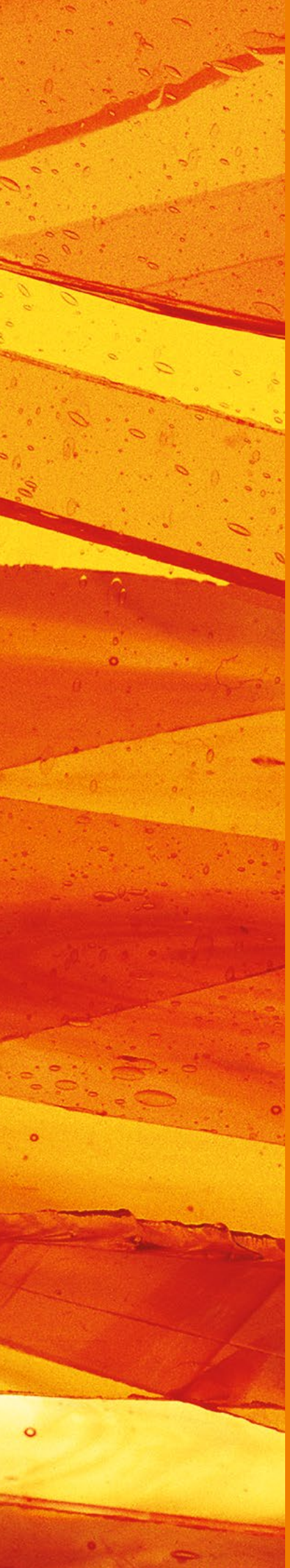

WHO recommendation on **Umbilical vein injection of oxytocin for the treatment of retained placenta**

World Health Organization

human reproduction programme hrp
research for impact
UNDP · UNFPA · UNICEF · WHO · WORLD BANK

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Acronyms and abbreviations

CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
DOI	declaration of interest
ERG	External Review Group
ESG	Evidence Synthesis Group
EtD	Evidence to Decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSG	Guideline Steering Group
HRP	UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
IU	international units
MPH-GDG	WHO Maternal and Perinatal Health Guideline Development Group
PICO	population (P), intervention (I), comparator (C), outcome (O)
PPH	postpartum haemorrhage
SDG	Sustainable Development Goal
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
UVI	umbilical vein injection
WHO	World Health Organization

Executive summary

Introduction

Postpartum haemorrhage (PPH) is commonly defined as a blood loss of 500 mL or more within 24 hours after birth and affects about 5% of all women giving birth around the world. Globally, nearly one quarter of all maternal deaths are associated with PPH and, in most low-income countries, it is the main cause of maternal mortality. Improving care during childbirth to prevent PPH is a necessary step towards the achievement of the health targets of the third Sustainable Development Goal (SDG 3), particularly target 3.1: reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030. Efforts to prevent and reduce morbidity and mortality due to PPH can help to address the profound inequities in maternal and perinatal health globally. To achieve this, skilled health personnel, health managers, policy-makers and other stakeholders need up-to-date and evidence-informed recommendations to guide clinical policies and practices.

In 2019, the Executive Guideline Steering Group (GSG) for the World Health Organization (WHO) maternal and perinatal health recommendations prioritized updating of the existing WHO recommendation: Umbilical vein injection of oxytocin for the treatment of retained placenta, in response to the availability of new evidence. The recommendation in this document thus supersedes the previous WHO recommendations on "intraumbilical vein injection of oxytocin for treatment of retained placenta" as published in the 2012 guideline, *WHO recommendations for the prevention and treatment of postpartum haemorrhage*.

Target audience

The primary audience for these recommendations includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women and their newborns during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

Guideline development methods

The updating of these recommendations was guided by standardized operating procedures in accordance with the process described in the WHO handbook for guideline development. The recommendations were initially developed and updated using this process, namely: (i) identification of priority questions and outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and future updating of the recommendations.

The scientific evidence supporting the recommendation was synthesized using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. An updated systematic review was used to prepare the evidence profiles for the prioritized question. WHO convened a meeting on 11–12 March 2020 where the Guideline Development Group (GDG) members reviewed, deliberated and achieved consensus on the strength and direction of the recommendation presented herein. Through a structured process, the GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity.

Recommendation

The GDG reviewed the balance between the desirable and undesirable effects and the overall certainty of supporting evidence, values and preferences of stakeholders, resource requirements and cost-effectiveness, acceptability, feasibility and equity. The GDG issued the new recommendation on umbilical vein injection (UVI) of oxytocin for the treatment of retained placenta, with remarks and implementation considerations. To ensure that the recommendation is correctly understood and applied in practice, guideline users may want to refer to the remarks, as well as to the evidence summary, including the considerations on implementation.

WHO recommendation on umbilical vein injection of oxytocin for the treatment of retained placenta

Umbilical vein injection of oxytocin is recommended for the treatment of retained placenta only in the context of rigorous research.

(Research-context recommendation)

Justification

- Evidence from trials that compared both umbilical vein injection of oxytocin versus expectant management and umbilical vein injection of oxytocin versus umbilical vein injection of saline suggest that this intervention may lead to a reduction in manual removal of placenta. However, the effect of this intervention on other priority outcomes (including infections, maternal satisfaction and length of hospitalization) is unclear. While the cost-effectiveness is not known, additional costs in supplies required to implement this intervention are probably negligible. When compared with injection of other solutions and uterotonics, no other umbilical vein injection regimen was shown to be clearly better than umbilical vein injection of oxytocin.

Remarks

- The Guideline Development Group acknowledged the potential of umbilical vein injectionof oxytocin in the treatment of retained placenta but considered the evidence of benefit in terms of manual removal of the placenta without impact on other priority outcomes insufficient to make a recommendation for routine clinical practice. The group agreed that high-quality randomized trials comparing umbilical vein injection of uterotonics with expectant management of women with retained placenta are needed, with the aim of demonstrating its impact on severe morbidity related to postpartum haemorrhage in addition to a reduction in manual removal of the placenta.
- When used in a research context, it is safer to consider the use of this intervention in situations in which retained placenta occurs in the absence of abnormal bleeding.
- There are three types of retained placenta, and umbilical vein injection is likely to be only effective in placenta adherens, the most common type of retained placenta, which occurs as a result of failed contraction of the retroplacental myometrium. To date, studies have not distinguished the subtypes before treatment, and this may have contributed to the results showing lack of efficacy of treatment with umbilical vein injection for retained placenta.

1. Introduction

1.1 Background

An estimated 295 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2017, and around 99% of these deaths occurred in low-resource settings *(1)*. Obstetric haemorrhage, especially postpartum haemorrhage (PPH), is responsible for more than a quarter of all maternal deaths worldwide *(2)*. In most low-income countries, PPH is the leading cause of maternal deaths. Thus, improving access to safe and effective interventions to prevent and treat PPH is critical to World Health Organization (WHO) strategic priorities (particularly universal health coverage) for achieving the targets of the third Sustainable Development Goal (SDG 3) *(3)*.

International human rights law includes fundamental commitments of States to enable women and adolescent girls to survive pregnancy and childbirth, as part of their enjoyment of sexual and reproductive health and rights, and living a life of dignity *(4)*. WHO envisions a world where "every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period" *(5)*. To provide good-quality care, skilled health personnel at all levels of the health system need to have access to appropriate medications and training in relevant procedures *(6)*. Health-care providers, health managers, health policy-makers and other stakeholders also need up-to-date, evidence-informed recommendations to guide clinical policies and practices to optimize quality of care and improve health-care outcomes.

PPH is commonly defined as a blood loss of 500 mL or more within 24 hours after birth and affects about 5% of all women giving birth around the world *(7)*. Severe maternal complications, such as organ dysfunction or death, generally occur following substantial blood loss that compromises maternal haemodynamic stability. Uterine atony is the most common cause of PPH and a leading cause of PPH-related maternal mortality worldwide *(8)*. Genital tract trauma (including vaginal or cervical lacerations and uterine rupture), retained placental tissue or maternal bleeding disorders can cause PPH. Although the majority of women presenting with PPH have no identifiable risk factor, grand multiparity, prolonged labour, prior history of PPH and multiple gestation are obstetric conditions that are associated with an increased risk of bleeding after birth *(9)*. In addition, anaemia is a common aggravating factor *(10)*.

