusion: Women in caesarean section, single detus, women in normal physiological condition, and women willing to participate in the study. Exclusion: Women and family refusing to participate, women that had severe pregnant complications such as: previa of placenta, postpartum bleeding, heart disease, diabetes with the need for insulin therapy, rupture of uterus, and twin pregnancy.	Age, mean (SD): G1) 27.71 (3.83) G2) 28.47 (4.23) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 156.78 (87.415) G2: 221.627 (197.234)
Group 10: Fluid and mattress warming								
Chebbout, 2017[79]	UK	Randomised controlled trial	132	G1) Forced air warming (FAW) G2) Conduction air mattress (CAM) G3) Standard care	Mean core temperature on entry to the recovery room.	Inclusion: elective CS, with or without tubal ligation surgery (sterilisation), under spinal anaesthesia, with a singleton uncomplicated pregnancy Exclusion: age <18 years; body mass index (BMI) <19 or >31 kg/m2; multiple pregnancy; coexisting maternal disease; pregnancy-induced disease; coagulation abnormality; thyroid disease; expected complex procedure; or grand multiparity	Age, mean (SD): G1) 32 (5.7) G2) 31.8 (5.4) G3) 31.6 (5.8) BMI, mean (SD) G1) 25.0 (3.1) G2) 24.9 (3.2) G3) 25.4 (3.2) Emergency CS, %: 0	G1:520 (190) G2: 540 (240) G3: 550 (200)
Chakladar, 2014[80]	UK	Randomised controlled trial	119	G1) Mattress Warming G2) Control	Incidence of postoperative hypothermia (defined as core temperature <36.0°C on admission to the recovery room)	Inclusion: All women undergoing elective CS Exclusion: Women who were unable to fully understand the trial and those aged <16 years	Age, mean (SD): G1) 33.6 (5.8) G2) 34.3 (5.9) BMI, mean (SD) G1) 24.8 (4.4) G2) 25.7 (5.9) Emergency CS, %: 0	G1: 500 (100-2500) G2: 600 (200-4000)
*Woolnough, 2009[81]	UK	Randomised controlled trial	75	G1) Room Temp fluid G2) Cabinet G3) Hotline fluid warmer	Temperature at 60 min from the time of combined spinal epidural insertion (CSE)	Inclusion: healthy women with uncomplicated single pregnancies, due for elective caesarean section at >37 weeks of gestation Exclusion: pyrexia, preeclampsia/eclampsia, drug therapy other than antacids and vitamins/minerals, and increased risk of intra-operative haemorrhage (such as placenta praevia or accreta).	Age, mean (SD): G1) 34.8 (5) G2) 35.8 (3.8) G3) 34.4 (4.7) BMI, mean (SD) G1) 26.8 (6.9) G2) 25.1 (5.4) G3) 25.1 (3.5) Emergency CS, %: 0	Median (IQR): G1: 500 (500-700) G2: 500 (500-800) G3: 500 (500-700)
Group 11: Abdominal binder								

Gustafson, 2018[83]	USA	Randomised controlled trial	60	G1) Abdominal binder G2) Usual Care	Postoperative pain	Inclusion: caesarean delivery at term (at least 39 weeks' gestation) scheduled in advance, singleton gestation confirmed by ultrasound in the current pregnancy, aged 18 - 39 years old, were able to read and understand spoken English, and had a body mass index of 20kg/m2 to 40 kg/m2 pre-pregnancy or at the first prenatal visit. Exclusion: bleeding disorder or use of anticoagulants, methadone usage, abnormal placenta (placenta previa or placenta accreta), preoperative haemoglobin less than 10mg/dL, or chorioamnionitis (intrauterine infection). Patients that had chronic pain syndrome, defined as participating in formal chronic pain management within the past year. Also, if onset of labour occurred prior to the time when the caesarean was scheduled, or if the following complications developed during the caesarean: placental abnormality (placenta accreta, increta, or percreta), vasa previa, caesarean hysterectomy due to severe haemorrhage, or organ damage (cystotomy, enterotomy, ureteral injury).	Age, mean (SD): G1) 28.5 (4.7) G2) 27.7 (4.4) BMI, mean (SD) G1) 28.9 (6.6) G2) 28.6 (6.3) Emergency CS, %: 0	G1: 655.17 (183.39) G2: 668.52 (150.73)
Ghana, 2017[82]	Iran	Randomised controlled trial	178	G1) Abdominal Binder G2) Control	Pain, measured using a visual analogue scale (VAS); distress, measured using the SDS; and haemoglobin and haematocrit levels (Haemoglobin and haematocrit levels were measured and Volume of blood lost was calculated using the formula of Shook et al.)	Inclusion: parity of 1 or 2 during the index pregnancy, to be literate, to have delivered at term after a singleton uncomplicated pregnancy, to have undergone Pfannenstiel incision on the skin and Kerr incision on the uterus at the site of a previous caesarean delivery (if any), to have a body mass index (calculated as weight in kilograms divided by the square of height in meters) of 18.5–25.9, and to have a haemoglobin level of >110 mg/L during the first trimester Exclusion: unable to tolerate the binder, were not willing to participate, were currently smokers or using opioids, had experienced rupture of membranes for longer than 6 hours, had any self-reported underlying disease, had a surgical duration longer than 1 hour, had undergone classic incision of the uterus, had undergone any concurrent surgeries (such as hysterectomy, myomectomy, or tubal ligation), had pre-eclampsia or eclampsia, had severe haemorrhage or haemorrhage leading to hysterectomy, had bleeding disorders or were using anticoagulants (such as heparin or warfarin), had experienced damage to body tissues during caesarean delivery, had undergone an emergency caesarean delivery, or had received general anaesthesia.	Age, mean (SD): G1) Query to check G2) BMI, mean (SD) G1) 22.6 (2.3) G2) 23.3 (2.4) Emergency CS, %: 0	G1: [201.8] [105.6-340] G2: [630.5] [428–872]
Group 12: Extra-abdominal versus intra-abdominal uterine repair								
Coutinho, 2008[84]	Brazil	Randomised controlled trial	670	G1) Extra-abdominal uterine repair G2) In situ uterine repair	Not stated	Inclusion: women with an indication for caesarean delivery (emergency or elective), with gestational age greater than 24 weeks, Exclusion: repeat caesarean deliveries (history of two or more caesarean deliveries), chorioamnionitis, history of previous surgery (gynaecologic or abdominal), third-	Age, mean (SD): G1) 24.7 (6.1) G2) 25.6 (6.3) BMI, mean (SD) G1) 29.8 (5.0) G2) 29.2 (4.9) Emergency CS, %: 0	G1: not stated G2: not stated PPH: G1: 186/325 G2: 179/312