Retained placenta is a potentially life-threatening complication of the third stage of labour when associated with PPH or infection. It complicates between 0.1 to 2% of births and is usually caused by a failed contraction of the retroplacental myometrium *(11,12)*. The standard treatment for this complication is manual removal of placenta, which requires a surgical theatre and anaesthesia and entails the risks associated with surgical procedures. Umbilical vein injection (UVI) consists of the administration of a solution via the umbilical cord vein, with or without uterotonic drugs. It is proposed as a noninvasive way of treating retained placenta, which, if effective, could prevent the complications associated with manual removal of placenta. Directing uterotonic treatment to the placental bed and the uterine wall may facilitate uterine contractions and placental separation. Among the various proposed methods of UVI, the most commonly reported is an injection (directly into the umbilical vein or through a catheter) of oxytocin diluted in saline solution. Other methods use other uterotonics with saline solutions or plasma expanders.

1.2 Rationale and objectives

WHO has established a new process for prioritizing and updating maternal and perinatal health recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating *(13,14)*. Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence base on benefits, harms, values placed on

outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness, or factors affecting implementation. The Executive GSG prioritized the updating of the existing WHO recommendations on UVI of oxytocin in anticipation of the publication of new and potentially important evidence on these interventions.

These updated recommendations were developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1] and GRADE Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CerQUAL)[2] methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders *(15)*. The recommendation published in this document thus supersedes the previous recommendations on UVI of oxytocin that were published in 2012 in *WHO recommendations for the prevention and treatment of postpartum haemorrhage (16)*. The primary aim of this recommendation is to improve the quality of care and outcomes for women giving birth, as they relate to PPH and its complications.

1.3 Target audience

The primary audience includes health professionals who are responsible for developing national and local health-care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

This recommendation will also be of interest to women giving birth in a range of resource settings (low to high), as well as members of professional societies involved in the care of pregnant women, staff of nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of maternal and perinatal health programmes.

1.4 Scope of the recommendation

Framed using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format, the questions for this recommendation were:

- For women in the third stage of labour with retained placenta (P), does the use of UVI of oxytocin (I) compared with expectant management (C) improve maternal outcomes (O)?
- For women in the third stage of labour with retained placenta (P), does the use of UVI of oxytocin (I) compared with other UVI regimens (C) improve maternal outcomes (O)?

1.5 Persons affected by the recommendation

The population affected by this recommendation includes all women with a retained placenta after vaginal birth in any setting.

[1] Further information is available at: http://www.gradeworkinggroup.org/.
[2] Further information is available at: https://www.cerqual.org/.

2. Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (15)*. In summary, the process included: (i) identification of the priority question and critical outcomes; (ii) retrieval of evidence; (iii) assessment and synthesis of evidence; (iv) formulation of the recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2019, UVI of oxytocin was identified by the Executive GSG as a high priority for development of a recommendation, in response to new, potentially important evidence on this question. Six main groups were involved in this process, with their specific roles described in the following sections.

2.1 Executive Guideline Steering Group (GSG)

The Executive GSG is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations *(13,14)*.

2.2 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health and Ageing managed the process of updating the recommendations. The WHO Steering Group drafted the key recommendation questions in PICO format, engaged the systematic review teams and guideline methodologists (that is, the Evidence Synthesis Group [ESG]), as well as the members of the GDG and the External Review Group (ERG) (see below). In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, drafted and finalized the guideline document, and will also manage the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

2.3 Guideline Development Group (GDG)

The WHO Steering Group identified a pool of approximately 50 experts and relevant stakeholders from the six WHO regions to constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). This pool consists of a diverse group of experts who are skilled in the critical appraisal of research evidence, implementation of evidence-informed recommendations, guideline development methods, and clinical practice, policy and programmes relating to maternal and perinatal health. Members of the MPH-GDG are identified in a way that ensures geographic representation and gender balance, and there were no perceived or real conflicts of interest. Members' expertise cuts across thematic areas within maternal and perinatal health.

From the MPH-GDG pool, 14 external experts and relevant stakeholders were invited to participate as members of the GDG for updating this recommendation. Those selected were a diverse group with expertise in research, guideline development methods, gender, equity and rights, clinical policy and programmes relating to PPH prevention and treatment.

The 14 GDG members for this recommendation were also selected in a way that ensured geographic representation and gender balance, and there were no important conflicts of interest. The GDG appraised the evidence that was used to inform the recommendation, advised on the interpretation of this evidence, formulated the final recommendation based on the draft prepared by the WHO Steering Group and reviewed and reached unanimous consensus for the recommendation in the final document. The members of the GDG are listed in Annex 1.

2.4 Evidence Synthesis Group (ESG)

WHO convened an ESG composed of guideline methodologists and systematic review teams to conduct or update systematic reviews, appraise the evidence and develop the Evidence to Decision (EtD) frameworks. A systematic review on this question was updated, supported by the Cochrane Pregnancy and Childbirth Group. The WHO Steering Group reviewed and provided input into the updated protocol and worked closely with the Cochrane Pregnancy and Childbirth Group to appraise the evidence using the GRADE methodology. Representatives of the Cochrane Pregnancy and Childbirth Group and a methodologist attended the GDG meeting to provide an overview of the available evidence and GRADE tables and to respond to technical queries from the GDG.

Systematic reviews of qualitative and cost-effectiveness studies were commissioned to generate evidence for other domains of the GRADE EtD frameworks. Researchers from the University of Central Lancashire, United Kingdom, conducted a systematic review of qualitative studies related to views and experiences of women and health-care providers on interventions for the prevention of PPH *(17)*. A scoping search demonstrated that there were no cost-effectiveness studies on the use of this intervention. These reviews were conducted in collaboration with the WHO Steering Group, whose members worked closely with all members of the ESG to review the evidence and prepare the GRADE EtD frameworks. All members of the ESG attended the GDG meetings to provide an overview of the synthesized evidence and to respond to technical queries from the GDG. The members of the ESG are listed in Annex 1.

2.5 External partners and observers

Representatives of the United States Agency for International Development (USAID), the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) participated in the GDG meetings as observers. These organizations, with their long history of collaboration with WHO in maternal and perinatal health guideline dissemination and implementation, were identified as potential implementers of the recommendations. The list of observers who participated in the GDG meetings is included in Annex 1.

2.6 External Review Group (ERG)

The ERG included six technical experts with interests and expertise in the provision of evidence-based care to prevent and treat PPH. The group was geographically diverse and gender balanced, and the members had no important conflicts of interest. The experts reviewed the final document to identify any factual errors and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision-making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendations, health-care professionals and policy-makers. It was not within the remit of this group to change the recommendations that were formulated by the GDG. Members of the ERG are listed in Annex 1.

2.7 Identification of priority questions and outcomes

The priority outcomes were aligned with those from the 2012 *WHO recommendations for prevention and treatment of postpartum haemorrhage (16)*. These outcomes were initially identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the 2012 guideline. After due consideration of the recently published core outcome set for prevention and treatment of PPH *(18)*, three additional outcomes – maternal death, maternal well-being and maternal satisfaction – were included for this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women and to ensure that the final set of recommendations would be woman-centred. Additionally, three process outcomes were removed – reduction of time from decision-making to implementation, availability of drugs and treatment, and accuracy in blood loss assessment – as they were

considered not relevant for this treatment intervention. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

2.8 Evidence identification and retrieval

Evidence to support this update was derived from several sources by the ESG working in collaboration with the WHO Steering Group.

2.8.1 Evidence on the effects of UVI of oxytocin

An existing systematic review was updated for the purpose of this update with the support of the Cochrane Pregnancy and Childbirth Group *(19)*. This systematic review was the primary source of evidence of effectiveness for this recommendation.

Randomized controlled trials relevant to the key question were screened by the review authors, and data on relevant outcomes and comparisons were entered into the Review Manager 5 (RevMan) software. The RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons and outcomes (those that were not relevant to the recommendation were excluded). The RevMan file was then exported to GRADE profiler software (GRADEpro), and GRADE criteria were used to critically appraise the retrieved scientific evidence *(20)*. Finally, evidence profiles (in the form of GRADE summary of findings tables) were prepared for comparisons of interest, including the assessment and judgements for each outcome and the estimated risks.