						semester haemorrhage or active gastrointestinal bleeding or both, and inability to consent		
*El-Khayat, 2014[85]	Egypt	Randomised controlled trial	1050	G1) Exteriorized uterine repair G2) In-situ Uterine repair	Surgery duration (time from the start of the skin incision until the end of the last suture)	Inclusion: All pregnant women with an indication for caesarean delivery Exclusion: chorioamnionitis, a high-risk pregnancy, a large uterine fibroid, pre-eclampsia, a bleeding disorder, or abnormal placentation	Age, mean (SD): G1) 27.1 (1.9) G2) 27.0 (2.0) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: G1) 59.6% G2) 59%	G1: not stated G2: not stated PPH: G1: 284/500 G2: 290/500
Orji, 2008[86]	Nigeria	Randomised controlled trial	210	G1) exteriorisation of uterus for repair G2) Non-exteriorisation of uterus	Decrease in packed cell volume at 48hrs post-op; estimated intraoperative blood-loss	Inclusion: caesarean delivery Exclusion: severe intra-abdominal adhesions and large fibroids preventing exteriorisation, history of venous embolism, bleeding disorder, cardiac defects, non-transverse uterine incision	Age, mean (SD): G1) 29.8 (6.6) G2) 29.5 (6.1) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: G1) 76.2 G2)86.7	G1: 459.8 (95.8) G2: 546.8 (156.1)
*Ezechi, 2005[87]	Nigeria	Randomised controlled trial	127	G1) closure after temporary exteriorisation of uterus G2) intraperitoneal closure	Not stated	Inclusion: women undergoing primary CS Exclusion: patients with antepartum haemorrhage, previous CS, multiple pregnancy, ruptured uterus, prolonged rupture of membrane, haemoglobin of less than 11g/dl, prolonged obstructed labour, clinically palpable fibroid and failed exteriorisation when the case is already randomised to exteriorisation group	Age, mean (SD): G1) 29.1 (4.5) G2) 29.3 (4.8) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 742 (328.9) G2: 872 (270.3)
*Mohr-Sasson, 2020[88]	Israel	Randomised controlled trial	95	G1) Intraperitoneal uterine repair G2) Extraperitoneal uterine repair	Any operative complication including excessive blood loss (>500 cc), intraoperative nausea, vomiting, and intraoperative pain.	Inclusion: elective operation and gestational age 37 weeks Exclusion: abnormal placentation, chorioamnionitis, previous other abdominal surgery, past complication during the first CD on operation report, bleeding disorder, or urgent operation	Age, mean (IQR): G1) 35 (31-38) G2) 34 (30-37) BMI, mean (SD) G1) 38.3 (38.2-39.5) G2) 38.3 (38.1-39.5) Emergency CS, %: 0	G1: 540 (29.83) G2: 452 (10.44)
*Siddiqui, 2007[89]	Canada	Randomised controlled trial	80	G1) exteriorized uterine repair G2) in situ uterine repair	Intraoperative, postdelivery nausea or vomiting	Inclusion: Term pregnant patients undergoing elective caesarean delivery Exclusion: Medical or obstetric conditions that could put them at risk for uterine atony and postpartum haemorrhage, such as placenta previa, multiple gestation, preeclampsia, macrosomia, hydramnios, and uterine leiomyomata.	Age, mean (SD): G1) 33 (4.7) G2) 34.1 (5.1) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 625 (489) G2: 653 (16)
*Abdellah, 2019[90]	Egypt	Randomised controlled trial	1120	G1) uterine exteriorization G2) intraperitoneal repair	Rate of intraoperative nausea and vomiting.	Inclusion: All pregnant women scheduled for repeat CD under spinal anesthesia, pregnant women with a single fetus at term of gestational age (>37 weeks) at physical status I or II, according to the American Society of Anesthesiology (ASA). Exclusion: Anemic women (Hb <8gm/dL) and those with multiple gestations, placenta praevia, premature rupture of membranes, chorioamnionitis, pre-eclampsia, diabetes	Age, mean (SD): G1) 28.34 (5.44) G2) 27.67 (5.22) BMI, mean (SD) G1) 27.04 (3.61) G2) 27.19 (3.38) Emergency CS, %: 35.1%	G1: 610.76 (165.9) G2: 576.1 (153.6)

						mellitus, current or previous history of heart disease, liver, renal disorders or known coagulopathy and with previous repair of ruptured uterus, abdominal or pelvic surgery other than CD		
Magann, 1993[92]	USA	Randomised controlled trial	120	G1) spontaneous removal/in situ repair G2) spontaneous removal/exteriorized repair G3) manual placental removal and in situ uterine repair G4) manual removal/exteriorized repair	Not stated	Inclusion: Caesarean delivery for obstetric reasons Exclusion: Presence of chorioamnionitis at the time of caesarean birth, patient refusal to participate following informed consent, and antenatal treatment with steroids or insulin.	Age, mean (SD): G1) 24.6 (4.4) G2) 22.6 (4.7) G3) 25.2 (6.9) G4) 22.5 (8.5) BMI, mean (SD) G1) G2) G3) G4) Emergency CS, %: not stated	G1: 640 (234) G2: 644 (644) G3: 1342 (549) G4: 1146 (280)
Magann, 1995[91]	USA	Randomised controlled trial	284	G1) spontaneous placental removal and in situ uterine repair G2) spontaneous placental removal and exteriorized uterine repair G3) manual placental removal and in situ uterine repair G4) manual placental removal and exteriorized uterine repair	Post-caesarean infectious morbidity rates in women receiving prophylactic antibiotics at the time of caesarean delivery. (?? Blood loss a primary outcome too)	Inclusion: not stated Exclusion: Prior caesarean delivery without labour, chorioamnionitis, or patient refusal to participate.	Age, mean (SD): G1) 23.6 (6.5) G2) 25.5 (6.3) G3) 24.6 (7.3) G4) 25.4 (6.6) BMI, mean (SD) G1) not stated G2) not stated G3) not stated G4) not stated Emergency CS, %: not stated	G1: 8321(218) G2: 844.4 (192.3) G3: 903.9 (181.5) G4: 966.9 (219.1)
Group 13: Placenta removal technique								
Ramadani, 2004[96]	Saudi Arabia	Randomised controlled trial	400	G1) manual placental removal G2) spontaneous placental separation	Intraoperative blood loss	Inclusion: consecutive pregnant woman who had transverse CS performed, emergency/elective Exclusion: Women with multiple gestations	Age, mean (SD): G1) 27 (5) G2) 28 (6) BMI, mean (SD) G1)not stated G2) not stated Emergency CS, %:	G1:713 (240) G2: 669 (253)
Kamel, 2018[93]	Egypt	Randomised controlled trial	574	G1) Spontaneous delivery G2) Manual removal	Not stated	Inclusion: elective CS at term Exclusion: anaemia, coagulation defects, multifetal gestation, pregnancy-induced hypertension, uterine fibroid and anomalies, and other factors increasing risk for primary postpartum haemorrhage (PPH) (including placenta previa). Any participants with abnormal placental	Age, mean (SD): G1) 28.7 (5.5) G2) 29.1 (5.5) BMI, mean (SD) G1) 28.0 (2.5) G2) 28.1 (2.6)	G1: 731.8 (426.7) G2: 875.2 (524.2) PPH: G1: 65/287

						adhesions (diagnosed by antenatal ultrasound, or during delivery by CS), tears or extensions into the lower uterine segment >1 cm, or uterine artery injury	Emergency CS, %: 0	G2: 122/287
McCurdy, 1992[97]	USA	Randomised controlled trial	62	G1) Spontaneous placental delivery G2) Manual placental delivery	Blood loss	Inclusion: Candidates for caesarean delivery for obstetric indications Exclusion: Age <18	Age, mean (SD): G1) 24.2 (5.5) G2) 24.5 (4.0) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 666 (271) G2: 967 (248)
Gol, 2004[98]	Turkey	Randomised controlled trial	200	G1) Manual removal of placenta G2) Spontaneous removal of placenta	Not stated	Inclusion: women having CS Exclusion:	Age, mean (SD): G1) not stated G2) not stated BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 589 (272) G2: 626 (253)
Waqar, 2008[99]	Pakistan	Randomised controlled trial	145	G1) Spontaneous delivery of placenta G2) Manual removal of placenta	Blood loss more than 1,000cc, difference in haemoglobin of more than 2gm/dl, blood transfusions, additional use of oxytocics, time interval between delivery of baby and placenta, total operating time (min)	Inclusion: All women undergoing elective or emergency CS Exclusion: pregnancy below 37 weeks, severe maternal anaemia, prolonged rupture of membranes with fever, placenta praevia, placenta accreta, clotting disorders.	Age, mean (SD): G1) 26.1 (4.87) G2) 25.57 (5.04) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: G1) 74.35% G2) 73.13%	G1: not stated G2: not stated PPH: G1: 10/78 G2: 8/67
Morales, 2004[94]	Switzerland and Belgium	Randomised controlled trial	472	G1) Spontaneous placental delivery G2) Manual placental delivery	Risk of significant blood loss (defined as a fall greater than 2.5 g/dL between the last haemoglobin measurement performed before randomisation and the measurement performed on the third post-operative day)	Inclusion: caesarean delivery elective or emergency; enough time to consent Exclusion: <34 weeks gestational age; multiple pregnancy; placenta praevia; intrapartum fever and suspected chorioamnionitis; clotting disorders	Age, mean (SD): G1) 31 (5.0) G2) 31 (5.2) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: G1) 34% G2) 34%	G1: 550 (378) G2: 546 (279) PPH: G1: 10/235 G2: 9/237