2.8.2 Evidence on values, resource use and cost-effectiveness, equity, acceptability and feasibility

For questions relating to the other domains of the GRADE EtD frameworks (other than effects – that is, resources, equity, acceptability and feasibility), new systematic reviews were commissioned from external experts. The external experts were asked to prepare a standard protocol before embarking on the review, including: (i) a clear and focused question; (ii) criteria for identification of studies, including search strategies for different bibliographic databases; (iii) methods for assessing risk of bias; and (iv) a data analysis plan. Each protocol was reviewed and endorsed by the WHO Steering Group before the respective review teams embarked on the review process. The entire systematic review development process was iterative, with the review teams in constant communication with the WHO Steering Group to discuss challenges and agree on solutions.

In this regard, a qualitative systematic review was conducted on the views and experiences of women and health-care providers on interventions to prevent PPH *(17)*. This review was used as the primary source of evidence on acceptability, feasibility and equity as they relate to the EtD frameworks for the uterotonic agents of interest. The search strategies for evidence identification and retrieval are detailed in this review *(17)*. Evidence for these domains (acceptability, feasibility and equity) was also supplemented by findings from a qualitative systematic review on women's views and experiences during intrapartum care *(21)*.

Evidence on resource use and cost-effectiveness was based on a systematic review of the literature. The review aimed to evaluate all available evidence regarding which uterotonic agents used for preventing PPH are cost-effective, according to the mode of birth and birth settings. Eligible studies were identified from the following databases from 1980 up to June 2018: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and the National Health Services Economic Evaluation Database. Additional eligible studies were also identified from the reference lists of eligible studies identified via searches of these databases. Eligible studies included those evaluating costs and cost-effectiveness of the uterotonic agents of interest (alone or in combination) in comparison with standard care, placebo or another uterotonic agent for the prevention of PPH in women in the third stage of labour, in any setting. Unit costs were extracted, as well as measures of costs, incremental costs and incremental cost-effectiveness.

2.9 Certainty assessment and grading of the evidence

The certainty assessment of the body of evidence for each outcome was performed using the GRADE approach *(20)*. Using this approach, the certainty of evidence for each outcome was rated as "high", "moderate", "low" or "very low", based on a set of established criteria. The final rating of certainty of evidence was dependent on the factors briefly described below.

Study design limitations: The risk of bias was first examined at the level of each individual study and then across the studies contributing to the outcome. For randomized trials, certainty was first rated as "high" and then downgraded by one ("moderate") or two ("low") levels, depending on the minimum criteria met by the majority of the studies contributing to the outcome.

Inconsistency of the results: The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas it was downgraded when the results were in different directions and confidence limits showed minimal or no overlap.

Indirectness: The certainty of evidence was downgraded when there were serious or very serious concerns regarding the directness of the evidence, that is, whether there were important differences between the research reported and the context for which the recommendation was being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes of interest.

Imprecision: This assessed the degree of uncertainty around the estimate of effect. As this is often a function of sample size and number of events, studies with relatively few participants or events, and thus wide confidence intervals around effect estimates, were downgraded for imprecision.

Publication bias: The certainty rating could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. Downgrading evidence by one level was considered where there was strong suspicion of publication bias.

Certainty of evidence assessments are defined according to the GRADE approach:

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual tool *(22)*. The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low and very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest.

2.10 Formulation of the recommendation

The WHO Steering Group supervised and finalized the preparation of summary of findings tables and narrative evidence summaries in collaboration with the ESG using the GRADE EtD framework. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For the priority questions, judgements were made on the impact of the intervention on each domain to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and ESG created summary documents for each priority question covering evidence on each domain:

- **Effects:** The evidence on the priority outcomes was summarized in this domain to answer the questions: "What are the desirable and undesirable effects of the intervention?" and "What is the certainty of the evidence on effects?" Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the intervention or the comparator. The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the intervention. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the intervention. Where the intervention showed evidence of potential harm and was also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result in a context-specific recommendation, with the context explicitly stated within the recommendation.
- **Values:** This domain relates to the relative importance assigned to the outcomes associated with the intervention by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: "Is there important uncertainty or variability in how much women value the main outcomes associated with the intervention?" When the intervention resulted in benefit for outcomes that most women consistently value (regardless of setting), this was more likely to lead to a judgement in favour of the intervention. This domain, together with the "effects" domain (see above), informed the "balance of effects" judgement.
- **Resources:** For this domain, the questions asked were: "What are the resources associated with the intervention?" and "Is the intervention cost-effective?" The resources required to implement UVI of oxytocin mainly include the costs of providing supplies, training, equipment and skilled human resources. A judgement in favour of or against the intervention was likely where the resource implications were clearly advantageous or disadvantageous, respectively.
- **Acceptability:** For this domain, the question was: "Is the intervention acceptable to women and health-care providers?" Qualitative evidence from systematic reviews exploring perceptions of PPH prevention and treatment by women and health-care providers has informed the judgements for this domain *(17)*. The lower the acceptability, the lower the likelihood of a judgement in favour of the intervention.
- **Feasibility:** The feasibility of implementing this intervention depends on factors such as the resources, infrastructure and training requirements, and the perceptions of health-care providers responsible for administering it. The question addressed was: "Is it feasible for the relevant stakeholders to implement the intervention?" Qualitative evidence from systematic reviews exploring perceptions of PPH prevention and treatment by women and health-care providers was used to inform judgements for this domain *(17)*. Where major barriers were identified, it was less likely that a judgement would be made in favour of the intervention.

- **Equity:** This domain encompasses evidence or considerations as to whether or not the intervention would reduce health inequities. Therefore, this domain addressed the question: "What is the anticipated impact of the intervention on equity?" The experiences and opinions of the GDG members were used to inform judgements for this domain. The intervention was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences are described in the Additional considerations subsections. Such considerations were derived from studies that might not have directly addressed the priority question but provided pertinent information in the absence of direct evidence. These considerations were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD frameworks, including evidence summaries, summary of findings tables and other documents related to each recommendation, to the GDG members two weeks in advance of the GDG meeting. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meeting. During the GDG meeting (11–12 March 2020), which was conducted under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD frameworks and any comments received through preliminary feedback, and formulated the recommendations. The purpose of the meeting was to reach consensus on each recommendation, including its direction and in some instances the specific context, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members. The GDG was asked to select one of the following categories for the recommendation:

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts (context-specific recommendation):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research (research-context recommendation):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided it takes the form of research that addresses unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

2.11 Management of declarations of interests

WHO has a robust process to protect the integrity of its normative work as well as to protect the integrity of individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflicts of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors are a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings according to the guidelines for declaration of interest (DOI) for WHO experts *(15)*. All GDG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in the guideline-related processes. The WHO Steering Group reviewed all DOI before finalizing the experts' invitations to participate. Where any conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the guideline and recommendation development

process. To ensure consistency, the WHO Steering Group applied the criteria for assessing the severity of conflicts of interest as outlined in the *WHO handbook for guideline development* to all participating experts. All findings from the DOI statements received were managed in accordance with the WHO procedures to assure the work of WHO and the contributions of its experts is, actually and ostensibly, objective and independent. The names and biographies of individuals were published online four weeks prior to the meeting. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare such conflicts of interest at the beginning of the GDG meeting, and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.12 Decision-making during the GDG meeting

During the meeting, the GDG reviewed and discussed the evidence summary and sought clarification. In addition to evaluating the balance between the desirable and undesirable effects of the intervention and the overall certainty of the evidence, the GDG applied additional criteria based on the GRADE EtD framework to determine the direction and strength of the recommendation. These criteria included stakeholders' values, resource implications, acceptability, feasibility and equity. Considerations were based on the experiences and opinions of the GDG members and supported by evidence from a literature search where available. EtD tables were used to describe and synthesize these considerations.

Decisions were made based on consensus, defined as the agreement by three quarters or more of the participants. None of the GDG members expressed opposition to the recommendation.

2.13 Document preparation

Prior to the online meeting, the WHO Steering Group prepared a draft version of the GRADE evidence profiles, the evidence summary and other documents relevant to the GDG's deliberation. The draft documents were made available to the participants of the meeting two weeks before the meeting for their comments. During the meeting, these documents were modified in line with the participants' deliberations and remarks. Following the meeting, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to the GDG and the ERG for their final review and approval.

2.14 Peer review

Following review and approval by GDG members, the final document was sent to eight external independent experts (comprising the ERG) who were not involved in the guideline panel for peer review. The WHO Steering Group evaluated the inputs of the peer reviewers for inclusion in this document. After the meeting and external peer review, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and improving language to address any lack of clarity.

3. Recommendation and supporting evidence

The following section outlines the recommendation and the corresponding narrative summary of evidence for the prioritized question. The EtD table, summarizing the balance between the desirable and undesirable effects and the overall certainty of the supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity that were considered in determining the strength and direction of the recommendation, is presented in the EtD framework (Annex 4).

The following recommendation was adopted by the GDG. Evidence on the effectiveness of this intervention was derived from the updated systematic review and summarized in GRADE tables (Annex 4). The certainty of the supporting evidence was rated as "moderate" for most of the critical outcomes.

To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional remarks reflecting the summary of the discussion by the GDG are included under the recommendation.

Umbilical vein injection of oxytocin is recommended for the treatment of retained placenta only in the context of rigorous research.

(Research-context recommendation)

Justification

- Evidence from trials that compared both umbilical vein injection of oxytocin versus expectant management and umbilical vein injection of oxytocin versus umbilical vein injection of saline suggests that this intervention may lead to a reduction in the manual removal of placenta. However, the effect of this intervention on other priority outcomes (including infections, maternal satisfaction and length of hospitalization) is unclear. While the cost-effectiveness is not known, additional costs in supplies required to implement this intervention are probably negligible. When compared with injection of other solutions and uterotonics, no other umbilical vein injection regimen was shown to be clearly better than umbilical vein injection of oxytocin.

Remarks

- The Guideline Development Group acknowledged the potential of umbilical vein injectionof oxytocin solution in the treatment of retained placenta but considered the evidence of benefit in terms of manual removal of the placenta without impact on other priority outcomes insufficient to make a recommendation for routine clinical practice. The group agreed that high-quality randomized trials comparing umbilical vein injection of uterotonics with expectant management of women with retained placenta are needed, with the aim of demonstrating its impact on severe postpartum haemorrhage-related morbidity in addition to a reduction in manual removal of the placenta.
- In research context, it is safer to consider the use of this intervention in situations in which retained placenta occurs in the absence of abnormal bleeding.
- There are three types of retained placenta and umbilical vein injection of oxytocin is likely to be only effective in treating placenta adherens, the most common type of retained placenta, which occurs as a result of failed contraction of the retroplacental myometrial. To date, studies have not distinguished the subtypes before treatment, and this may have contributed to the results showing lack of efficacy of treatment with umbilical vein injection for retained placenta.

4. Dissemination, adaptation and implementation of the recommendation

The dissemination and the implementation of this recommendation are to be considered by all stakeholders involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase women's access to maternal health care and to strengthen the capacity at health-care facilities of all levels to ensure they can provide high-quality services to all women giving birth. It is therefore crucial that this recommendation be translated into care packages and programmes at country and health-care facility levels, where appropriate.

4.1 Recommendation dissemination

The recommendation will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. This recommendation will also be available on the WHO website and the WHO Reproductive Health Library.[1] Updated recommendations are also routinely disseminated during meetings or scientific conferences attended by WHO maternal and perinatal health staff.

The recommendation document will be translated into the six United Nations languages and disseminated through the WHO regional offices. Technical assistance will be provided to any WHO regional office willing to translate the full recommendation into any of these languages.

4.2 Adaptation

National and subnational subgroups may be established to adapt and implement this recommendation based on an existing strategy. This process may include the development or revision of existing national guidelines or protocols based on the updated recommendation.

Existing global models such as those for WHO antenatal and intrapartum care guidelines can be adapted to different countries, contexts and individual needs and preferences of women. The conceptual basis of these models is to drive improvements in the quality of maternal health care, by aiming to achieve the best possible physical, emotional and psychological outcomes for the woman and her baby, irrespective of the influence of generic policies that may exist within and across health systems and countries. Both models address relevant health policy, organizational and user-level considerations. These models thus support implementation of WHO recommendations and are intended to be adapted by stakeholders and partners at regional, country and local levels into locally appropriate documents and tools.

The successful introduction of evidence-based policies (relating to updated recommendations) depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of existing national or local guidelines and protocols, often supported by ministries of health, United Nations agencies, local professional societies and other relevant leadership groups. An enabling environment should be created for the use of this recommendation, including changes in the behaviour of health-care practitioners to enable the use of evidence-based practices.

In the context of humanitarian emergencies, adaptation of the current recommendation should consider the integration and alignment with other response strategies. Additional considerations for the unique needs of women in emergency settings, including their values and preferences, should be made. Context-specific tools and toolkits may be required

[1] Available at: www.who.int/rhl.

in addition to standard tools to support the implementation of the recommendation in humanitarian emergencies by stakeholders.

4.3 Implementation research considerations

- UVI of oxytocin is recommended only in the context of rigorous research. This rating category indicates that there are important uncertainties about this intervention. The implementation can still be undertaken at a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related to effectiveness, as well as acceptability and feasibility.
- Relevant stakeholders (particularly those involved in programmes to prevent and treat PPH) should be informed that there is currently insufficient evidence to recommend in favour of or against the use of UVI of oxytocin for the treatment of retained placenta. Providers who elect to use this intervention (and women to whom it is given) should be informed of these uncertainties.
- This recommendation should not detract from the importance of good-quality care after childbirth to prevent and treat PPH, including the use of uterotonics, tranexamic acid, intravenous fluids and blood products.
- To assess effectiveness, rigorous research should in this case be done through randomized trials.
- There is currently no standardized dilution regimen for oxytocin for UVI. Oxytocin dose from available evidence ranged from 10 international units (IU) to 100 IU. Likewise, the volume of saline used for dilution ranges from 10 mL to 30 mL.
- The injection methods are either direct injection into the umbilical vein or via an infant mucus aspiration catheter introduced along the umbilical vein to 5 cm from the placental insertion. The use of the catheter, with an additional 30 mL of saline solution, has proven more effective to reach the placental bed than direct injection *(23)*.

5. Research implications

The GDG identified important knowledge gaps that need to be addressed through primary research, which may have an impact on this recommendation. The following questions were identified as those that demand urgent priority:

In women with retained placenta,

- is UVI of oxytocin more effective than expectant management in reducing PPH-related maternal mortality and morbidity?
- is UVI of oxytocin more effective than intramuscular or intravenous oxytocin administration in reducing PPH-related maternal mortality and morbidity?
- is UVI of other uterotonics (carbetocin, prostaglandins) more effective than UVI of oxytocin in reducing PPH-related maternal mortality and morbidity?
- is UVI effective in only certain types of retained placenta and, if so, can that type be accurately diagnosed clinically prior to the UVI?

6. Applicability issues

6.1 Anticipated impact on the organization of care and resources

If UVI of oxytocin was proven effective to treat retained placenta, updated training curricula and provision of training to relevant health workers will be required. In addition, measures to ensure sustainable supply of oxytocin and the necessary injection equipment (which are typically available in maternity care settings) are required.

6.2 Monitoring and evaluating guideline implementation

As this is a recommendation in the context of rigorous research, implementation of this recommendation should ideally be conducted in the context of high-quality randomized controlled trials that could help to address the uncertainties around benefits and harms of this intervention.

However, if UVI of oxytocin is implemented into care for women with retained placenta, the impact of this recommendation on important health outcomes should be monitored at health service, district and national level.

The uncertainties regarding the benefits and potential harms of this intervention should not detract from the importance of broader efforts to monitor and evaluate the quality of maternal and newborn health care. Any such monitoring and evaluation activities should adopt clearly defined review criteria and indicators; these could be associated with locally agreed targets and aligned with the standards and indicators described in the WHO document *Standards for improving quality of maternal and newborn care in health facilities (24)*.

7. Updating the recommendation

The Executive GSG convenes annually to review WHO's current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. Accordingly, this recommendation will be reviewed and prioritized by the Executive GSG. If new evidence that could potentially impact the current evidence base is identified, the recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concerns about the validity of the recommendation should be promptly communicated to the guideline implementers, in addition to any plans to update the recommendation.

WHO welcomes suggestions regarding additional questions for inclusion in the updated recommendation. Please email your suggestions to srhmph@who.int.