*Altraigey, 2018[95]	Saudi Arabia	Randomised controlled trial	345	G1) Cord Traction G2) Manual Removal	Perioperative blood loss	Inclusion: study recruited young women (20–35 years) with singleton uncomplicated pregnancies who attended the outpatient antenatal clinic and were scheduled for elective delivery by CS at term. Exclusion: Pre-operative exclusion: Emergency CS, multifetal gestations, preterm deliveries, maternal anaemia (HB < 10 gm/dl), hypertensive disorders, rupture of foetal membranes, chorioamnionitis, placental abruption, placenta previa, placenta accreta, coagulopathy and segment CS and/or surgical complications that could increase bleeding and/or necessitate intraoperative or postoperative blood transfusion. Postoperative exclusion criteria included incomplete follow up and any postoperative complication that could affect the studied outcomes and that was not related to the mode of placental delivery. These complications included internal haemorrhage, significant medical disease and/or any other risk factor that would affect the risk of bleeding during CS. Intraoperative exclusion criteria included intraperitoneal adhesions, upper reexplanation, hemolysis, fever, sepsis and/or hematoma.	Age, mean (SD): G1) Query to check (5) G2) 30 (5) BMI, mean (SD) G1) 27 (5) G2) 27 (5) Emergency CS, %: 0	Median, (IQR): G1: 500 (500-700) G2: 500 (400-500) PPH: G1: 2/170 G2: 1/175
Miscellaneous interventions:								
Galaal, 2000[100]	Oman	Randomised controlled trial	60	G1) Closure of peritoneum G2) Non-closure of the peritoneum	Not stated	Inclusion: not stated Exclusion: not stated	Age, mean (SD): G1) 28 G2) 26 BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 483.3 (187.7) G2: 400 (177.6)
Malvasi, 2010[101]	Italy	non-randomised controlled trial	474	G1) Open visceral peritoneum G2) Sutured visceral peritoneum	Not stated	Inclusion: healthy primipara at term with low-risk pregnancies. The indications for CS included: CS for macrosomia (44500 g) at term, dystocia of labor in the first stage (cervical dilatation 45 cm) of labor and at second stage of labor. Exclusion: general and genitourinary infection, coagulopathies, anticoagulation treatment, hypertension and HELLP syndrome, >36hrs rupture of membranes	Age, mean (SD): G1) 27.8 (4.1) G2) 28.2 (3.1) BMI, mean (SD) G1) 24.1 (1.8) G2) 23.9 (1.7) Emergency CS, %: not stated	G1: 219 (40.1) G2: 243 37.2)
Altinbas, 2013[102]	Turkey	Randomised controlled trial	110	G1) Closure of parietal peritoneal layer G2) Control	Not stated	Inclusion: Women undergoing CS Exclusion: (1) a history of severe medical conditions such as diabetes mellitus or moderate-severe hypertension, (2) anticoagulation therapy, (3) a history of other major abdominal surgery, (4) multiple gestations and (5) a history of any thrombophilic disorders.	Age, mean (SD): G1) 27.9 (5.17) G2) 30.1 (5.92) BMI, mean (SD) G1) 30.4 (4.42) G2) 30.02 (5.12) Emergency CS, %: not stated	G1: 487.9 (217.01) G2: 544.87 (237.64)
Kadir, 2006[103]	UK	Randomised controlled trial	120	G1) Non-dissection G2) Dissection	Not stated	Inclusion: Women undergoing elective (planned) CSs Exclusion: had more than two previous CSs, post-operative complications after their previous CSs, abdominal vertical incisions or a previous myomectomy	Age, mean (SD): G1) 29.86 (5.86) G2) 30.26 (5.05) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 564.2 (217.14) G2: 601.8 (358.44)

Bennich, 2016[104]	Denmark	Randomised controlled trial	76	G1) Single-layer closure G2) Double layer closure	Residual myometrial thickness	Inclusion: women with a singleton first-time delivery without preterm rupture of membranes, contractions or dilatation of the cervix Exclusion: Primary exclusion criteria were: former uterine surgery, such as myomectomy, or surgery involving the cavity; fibroids located in the cervical or the cervical–corporal border; inflammatory bowel disease; systemic lupus erythematosus; rheumatoid arthritis; and insulin-dependent diabetes mellitus. Secondary exclusion criteria were the need for more than three additional single sutures for hemostasis and reoperation following the CS.	Age, mean (SD): G1) 30.3 (4.5) G2) 30.5 (5.5) BMI, mean (SD) G1) 24.6 (4.8) G2) 24.1 (3.5) Emergency CS, %: 0	G1: 416 (173) G2: 409 (277)
Cao, 2017[105]	China	non-randomised controlled trial	134	G1) 3D MRI model for uterine incision G2) Control	Not stated	Inclusion: singleton pregnancy and a diagnosis of placenta previa by prenatal ultrasonography. Exclusion: multiple pregnancy, placental abruption, pre-eclampsia, diabetes mellitus (including gestational diabetes), uterine leiomyoma, hematologic disorders, moderate-to-severe anemia, and intrauterine fetal death	Age, mean (SD): G1) 31.62 (3.84) G2) 30.86 (5.41) BMI, mean (SD) G1) 23.12 (4.13) G2) 23.61 (5.42) Emergency CS, %: G1) 27% G2) 33%	G1: 678.65 (649.54) G2: 933.96 (695.25)
*Dunn, 2016[106]	USA	Randomised controlled trial	536	G1) Alexis Retractor G2) Standard Retractor	Postoperative haemoglobin and haematocrit.	Inclusion: Women undergoing non-emergent cesarean delivery via planned Pfannenstiel incision Exclusion: emergent delivery, planned vertical incision, active skin infection, and chorioamnionitis	Age, mean (SD): G1) 28 (5.6) G2) 27.7 (5.5) BMI, mean (SD) G1) 34.6 (9.3) G2) 34.6 (7.3) Emergency CS, %: 0	G1: 1046 (142.2) G2: 1048.4 (139.8)
*Eke, 2019[107]	USA	Randomised controlled trial	206	G1) Uterine cleaning G2) No uterine cleaning	Proportion of postpartum endomyometritis development	Inclusion: women with singleton or multiple pregnancies, in vertex or breech presentation with intact membranes presenting to the labor and delivery suite for planned elective cesarean delivery Exclusion: conditions that predisposed them to endomyometritis prior to cesarean delivery, including preterm premature rupture of the fetal membranes, prolonged rupture of membranes prior to CS, diagnosed chorioamnionitis prior to CS, uncontrolled diabetes mellitus, chronic steroid therapy use, and immunosuppressive disorders (e.g. HIV infection).	Age, mean (SD): G1) 27.5 (4.18) G2) 28.3 (4.73) BMI, mean (SD) G1) 29.9 range: (24.8–37.3) G2) 30.2 range: (24.1–37.10) Emergency CS, %: 0	G1: 820 (297.4) G2: 8119 (276.5)
Gupta, 2016[108]	USA	Randomised controlled trial	33 analysed (53 consented for study)	G1) Continuous non-invasive arterial pressure (CNAP) monitor used by anaesthesia provider G2) non-invasive blood pressure (NIBP) monitor used by anaesthesia provider	Not stated	Inclusion: pregnant patients aged 18 years and above who presented for elective CS under subarachnoid blockade Exclusion: asa class iv and v pregnant patients, age less than 18 years, patients with cardiac arrhythmia, vascular pathologies of the upper limbs (recent vascular surgery, raynaud's disease, vascular stenosis), any contraindication for sab and emergency CSs. patients with an arm-to-arm differences of more than 10mmhg in systolic and/or diastolic pressures at baseline (right arm pressures vs. left arm pressures) were excluded from the study	Age, mean (SD): G1) 28.2 (6.1) G2) 29.9 (6.1) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 617.6 (174.1) G2: 758.4 (208.2)