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Annex 1. External experts and WHO staff involved in the preparation of the recommendation

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Annex 2. Priority outcomes used in decision-making

Critical outcomes:

- Maternal death
- Additional blood loss ≥ 500 mL
- Additional blood loss ≥ 1000 mL
- Blood transfusion
- Additional uterotonics
- Invasive nonsurgical interventions (including manual removal of placenta, curettage and artery embolization)
- Surgical interventions (including hysterectomy)
- Maternal temperature ≥ 40 °C
- Procedure-related complications
- Infections
- Severe morbidity
- Maternal transfer

Important outcomes:

- Mean blood loss
- Postpartum anaemia
- Additional non-surgical interventions (for example, external aortic compression and compression garments)
- Nausea, vomiting or shivering
- Maternal temperature ≥ 38 °C
- Delayed initiation of breastfeeding
- Prolonged hospitalization
- Maternal well-being
- Maternal satisfaction

Annex 3. Summary and management of declared interests from GDG members

Name	Expertise contributed to guideline development	Declared interest	Management of conflict of interest
Oluwarotimi I Akinola	Content expert and end-user	None declared	Not applicable
Melania Amorim	Content expert and end-user	None declared	Not applicable
Brendan Carvalho	Content expert and end-user	Serves as technical consultant for Gauss Surgical (company that measures peripartum and operative blood loss). Receives share options from Gauss Surgical.	The conflict was not considered serious enough to affect Guideline Development Group (GDG) membership or participation.
Catherine Deneux-Tharaux	Content expert and end-user	None declared	Not applicable
Tippawan Liabsuetrakul	Content expert and end-user	None declared	Not applicable
Martin Meremikwu	Content expert and end-user	None declared	Not applicable
Suellen Miller	Content expert and end-user	Serves as a technical advisor to the Blue Fuzion Group who manufactures and distributes one brand of non-pneumatic anti-shock garment, the LifeWrap. UCSF receives a royalty for the trademark.	The conflict was not considered serious enough to affect GDG membership or participation.
Ashraf Nabhan	Content expert and implementer	None declared	Not applicable
Mari Nagai	Content expert and end-user	None declared	Not applicable
Hayfaa Wahabi	Content expert and end-user	None declared	Not applicable
Dilys Walker	Content expert and end-user	Co-founder and President of the nongovernmental organization PRONTO International. PRONTO designs and implements simulation and team training for obstetric and neonatal emergencies, including postpartum haemorrhage. Professor Walker has donated funds to the organization. PRONTO International has the rights to the low-tech birth simulator, PARTO Pants and the PRONTO Pack simulation training kit.	The conflict was not considered serious enough to affect GDG membership or participation.

Andrew Weeks	Content expert and end-user	Chief investigator of the COPE trial, and co-inventor of the Butterfly device to treat postpartum haemorrhage as well as chief investigator of the development study. Both funded by NIHR (United Kingdom) research grants to the University of Liverpool. The University is the device patent holder but, as co-inventor, Professor Weeks would receive a share of the profits.	The conflict was not considered serious enough to affect GDG membership or participation.

Annex 4. Evidence to Decision frameworks

4.1 Umbilical vein injection of oxytocin solution compared to expectant management

Question

Following is the question of interest in PICO (population (P), intervention (I), comparator (C), outcome (O)) format:

- For women in the third stage of labour with retained placenta (P), does the use of UVI of oxytocin (I) compared to expectant management (C) improve maternal outcomes (O)?

Problem: Treating retained placenta

Perspective: Clinical practice recommendation – population perspective

Population (P): Women in the third stage of labour, with a diagnosis of retained placenta

Intervention (I): UVI of oxytocin

Comparator (C): Expectant management

Setting: Hospital or community setting

Subgroups: If required.

Priority outcomes (O):[1]

Critical outcomes:

- Maternal death
- Additional blood loss ≥ 500 mL
- Additional blood loss ≥ 1000 mL
- Blood transfusion
- Additional uterotonics
- Invasive nonsurgical interventions (including manual removal of placenta [MROP], curettage and artery embolization)
- Surgical interventions (including hysterectomy)
- Maternal temperature ≥ 40 °C
- Procedure-related complications
- Infections
- Severe morbidity
- Maternal transfer

[1] These outcomes reflect the prioritized outcomes used in the development of this recommendation, in *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (2012). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

Important outcomes:

- Mean blood loss
- Postpartum anaemia
- Additional nonsurgical interventions (for example, external aortic compression and compression garments)
- Nausea, vomiting or shivering
- Maternal temperature ≥ 38 °C
- Delayed initiation of breastfeeding
- Prolonged hospitalization
- Maternal well-being
- Maternal satisfaction

Assessment

Effects of interventions

What is the effect of treating retained placenta with UVI with oxytocin on the priority outcomes?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of UVI for treating retained placenta is from an update of a Cochrane Review that now includes 24 trials (2348 women) *(1)*. Twenty-three of these trials (2302 women) included women who received UVI with oxytocin to treat retained placenta. However, two trials did not contribute data to the analyses, one because of inconsistencies in the reported data (44 women), and another due to a lack of information about the number of women in each group in the only available abstract (37 women). Two groups (16 women) from one four-arm trial were also excluded from the analyses because those trial arms did not meet the review inclusion criteria.

The trials that contributed data to the analyses took place in hospital settings in Argentina, Belgium, Denmark (four trials), Egypt (two trials), Finland, Hong Kong SAR (China), India, Israel, Italy, Malaysia (two trials), the Netherlands, Pakistan (two trials), Uganda and the United Kingdom (four trials). The largest trial involved 13 centres across Pakistan, Uganda and the United Kingdom. Ten trials involved multiple centres in single countries, ranging from two to 11 sites. The remaining 11 trials were undertaken in a single hospital.

The number of women randomized in the trials ranged from 30 to 577 women. Thirteen trials included only women with singleton pregnancies and, in the other eight trials contributing data, this was not described. Some trials specified a minimum gestational age or age range in the inclusion criteria: ≥ 20 weeks (one trial); ≥ 28 weeks (four trials); ≥ 34 weeks (three trials); 34–42 weeks (one trial); ≥ 37 weeks (two trials). One trial described women as both term and preterm, and in nine trials gestational age was not reported.

Fourteen studies excluded women with postpartum haemorrhage (PPH) or bleeding requiring immediate treatment, hypovolaemic shock or haemodynamic instability. However, PPH status at trial entry was not explicit in the remaining studies. In terms of management of the third stage of labour, 15 trials reported that women in both the treatment and control groups experienced active management of the third stage of labour, although the oxytocic drug, dose and route varied considerably; in three trials,

some but not all women in both groups received oxytocic drugs; and the remaining six studies did not provide information about management of the third stage.

Although most trials contributing data to the analyses diagnosed retained placenta 30 minutes post-birth, the time point for diagnosis varied between trials. Two trials (reporting data on 73 women) diagnosed retained placenta 15 minutes post-birth; six trials (295 women) at 20 minutes, although in one of these trials (81 women), treatment was administered at 30 minutes; 11 trials (1736 women) at 30 minutes; one trial (54 women) at 45 minutes; and one trial (28 women) at 60 minutes.

Most trials prespecified a time point post-treatment (or post-diagnosis of retained placenta in the expectant management group) for MROP. MROP was at 15 minutes post-treatment/diagnosis in four trials (reporting data on 163 women); at 30 minutes in 11 trials (1388 women); at 40 minutes in one trial (37 women); at 30–45 minutes in one trial (200 women); and at 45 minutes in one trial (81 women). In one trial (200 women), MROP was based on the judgement of the attending obstetrician; in the remaining two trials (117 women), the protocol for MROP was not described in the trial reports.

In the trials comparing UVI of oxytocin versus expectant management (seven trials, 554 women), oxytocin was administered in saline solution, but the dose and the total volume of solution varied between trials. The expectant management strategies also varied, between no active treatment (two trials), controlled cord traction (one trial, received by all women in both groups), standard care to expel the placenta (detail not described; one trial, received by all women in both groups), and in one further trial women were "treated 'conservatively' with planned manual removal of the placenta".

UVI of oxytocin solution versus expectant management

- Oxytocin 10 IU plus saline solution 10 mL versus expectant management (one trial, 35 women)[1]
- Oxytocin 10 IU plus saline solution 20 mL versus expectant management (two trials, 173 women)
- Oxytocin 20 IU plus saline solution 18 mL versus expectant management (one trial, 191 women)
- Oxytocin 20 IU plus saline solution 20 mL versus expectant management (one trial, 52 women)
- Oxytocin 100 IU plus saline solution 20 mL versus expectant management (one trial, 42 women)
- Oxytocin 100 IU plus saline solution 30 mL versus expectant management (one trial, 61 women).