Meng, 2018[109]	China	Randomised controlled trial	75	G1) Controlled hypotension: 80% of basal blood pressure (BP) after delivery of fetus G2) Controlled hypotension + 70% of basal BP after delivery of fetus G3) BP maintained in normal range after delivery of fetus	Blood loss; neonatal apgar score	Inclusion: 18-45 years old; 28-40 weeks gestation; planned CS; dangerous placenta praevia; placenta praevia plus accreta; expected intraoperative blood loss>1000ml Exclusion: Age <18 or >45; combined systemic disease; urgent or immediate CS; expected intraoperative blood loss < 1000ml; rapid bleeding requiring vasopressors to maintain blood pressure; patient refusal	Age, mean (SD): G1) 32.8 (3.9) G2) 34.1 (3.4) G3) 31.3 (4.2) BMI, mean (SD) G1) not stated G2) not stated G3) not stated Emergency CS, %: 0	G1: 1855.8 (710.6) G2: 1628.4 (628.5) G3: 2246.5 (708.4)
Morales, 2019[110]	Panama	Randomised controlled trial	1065	G1) Cephalad-caudad expansion of uterine incision G2) Transverse extension of uterine incision	Decrease in Hb level at 24hrs post-op	Inclusion: caesarean delivery Exclusion: previous uterine scar; =<33+6 gestataionl age; multiple pregnancy; bleeding disorder; pathology associated with excess bleeding; Hb <10.5g/dl; uterine atony	Age, mean (SD): G1) 25.94 (6.02) G2) 26.22 (7.84) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: G1) 68.7 G2) 69.32	G1: 560 (105) G2: 565 (120)
Beckmann, 2014[111]	Australia	Randomised controlled trial	52	G1) Prophylactic Bakri balloon following placenta delivery G2) Control	Clinician's decision to undertake further intervention to control bleeding, and the difference between preoperative and postoperative haemoglobin concentrations	Inclusion: All women with a live singleton pregnancy at or beyond 24 + 0 weeks undergoing CD in the setting of a known low-lying placenta/placenta previa (leading edge of placenta less than 20 mm from the cervical os). An ultrasound scan was required to confirm the placental location a maximum of 2 weeks prior to the planned CD date. Exclusion: Women with a suspected placenta accreta, congenital abnormalities of the uterine cavity, or submucosal uterine fibroids greater than 5 cm and those aged less than 18 year2s	Age, mean (SD): G1) 31.8 (5.5) G2) 32.6 (5.2) BMI, mean (SD) G1) 24.2 (4.8) G2) 24.7 (6.5) Emergency CS, %: G1) 36 G2)33.3	G1: 918 (610) G2: 770 (513)
*Yu, 2020[112]	Hong Kong	Randomised controlled trial	40	G1) Internal iliac artery balloon occlusion G2) Standard management	Not stated	Inclusion: Placenta previa patients who were planned for Caesarean delivery Exclusion: (1) age of less than 18 years; (2) mentally handicapped or severely ill; (3) fetus diagnosed with in-utero death; (4) had contraindication for internal iliac artery balloon occlusion; (5) unstable clinical condition in which patients could not be send to interventional radiology suite for pre-operative internal iliac artery catheter placement; (6) unable to understand English or Chinese to give consent; and (7) ultrasonic features suggestive of placenta accreta spectrum. The recruited subjects were reassessed within 1 week before the	Age, median (IQR): G1) 35.3 (31.5-37.6) G2) 36.6 (32.7 – 39.1) BMI, mean (SD) G1) 27.0 (24.9-29.4) G2) 26.9 (24.5-29.7) Emergency CS, %: 7.5%	Median (IQR) G1: 1451 (1024-2388) G2: 1454 (888-2300)

						operation, when a transvaginal ultrasound scan was repeated to double check the distance between the placental edge and the internal os.		
*Samy, 2019[113]	Egypt	Randomised controlled trial	1086	G1) Balloon Uterine Artery Ligation G2) control	Amount of blood loss during cesarean	Inclusion: elective or emergency cesarean plus one or more of the following conditions: maternal anemia (at least 7 g/dL hemoglobin), macrosomia (>4 kg), twin and high-order pregnancy, polyhydramnios, grand multipara, previous history of atonic PPH, prolonged vaginal delivery, and chorioamnionitis. Exclusion: placenta previa, bleeding tendency (congenital or acquired), prepartum hemorrhage, and no risk of uterine atony.	Age, mean (SD): G1) 29.6 (3.1) G2) 30.2 (2.8) BMI, mean (SD) G1) 29.1 (3.0) G2) 28.9 (2.7) Emergency CS, %: 22	G1: 770.5 (51.3) G2: 945.7 (39.8)
*Sanad, 2018[114]	Egypt	Randomised controlled trial	140 'eligible patients' - patients withdrawn/excluded before analysis in both groups	G1) uterine artery ligation G2) control	The amount of intra-operative blood loss. – The change in pre and post-partum hemoglobin.	Inclusion: patients diagnosed with central placenta previa diagnosed with two-dimensional ultrasound scan at 28 weeks' gestation and remained so till the time of planned cesarean delivery. Central placenta previa was defined as placental localization in the lower uterine segment either anteriorly or posteriorly. Laterally situated placenta was not considered "central" Exclusion: a) known bleeding disorder, b) patients with hypertensive disorders or developed preeclampsia (PET) during the study, c) patients who had antepartum hemorrhage (APH) and delivered by emergency caesarean section, and d) patients with anterior placenta previa that were diagnosed antenatally with color Doppler ultrasound and MRI to have placenta accreta	Age, mean (SD): G1) 33.5 (4.8) G2) 34.1 (4.7) BMI, mean (SD) G1) 28.9 (4.7) G2) 29.2 (5.1) Emergency CS, %: 0	G1: 569.3 (202.1) G2: 805.1 (224.5)
*Tuuli, 2012[115]	USA	Randomised controlled trial	259	G1) Bladder flap G2) No bladder flap	Total operating time	Inclusion: Women undergoing primary or repeat cesarean delivery at gestational age of 32 weeks of gestation or more. Exclusion: Women undergoing emergent cesarean deliveries, planned vertical uterine incision, and those with previous laparotomies besides cesarean deliveries	Age, mean (SD): G1) 27.4 (5.8) G2) 26.6 (5.7) BMI, mean (SD) G1) 41.5 (10.2) G2) 40.3 (9.0) Emergency CS, %: 0	Median (IQR): G1: 800 (400-3,500) G2: 800 (300-2,000)
*Komoto, 2005[116]	Japan	Randomised controlled trial	124	G1) Closure of the peritoneum G2) Non-closure of the peritoneum	Not stated	Inclusion: Exclusion: Patients with medical complications, such as systemic lupus erythematosus (SLE), diabetes mellitus (DM), and idiopathic thrombocytopenic pur- pura (ITP), were excluded.	Age, mean (SD): G1) 32.7 (4.1) G2) 31.4 (3.8) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %:	PPH: G1: 4/70 G2: 3/54
Shao, 2014[117]¹¹⁷¹¹⁷	China	Case-control study	400	G1) High uterine incision G2) Traditional uterine incision	Blood loss	Inclusion: primary caesarean section Exclusion: not stated	Age, mean (SD): G1) 32.8 (5.5) G2) 33.9 (5.1) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 198 (60.1) G2: 330.1 (68.5)

Razzaq, 2016[118]	Pakistan	Randomised controlled trial	212	G1) Blunt expansion of uterine incision G2) Sharp expansion of uterine incision	Intraoperative blood loss	Inclusion: single pregnancy confirmed on ultrasound; term >37 weeks gestational age, elective/emergency lower segment caesarean seftion, age 18-35 yrs Exclusion: multiple pregnancy; abnormal presentation; PET; bleeding disorders; previous classic uterine incision	Age, mean (SD): G1) 26.51 (4.69) G2) 25.51 (5.17) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 365.51 (644.77) G2: 407.41 (62.67)
Paris, 2014[119]	USA	Randomised controlled trial	226	G1) Warmed IV fluids G2) Warmed under body pad G2) usual care	Not stated	Inclusion: presented for planned singleton CB Exclusion: unplanned CB, failure to receive postoperative Duramorph, or planned postpartum tubal ligation during CB	Age, mean (SD): G1) 31.93 (5.35) G2) 32.44 (5.29) G3) 30.87 (4.37) BMI, mean (SD) G1) 32.43 (6.34) G2) 32.18 (6.31) G3) 32.73 (6.6) Emergency CS, %: 0	G1: 826.47 (156.09) G2: 788.89 (239.60) G3: 783.80 (199.78)
Kaya, 2016[120]	Turkey	Randomised controlled trial	231	G1) Extra-abdominal removal of placenta G2) Intra-abdominal removal of placenta	Amount of intra-abdominal haemorrhagic fluid during the CS, after closure the uterine incision and repositioning of the uterus, duration of operation and estimated blood loss during surgery.	Inclusion: participants older than 18 years with term pregnancies, undergoing CS according to the obstetrical indications. Under spinal anesthesia Exclusion: uterine anomalies, multiple gestations, polyhydramnios, chorioamnionitis, a large uterine fibroid (> 5 cm) or multiple myomas that increases the size of uterus, pre-eclampsia, placenta previa, ultrasonographic findings of morbidly adherent placenta, women with known coagulation disorders, and abnormal preoperative activated partial partial thromboplastin time (APTT), prothrombin time (PT) and international normalization ratio (INR).	Age, mean (SD): G1) not stated G2) not stated BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: not stated	G1: 608 (121) G2: 570 (140)
Sharma, 1995[121]	UK	Randomised controlled trial	148	G1) placental drainage G2) cord traction	Maternal blood loss	Inclusion: Women having a caesarean section Exclusion: not stated	Age, mean (SD): G1) 27.5 (not stated) G2) 29.2 (not stated) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 71	Median (IQR): G1: 680 (300-1000) G2: 700 (350-950)
Magann, 1993[122]	USA	Randomised controlled trial	100	G1) Spontaneous placental detachment with in situ uterine repair G2) Spontaneous placental detachment with exteriorized uterine repair G3) Manual placental removal with in	Not stated	Inclusion: CSs for fetal distress, failure to progress, cephalopelvic disproportion, pregnany-induced hypertension (without hematological abnormalities), and repeat caesarean births. Exclusion: Not stated	Age, mean (SD): G1) not stated G2) not stated G3) not stated G4) not stated BMI, mean (SD) G1) not stated G2) not stated G3) not stated G4) not stated Emergency CS, %: not stated	G1: 635.6 (230.5) G2: 639.2 (235.5) G3: 1330 (547.7) G4: 1143 (276.5)