Effects of UVI of oxytocin solution versus expectant management

It is unclear whether UVI of oxytocin solution has an effect on **maternal death**, **additional blood loss ≥500 mL**, **additional blood loss ≥1000 mL** and the use of **additional uterotonics**. The evidence for all four outcomes was assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as of very low certainty.

Blood transfusion: Low-certainty evidence suggests that UVI of oxytocin solution may make little or no difference to blood transfusion when compared with expectant management (four trials, 339 women; 20/168 versus 24/171; risk ratio [RR] 0.81, 95% confidence interval [CI] 0.47 to 1.38).

[1] The number of women detailed is the total number of women for whom data were available in both groups for all trials included in this comparison.

Invasive nonsurgical interventions: Low-certainty evidence suggests that UVI of oxytocin solution may reduce the need for **MROP** when compared with expectant management (seven trials, 546 women; 131/282 versus 159/264; average RR 0.73, 95% CI 0.56 to 0.95). It is unclear what effect the intervention has on the risk of women requiring **instrumental evacuation of retained products of conception** (very-low-certainty evidence).

It is also unclear what effect UVI of oxytocin solution has on the priority outcomes **infections**, **severe maternal morbidity**, **mean blood loss (in mL)**, **postpartum anaemia** (the Cochrane review reported the proxy outcomes **haemoglobin 24–48 hours postpartum** and **haemoglobin 40–45 days postpartum**), **prolonged hospitalization** (**stay in hospital for more than two days** was reported), and **maternal satisfaction** (**maternal dissatisfaction with third stage management** was reported). The evidence for all of these outcomes was of very low certainty. No other priority outcomes were reported under this comparison.

Additional considerations

A separate 2012 Cochrane review assessed the effectiveness of UVI (alone or with any uterotonic drug) for the routine management of the third stage of labour and identified nine studies (1118 women) *(2)*. Comparing UVI of normal saline plus oxytocin with UVI of saline only (six studies, 394 women), there was no evidence of difference in any of the relevant outcomes. Other comparisons included only one study for each, and there was no relevant information available. The authors concluded that there was insufficient evidence to support the routine use of oxytocin (or other uterotonics) with normal saline via UVI for the active management of the third stage of labour until new evidence is available.

Desirable effects

How substantial are the desirable anticipated effects of UVI of oxytocin versus expectant management?

Judgement

— Don't know	— Varies	— Trivial	— Small	✓ Moderate	— Large

Undesirable effects

How substantial are the undesirable anticipated effects of UVI of oxytocin versus expectant management?

Judgement

✓ Don't know	— Varies	— Large	— Moderate	— Small	— Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of UVI of oxytocin versus expectant management?

— No included studies	✓ Very low	— Low	— Moderate	— High

Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with UVI of oxytocin for retained placenta?

Research evidence

In a review of qualitative studies evaluating "what women want" from intrapartum care, findings indicate that most women want a normal birth (with good outcomes for mother and baby) but acknowledge that medical intervention may sometimes be necessary *(high confidence) (3)*. Most women, especially those giving birth for the first time, are apprehensive about labour and birth *(high confidence)* and wary of medical interventions, although, in certain contexts and/or situations, women welcome interventions to address recognized complications *(low confidence)*. Where interventions are introduced, women would like to receive relevant information from technically competent health-care providers who are sensitive to their needs *(high confidence)*.

Findings from an update of a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and providers suggest that women do not recognize the clinical definitions of blood loss or what might be considered "normal" blood loss *(moderate confidence) (4)*. Furthermore, in some low- and middle-income countries (LMICs), women place a greater value on the expulsion of so-called "dirty blood", which they perceive as a normal cleansing process and something that should not be prevented *(moderate confidence)*.

The same review highlighted women's need for information about PPH, ideally given during antenatal care *(moderate confidence)*, and the importance of kind, clinically competent staff with a willingness to engage in shared decision-making around PPH management *(moderate/low confidence)*. In addition, it was found that women are concerned about feelings of exhaustion and anxiety (at being separated from their babies) following PPH, as well as the long-term psychological effects of experiencing PPH and the negative impact this may have on their ability to breastfeed *(moderate/low confidence)*.

Additional considerations

None.

Judgement

—	—	✓	—
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour UVI of oxytocin or expectant management?

Judgement

✓ Don't know	— Varies	— Favours expectant manage-ment	— Probably favours expectant manage-ment	— Does not favour either	— Probably favours UVI of oxytocin	— Favours UVI of oxytocin

Resources

How large are the resource requirements (costs) of favouring UVI of oxytocin?

Research evidence

The Cochrane review on UVI for retained placenta did not prespecify any cost or economic outcomes. A literature search did not identify any cost-effectiveness studies related to this intervention.

Additional considerations

This intervention requires items (oxytocin, needle, syringe, normal saline, gloves) that are typically available in adequately equipped hospital settings. Performing this intervention would be considered part of the expertise of skilled health personnel.

While no cost-effectiveness evidence was identified, reduction in the need for MROP (an invasive procedure requiring general anaesthesia, which may also necessitate transfer to a higher level of care) would likely reduce costs.

Main resource requirements

Resource	Description
Staff	Oxytocin administered via UVI by skilled health-care personnel.
Training	Training to administer injections, and to monitor and manage expected and unexpected side-effects, is part of standard maternity staff training. However, additional training would be required if this intervention is to be introduced in settings where it has not previously been available.
Supplies	■ Oxytocin indicative cost per 10 IU: US$ 0.22–1.19 *(5,6)* ■ Needle and syringe cost: Approximately US$ 0.07 *(6)* ■ Normal saline: Median price of USD$ 1 per litre *(7)* ■ Gloves.
Equipment and infrastructure	Oxytocin cold chain storage and transport costs Cost per birth: Possibly US$ 0.84 in a low-resource setting *(8)*.
Time	Minimal
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

✓ Don't know	— Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

✓ No included studies	— Very low	— Low	— Moderate	— High

Cost-effectiveness

Judgement

✓ Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours oxytocin	— Favours oxytocin

Equity

What would be the impact of UVI of oxytocin on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

The 2015 World Health Organization (WHO) State of inequality report indicates that women who are poor, least educated and who reside in rural areas have lower coverage of health interventions and worse health outcomes than more advantaged women *(9)*. Therefore, reducing maternal morbidity due to PPH could have a positive impact on health equity and improve outcomes among disadvantaged women. Reducing the need for MROP or curettage to treat retained placenta (which may require transfer to a higher level of care) would probably reduce inequities for women giving birth in primary health facilities. On the other hand, the skilled health personnel at primary health level would have to acquire another expertise, which might be less feasible in low-resource settings.

Judgement

— Don't know	✓ Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased

Acceptability

Is UVI of oxytocin acceptable to key stakeholders?

Research evidence

No direct evidence relating to the acceptability of UVI of oxytocin for the treatment of retained placenta from either women or providers was identified. However, intravenous oxytocin is widely used internationally and in a range of resource settings (low to high) *(4)*.

Additional considerations

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health-care providers has provided indirect evidence in relation to oxytocin use in the postpartum period *(4)*. Findings indicate that providers recognize the benefits of using oxytocin to prevent PPH and hasten the delivery of the placenta *(moderate confidence)*. However, in some LMIC settings, providers hold the perception that the intravenous oxytocin may actually cause retained placenta when administered preventatively or may contribute to PPH when given to induce labour *(moderate confidence)*. In rural LMIC settings where access to health facilities may be limited, community-based health providers (usually traditional birth attendants) prefer to use traditional techniques (massage) and herbal medicines to treat retained placenta *(moderate confidence)*.

There were no findings from studies of women's perceptions relating to the acceptability of oxytocin.

Judgement

✓ Don't know	— Varies	— No	— Probably No	— Probably Yes	— Yes

Feasibility

Is UVI of oxytocin feasible to implement?

Research evidence

No direct evidence relating to the feasibility of using a uterotonic for the treatment of retained placenta from either women or providers was identified. However, intravenous oxytocin is widely used internationally and in a range of resource settings (low to high) *(4)*.

Additional considerations

This intervention requires items (oxytocin, needle, syringe, normal saline, gloves) that are typically available in adequately equipped health facilities providing normal delivery care by a skilled birth attendant. Performing this intervention would be considered part of the expertise of skilled health personnel.