				situ uterine repair G4) Manual placental removal with exteriorized uterine repair.				
Treatment interventions:								
*Barinov, 2017[123]	Russia	Non-randomised controlled trial	119	G1) Combined strategy of haemorrhage management G2) Conventional management	Rate of peripartum hysterectomies	Inclusion: gestational age between 28 and 42 weeks, labour or postpartum period Exclusion: pregnancy-related (gestational age 528 weeks, multiple pregnancy, cervical insufficiency, recurrent pregnancy loss, umblical cord prolapse during labour, chorioamnionitis, injury during labour), maternal (congenital abnormalities of the reproductive system, infectious diseases, tumours, evidence of sub- or decompensation of chronic internal diseases) and foetal (foetal chromosomal pathology or congenital malformations, and congenital foetal viral or microbial infection)	Age, mean (SD): G1) not stated G2) not stated BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 1836 (108) G2: 2502 (203)
*El-Sokkary, 2016[124]	Egypt	Randomised controlled trial	160	G1) Modified technique of B-lynch suture G2) Classical technique of B-lynch	Successful: if the bleeding stopped and no need for hysterectomy/ Unsuccessful: if the bleeding continued and there is a need for hysterectomy	Inclusion: Patients under general anesthesia with atonic postpartum hemorrhage refractory to uterine massage, ecbolics (oxytocin 30 units IM, methergine 0.25 mg, misoprostol 1000 µg rectal) and bimanual compression. Exclusion: Patients with traumatic PPH, DIC, bleeding diathesis, retained parts of the placenta or cases with uterine anomalies	Age, mean (SD): G1) 29.6 (4.5) G2) 29.3 (5.1) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 324 (105) G2: 568 (209)
Kavak, 2013[125]	Turkey	Randomised controlled trial	13	G1) Endouterine square haemostatic sutures G2) Bakri balloon	Not stated	Inclusion: elective CS with antenatal diagnosis of complete placenta praevia with intractable haemorrhage Exclusion: serious medical, hematological or surgical diseases; placental implantation anomalies such as placenta accreta/increta/percreta; history of thromboembolism; emergency CS; macrosomia; polyhydramnios; preeclampsia; gestational diabetes; intrauterine growth retardation; and presence of multiple gestations.	Age, mean (SD): G1) 32.5 (7.7) G2) 33.0 (3.4) BMI, mean (SD) G1) not stated G2) not stated Emergency CS, %: 0	G1: 1946 (242) G2: 1520 (92)
Maher, 2016[126]	Saudi Arabia	Cohort study	112	G1) Bakri Balloon G2) Non-balloon protocol	Prevention of hysterectomy	Inclusion: women of any age, parity, carrying single or multiple pregnancies and with a gestational age suitable for neonatal care according to the hospitals' protocols, prepared for CS because of low lying placenta (lower edge of the placenta < 2 cm from the cervical os) or placenta previa (partially or completely covering the cervical os) Exclusion: uterine and placental implantation anomalies, such as placenta accreta, increta or percreta, and refusal to participate in the study.	Age, mean (SD): G1) 29.25 (4.62) G2) 28.7 (5.13) BMI, mean (SD) G1) 27.76 (2.52) G2) 25.45 (2.64) Emergency CS, %: G1) 16.7 G2) 15.0	G1: 1386.1 (366.67) G2: 1707 (446.61)
Khalil, 2011[127]	Saudi Arabia	Randomised controlled trial	50	G1) Bakri balloon and traction stitch	Displacement of Bakri balloon used as	Inclusion: severe atonic PPH during emergency cesarean delivery, cesarean for different indications at 6 cm to full dilation of the cervix, failed attempts at medical treatment,	Age, median (IQR): G1) 32 (46-20) G2) 31 (46-20) BMI, mean (SD)	Median (IQR) G1: 1700 (1500-3100)

				G2) Bakri balloon without traction stitch	a uterine tamponade	Exclusion: Women less than 28 weeks pregnant, and those with traumatic bleeding and placenta previa were excluded. Also cases of coagulopathy	G1) not stated G2) not stated Emergency CS, %: 100	G2: 2100 (1600-4900)
Wei, 2020[128]	China	Randomised controlled trial	204	G1) Balloon catheter G2) Gauze packing	The rate of successful haemostasis without the need for additional surgical interventions, involving artery embolization, hysterectomy, or replaced by another form of intrauterine tamponade.	Inclusion: placenta previa diagnosed before delivery, age ≥18 years, gestation ≥28 weeks of pregnancy, and requiring CD. Exclusion: suspected deeply invasive placenta accreta, fever above 38°C or chorioamnionitis at CD, uterine malformation found at operation, preoperational uterine artery embolisation, uterine bleeding controlled following placenta delivery, after uterotonics and/or local myometrium sutures, or the women had no desire to preserve the uterus.	Age, mean (SD): G1) 31.1 (4.9) G2) 32.2 (4.8) BMI, mean (SD) G1) 22.5 (2.7) G2) 22.2 (2.2) Emergency CS, %: not stated	Median (IQR): G1: 895 (612.3–1297.8) G2: 1156 (882.5–1453.3)
Hofmeyr, 2019[129]	South Africa	Randomised controlled trial	45	G1) Early uterine suction tamponade G2) Delayed uterine suction tamponade	Uterine blood loss measured during the caesarean procedure and until removal of the catheter and massage of the uterus.	Inclusion: low-risk pregnancy; age 18–45 years; planned caesarean; and informed consent Exclusion: participation in another clinical trial and presence of serious medical complications.	Age, median (IQR): G1) 32 (19-43) G2) 32 (19-43) BMI, mean (SD) G1) 35 (24-54) G2) 32 (21-58) Emergency CS, %: not stated	G1: 149 (13-466) G2: 126 (24-462

Appendix 5: PRISMA NMA Checklist

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	12
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	1 – word count and level of detail limited by thesis requirements.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	13
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	13
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	14
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the*	14

		treatment network, and note whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	15
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	15-16
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	16
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	16
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	16-17
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	17
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	18
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	18-19
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	19
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	19
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	20
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:	n/a

		• Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	21
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	22
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	21
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	23-49
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	23-61
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	23-49
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	23-49
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being	23-61

		studied.	
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	62-64
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	64-66
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	68
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	n/a

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix 6

Delphi Study Summarised Group Scores

** upgraded to the final list of recommended interventions in round four.*	Round Two Scores		Round Three Scores	
	Effectiveness, median (IQR)	Feasibility, median (IQR)	Effectiveness, median (IQR)	Feasibility, median (IQR)
Community based interventions				
Community information, education and communication regarding reproductive health (e.g. knowledge on risks, the early recognition of danger signs in pregnancy, and the advantages of seeking healthcare at an early stage).	7 (6-8)	6 (5-8)	7 (7-8)	7 (6-7)
Availability of contraception and family planning.	7 (6-9)	6 (4-8)	7.5 (7-9)	7 (6-8)
Antenatal care and assessment interventions				
Routine pre-operative risk assessment and risk stratification for peripartum haemorrhage	8 (7-9)	7 (6-8)	8 (7-9)	7 (7-8)
Routine screening for anaemia and patient blood management programme	7 (7-8.5)	7 (5-8)	8 (7-8)	7 (6-8)
Routine antenatal assessment by the anaesthesia provider for all women for planned caesarean section.	8 (7-9)	8 (5-8)	8(7-9)	7 (6-8)
Maternal education on the early self-recognition of signs and symptoms of peri-partum haemorrhage.	7 (6-8)	7 (6-8)	7 (6-8)	7 (6-8)
Peri-operative interventions				
Routine use of a Surgical Safety Checklist modified for caesarean section use.	8 (6.25-9)	7 (6-8.75)	8 (7-9)	8 (7-8)
Implementation of a standardised peri-partum haemorrhage protocol.	9 (7.75-9)	9 (7-9)	9 (8-9)	8 (7-9)
Intrapartum monitoring: routine, close monitoring of mother and foetus during intrapartum period.	8 (7-9)	7 (6-8)	8 (7-8.25)	7 (6-8)

Early and increased surveillance of vital signs in the postpartum period, possibly in a dedicated environment.	8 (7-9)	7 (6-8)	8 (7-9)	7 (6-8)
*Routine use of modified early obstetric warning score in the postoperative period, or routine active monitoring for haemorrhage e.g. shock index.	7 (7-9)	6 (6-8)	7 (7-8)	6 (6-8)
Early involvement of anaesthesia providers in the management of patients at risk.	8 (7-9)	7 (6-9)	8 (7-8)	8 (7-8)
Availability of a peri-partum haemorrhage 'package' containing all items required to manage post-partum haemorrhage.	8 (7-9)	7 (6-7)	8 (7-9)	7 (6-7)
Availability of emergency blood products.	9 (8-9)	7 (5.75-8)	9 (8-9)	7 (5-8)
Availability of first line uterotonic agents.	9 (8-9)	8 (7-9)	9 (8-9)	8 (8-9)
Availability of alternative/second line uterotonic agents.	8 (7-9)	7 (6-9)	8 (8-9)	7 (7-8)
Availability of tranexamic acid.	8 (7-9)	7 (6-9)	8 (7-8)	8 (6-8)
Ability to perform active management of the third stage of labour.	9 (8-9)	9 (7.75-9)	9 (8-9)	9 (8-9)
Ability to perform uterine massage and bimanual compression.	8 (7-9)	8 (7-9)	8 (7-9)	8 (7-8)
Ability to perform hysterectomy and uterine artery ligation.	9 (8-9)	7 (6-9)	8 (8-9)	7 (6-8)
*Ability to perform B-lynch and compression sutures.	8 (7-9)	7 (5-8)	8 (7-8)	6 (5-7)
*Ability to perform balloon tamponade.	8 (6-8.25)	6.5 (5-8)	7 (6-8.25)	6 (5-8)
Health System Strengthening Interventions				
Ensuring a minimum training standard for healthcare providers.	8.5 (8-9)	8 (6-8.25)	8 (8-9)	8 (7-8)
Advocating to key stakeholders about the importance of reducing maternal morbidity and mortality related to peripartum haemorrhage.	8.5 (7.75-9)	7 (6-9)	8 (7-9)	7 (6.75-8)
Establishing smooth and timely referral patterns between levels of care.	8 (7-9)	7 (6-8)	8 (7.75-9)	7 (6-8)
Reducing delays in receiving care once at the healthcare facility.	8 (8-9)	7 (6-8)	8 (8-9)	7 (6-8)
Multidisciplinary simulation and team training.	8.5 (8-9)	7 (6-8)	8 (8-9)	7 (6-7)
*Available resources to perform caesarean sections 24 hours a day.	9 (8-9)	7 (6-8.25)	9 (8-9)	6 (5.75-7)

Interventions not included in the final list of recommended intervention				
Availability of a specialist obstetrician and anaesthetist.	9 (8-9)	6 (5-7)	9 (8-9)	6 (4-7)
Early, comprehensive antenatal consultation with regular follow up.	8 (5.5-9)	7 (6-8)	8 (6.75-8)	6.5 (6-8)
Providing mentorship and support networks to non-physician surgery providers and non-physician anaesthesia providers.	8 (6-9)	7 (6-8)	8 (6-8.25)	6 (5.75-7)
Creation of multidisciplinary peri-partum haemorrhage response team with a rapid alert and call network.	8 (7-9)	6 (5-7)	8 (7-9)	6 (5-7)
Ensuring repeat caesarean sections are only performed by experienced providers.	8 (6.75-9)	6 (4.75-7)	8 (7-8)	6 (5-7)
Accurate and quantitative measurement of peripartum blood loss.	7 (5-8)	6 (5-7)	7 (6-8)	6 (5-7)
Routine ultrasound localisation of the placenta, prior to labour.	7 (6-8)	5 (4-7)	7 (6-8)	5 (4-7)
Availability of anti-shock garments.	7 (5-8)	5.5 (4-7)	7 (6-7)	5 (3-6)
A routine pre-operative coagulation assessment.	6 (4-7.5)	5 (3-6)	6 (4-7)	5 (3-6)
Intraoperative blood salvage.	6.5 (5-8.25)	4 (2.75-6)	6 (5.75-8)	4 (3-5)
Ability to perform arterial embolization.	7 (4-8)	3 (1.75-4)	7 (5-8)	3 (2-4)