Indirect findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and health-care providers suggest that resource constraints may influence effective use of oxytocin for retained placenta, particularly in LMICs *(high confidence) (4)*. Inconsistent supplies and concerns about oxytocin storage in areas with limited/inconsistent electricity hinder utilization, and a lack of experienced staff to administer the injection limits use in certain contexts *(high confidence)*. In a wide variety of settings, health-care providers feel they need more training in third-stage management as well as specific training on when/how to administer oxytocin *(high confidence)*.

Injectable oxytocin is already widely available in a range of resource settings (low to high) and has multiple applications (such as for PPH prevention and treatment as well as labour induction). Oxytocin (10 IU in 1 mL for injection) is listed in the WHO Model list of essential medicines *(10)*.

Judgement

— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes

Summary of judgements table

Desirable effects	— Don't know	— Varies		— Trivial	— Small	✓ Moderate	— Large
Undesirable effects	✓ Don't know	— Varies		— Large	— Moderate	— Small	— Trivial
Certainty of the evidence	— No included studies			✓ Very low	— Low	— Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	— Don't know	— Varies	— Favours expectant management	— Probably favours expectant management	— Does not favour either	✓ Probably favours UVI with oxytocin	— Favours UVI with oxytocin
Resources required	✓ Don't know	— Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Certainty of the evidence on required resources	✓ No included studies			— Very low	— Low	— Moderate	— High
Cost-effectiveness	✓ Don't know	— Varies	— Favours placebo/no treatment	— Probably favours placebo/no treatment	— Does not favour either	— Probably favours oxytocin	— Favours oxytocin
Equity	— Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	✓ Probably increased	— Increased
Acceptability	✓ Don't know	— Varies		— No	— Probably No	— Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No	— Probably No	✓ Probably Yes	— Yes

Summary of findings table

Question: UVI of oxytocin compared with expectant management for management of retained placenta
Setting: Hospital (Argentina, Belgium, Denmark, Malaysia, Netherlands, United Kingdom)
Reference: Kumar N, Jahanfar S, Haas DM, Weeks AD. Umbilical vein injection for management of retained placenta. Cochrane Database Syst Rev (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI with oxytocin solution	Expectant management	Relative (95% CI)	Absolute (95% CI)		
MATERNAL DEATH												
2	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/45 (0.0%)	0/48 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
ADDITIONAL BLOOD LOSS ≥ 500 ML												
3	randomized trials	serious[c]	not serious	not serious	very serious[d]	none	32/126 (25.4%)	26/119 (21.8%)	**RR 1.00** (0.45 to 2.22)	**0 fewer per 1000** (from 120 fewer to 267 more)	⨁◯◯◯ VERY LOW	CRITICAL
ADDITIONAL BLOOD LOSS ≥ 1000 ML												
2	randomized trials	serious[c]	not serious	not serious	very serious[e]	none	7/100 (7.0%)	5/90 (5.6%)	**RR 1.23** (0.41 to 3.74)	**13 more per 1000** (from 33 fewer to 152 more)	⨁◯◯◯ VERY LOW	CRITICAL
BLOOD TRANSFUSION												
4	randomized trials	serious[f]	not serious	not serious	serious[g]	none	20/168 (11.9%)	24/171 (14.0%)	RR 0.81 (0.47 to 1.38)	**27 fewer per 1000** (from 74 fewer to 53 more)	⨁⨁◯◯ LOW	CRITICAL
ADDITIONAL UTEROTONICS												
1	randomized trials	serious[c]	not serious	not serious	very serious[h]	none	10/30 (33.3%)	20/30 (66.7%)	**RR 0.50** (0.28 to 0.88)	**333 fewer per 1000** (from 480 fewer to 80 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI with oxytocin solution	Expectant management	Relative (95% CI)	Absolute (95% CI)		
INVASIVE NONSURGICAL INTERVENTIONS – MANUAL REMOVAL OF THE PLACENTA												
7	randomized trials	very serious[i]	not serious	not serious	not serious	none	131/282 (46.5%)	159/264 (60.2%)	**RR 0.73** (0.56 to 0.95)	**163 fewer per 1000** (from 265 fewer to 30 fewer)	⨁⨁◯◯ LOW	CRITICAL
SURGICAL INTERVENTIONS – INSTRUMENTAL EVACUATION OF RETAINED PRODUCTS OF CONCEPTION												
2	randomized trials	serious[f]	not serious	not serious	very serious[j]	none	23/124 (18.5%)	32/118 (27.1%)	**RR 0.68** (0.43 to 1.06)	**87 fewer per 1000** (from 155 fewer to 16 more)	⨁◯◯◯ VERY LOW	CRITICAL
INFECTION												
1	randomized trials	seriousc	not serious	not serious	very serious[k]	none	5/93 (5.4%)	4/86 (4.7%)	**RR 1.16** (0.32 to 4.16)	**7 more per 1000** (from 32 fewer to 147 more)	⨁◯◯◯ VERY LOW	CRITICAL
SERIOUS MATERNAL MORBIDITY (HYSTERECTOMY, ADMISSION TO INTENSIVE CARE, RENAL OR RESPIRATORY FAILURE, AND OTHER ADDITIONAL SURGICAL PROCEDURES TO TREAT PPH OTHER THAN MANUAL REMOVAL OF PLACENTA, RELATED TO THE RANDOMIZED INTERVENTIONS)												
2	randomized trials	serious[c]	not serious	not serious	very serious[b]	none	0/45 (0.0%)	0/45 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
MEAN BLOOD LOSS (ML)												
2	randomized trials	very serious[l]	seriousm	not serious	very serious[d]	none	88	84	-	**MD 20.92 lower** (233.56 lower to 191.71 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
POSTPARTUM ANAEMIA – HAEMOGLOBIN 24–48 HOURS POSTPARTUM, G%												
1	randomized trials	serious[f]	not serious	not serious	very serious[n]	none	85	81	-	**MD 0** (0.61 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI with oxytocin solution	Expectant management	Relative (95% CI)	Absolute (95% CI)		
POSTPARTUM ANAEMIA - HAEMOGLOBIN 40-45 DAYS POSTPARTUM, G%												
1	randomized trials	serious[f]	not serious	not serious	very serious[n]	none	47	49	-	**MD 0.5 higher** (0.14 lower to 1.14 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
PROLONGED HOSPITALIZATION (STAY AT HOSPITAL MORE THAN TWO DAYS)												
1	randomized trials	serious[c]	not serious	not serious	very serious[o]	none	19/94 (20.2%)	16/86 (18.6%)	**RR 1.09** (0.60 to 1.97)	**17 more per 1000** (from 74 fewer to 180 more)	⨁◯◯◯ VERY LOW	IMPORTANT
MATERNAL DISSATISFACTION WITH THIRD-STAGE MANAGEMENT												
1	randomized trials	very serious[l]	not serious	not serious	very serious[h]	none	6/18 (33.3%)	21/24 (87.5%)	**RR 0.38** (0.19 to 0.74)	**543 fewer per 1000** (from 709 fewer to 228 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **RR**: risk ratio; **MD**: mean difference; **UVI**: umbilical vein injection

[a] Data provided by studies at moderate and high risk of bias.
[b] Small sample size. No events, not estimable.
[c] All of pooled effect provided by study (or studies) at moderate risk of bias.
[d] Small sample size. Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.
[e] Small sample size, few events. Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.
[f] Majority of pooled effect provided by study (or studies) at moderate risk of bias.
[g] Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.
[h] Single study with small sample size and few events.
[i] Majority of pooled effect provided by studies at high risk of bias for this outcome.
[j] Small sample size. Wide CI crossing the line of no effect and also including appreciable reduction in risk with oxytocin injection.
[k] Single study with small sample size and few events. Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.
[l] Majority of pooled effect provided by study at high risk of bias.
[m] Severe statistical heterogeneity (I^2=80%).
[n] Single study with small sample size.
[o] Single study with small sample size. Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.

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4.2 Umbilical vein injection of oxytocin compared to other umbilical vein injection regimens

Question

Following is the question of interest in PICO (population (P), intervention (I), comparator (C), outcome (O)) format:

- For women in the third stage of labour with retained placenta (P), does the use of UVI of oxytocin (I) compared to other UVI regimens (C) improve maternal outcomes (O)?

Problem: Retained placenta

Perspective: Clinical practice recommendation – population perspective

Population (P): Women in the third stage of labour, with a retained placenta

Intervention (I): UVI of oxytocin

Comparator (C): UVI of solution without uterotonics; with another uterotonics; UVI of plasma expander

Setting: Hospital or community setting.

Priority outcomes (O):[1]

Critical outcomes:

- Maternal death
- Additional blood loss ≥ 500 mL
- Additional blood loss ≥ 1000 mL
- Blood transfusion
- Additional uterotonics
- Invasive nonsurgical interventions (including manual removal of placenta [MROP], curettage and artery embolization)
- Surgical interventions (including hysterectomy)
- Maternal temperature ≥ 40 °C
- Procedure-related complications
- Infections
- Severe morbidity
- Maternal transfer

Important outcomes:

- Mean blood loss
- Postpartum anaemia
- Additional nonsurgical interventions (for example, external aortic compression and compression garments)
- Nausea, vomiting or shivering

[1] These outcomes reflect the prioritized outcomes used in the development of this recommendation, in *WHO recommendations for the prevention and treatment of postpartum haemorrhage* (2012). The outcomes "maternal well-being" and "maternal satisfaction" have been added as part of this update.

- Maternal temperature ≥ 38 °C
- Delayed initiation of breastfeeding
- Prolonged hospitalization
- Maternal well-being
- Maternal satisfaction

Assessment

Effects of interventions

What is the effect of treating retained placenta with UVI of oxytocin on the priority outcomes, when compared with other UVI regimens?

Research evidence

Summary of evidence

Source and characteristics of studies

Evidence on the effects of UVI for treating retained placenta is from an updated Cochrane Review that includes 24 trials (2348 women) *(1)*. Twenty-three of these trials (2302 women) included women who received UVI of oxytocin to treat retained placenta. However, two trials did not contribute data to the analyses, one because of inconsistencies in the reported data (44 women), and another due to a lack of information about the number of women in each group in the available abstract (37 women). Two groups (16 women) from one four-arm trial were also excluded from the analyses, because those trial arms did not meet the review inclusion criteria.

The trials that contributed data to the analyses took place in hospital settings in Argentina, Belgium, Denmark (four trials), Egypt (two trials), Finland, Hong Kong SAR (China), India, Israel, Italy, Malaysia (two trials), the Netherlands, Pakistan (two trials), Uganda and the United Kingdom (four trials). The largest trial involved 13 centres across Pakistan, Uganda and the United Kingdom. Ten trials involved multiple centres in single countries, ranging from two to 11 sites. The remaining 11 trials were undertaken in a single hospital.

The number of women randomized in the trials ranged from 30 to 577 women. Thirteen trials included only women with singleton pregnancies and, in the other eight trials contributing data, this was not described. Some trials specified a minimum gestational age or age range in the inclusion criteria: ≥ 20 weeks (one trial); ≥ 28 weeks (four trials); ≥ 34 weeks (three trials); 34–42 weeks (one trial); ≥ 37 weeks (two trials). One trial described women as both term and preterm, and in nine trials gestational age was not reported.

Although most trials contributing data to the analyses diagnosed retained placenta 30 minutes after birth, the time point for diagnosis varied between trials. Two trials (reporting data on 73 women) diagnosed retained placenta 15 minutes after birth; six trials (295 women) at 20 minutes, although in one of these trials (81 women), treatment was administered at 30 minutes; 11 trials (1736 women) at 30 minutes; one trial (54 women) at 45 minutes; one trial (28 women) at 60 minutes.

Most trials prespecified a time point post-treatment (or post-diagnosis of retained placenta in the expectant management group) for MROP. MROP was at 15 minutes post-treatment/diagnosis in four trials (reporting data on 163 women); at 30 minutes in 11 trials (1388 women); at 40 minutes in one trial (37 women); at 30–45 minutes in one trial (200 women); and at 45 minutes in one trial (81 women). In one trial (200 women), MROP was based on the judgement of the attending obstetrician; in the

remaining two trials (117 women), the protocol for MROP was not described in the trial reports.

The trials considered in this evidence summary compared UVI of oxytocin solution versus UVI of saline solution; plasma expander; prostaglandin solution; ergometrine solution; and carbetocin solution (although in the comparison with prostaglandins and carbetocin, women receiving oxytocin were analysed as the control group). Five trials (all oxytocin versus saline) administered a placebo. All drugs were administered in saline solution, but the dose and the total volume of solution administered varied between trials, and different types of prostaglandins were used:

UVI of oxytocin solution versus UVI of saline solution

- Oxytocin 10 IU plus saline solution 10 mL versus saline solution 10 mL (one trial, 35 women)[1]
- Oxytocin 10 IU plus saline solution 19 mL versus saline solution 20 mL (one trial, 30 women)
- Oxytocin 10 IU plus saline solution 20 mL versus saline placebo 1 mL plus saline solution 20 mL (four trials, 284 women)
- Oxytocin 20 IU plus saline solution 18 mL versus saline solution 20 mL (one trial, 193 women)
- Oxytocin 20 IU plus saline solution 20 mL versus saline solution 20 mL (one trial, 52 women)
- Oxytocin 30 IU plus saline solution 20 mL versus saline solution 20 mL (one trial, 18 women)
- Oxytocin 30 IU plus saline solution 27 mL versus saline solution 30 mL (one trial, 35 women)
- Oxytocin 50 IU plus saline solution 25 mL versus sterile water placebo 5 mL plus saline solution 25 mL (one trial, 577 women)
- Oxytocin 50 IU plus saline solution 25 mL versus saline solution 30 mL (two trials, 91 women)
- Oxytocin 100 IU plus saline solution 20 mL versus saline solution 30 mL (two trials, 79 women).

UVI of oxytocin solution versus plasma expander

- Oxytocin 50 IU plus saline solution 15 mL versus Dextran 70, 20 mL (one trial, 109 women).

UVI of prostaglandin solution versus UVI of oxytocin solution

- Prostaglandin F2α (carboprost) 20 mg plus saline solution 20 mL versus oxytocin 30 IU plus saline solution 20 mL (one trial, 21 women)

Misoprostol 800 μg plus saline solution 30 mL versus oxytocin 20 IU plus saline 30 mL (one trial, 51 women)

Misoprostol 800 μg plus saline solution 30 mL versus oxytocin 50 IU plus saline 25 mL (one trial, 41 women)

Misoprostol 800 μg plus saline solution 30 mL versus oxytocin 50 IU plus saline 30 mL (one trial, 60 women).

[1] The number of women detailed is the total number of women for whom data were available in both groups for all trials included in this comparison.

UVI of oxytocin solution versus UVI of ergometrine solution

Oxytocin 20 IU plus saline solution 30 mL versus ergometrine 0.2 mg in saline solution 30 mL (one trial, 53 women).

UVI of carbetocin solution versus UVI of oxytocin solution

Carbetocin 1 mL (containing 100 μg) plus saline solution 20 mL versus oxytocin 20 IU plus saline 20 mL (one trial, 200 women).

Effects of UVI of oxytocin solution versus UVI of saline solution

Maternal death: It is unclear what effect UVI of oxytocin solution has on maternal death when compared with UVI of saline solution (five trials, 782 women; 1/398 versus 0/384; risk ratio [RR] 2.93, 95% confidence interval [CI] 0.12 to 71.59; low-certainty evidence).

Additional blood loss ≥ 500 mL: High-certainty evidence suggests that the use of UVI of oxytocin solution makes no or little difference to the risk of additional blood loss ≥ 500 mL when compared with UVI of saline solution (six trials, 887 women; 132/453 versus 129/434; RR 0.98, 95% CI 0.80 to 1.20; high-certainty evidence).

Additional blood loss ≥ 1000 mL: Moderate-certainty evidence suggests that UVI of oxytocin solution probably makes little or no difference to this outcome when compared with UVI of saline solution (four trials, 766 women; 37/391 versus 33/375; RR 1.08, 95% CI 0.70 to 1.68).

Blood transfusion: Moderate-certainty evidence suggests that this intervention probably makes little or no difference to the need for blood transfusion (seven trials, 974 women; 64/493 versus 58/481; RR 1.08, 95% CI 0.78 to 1.49).

Additional uterotonics: Moderate-certainty evidence suggests that UVI of oxytocin solution probably makes little or no difference to this outcome when compared with UVI of saline solution (four trials, 678 women; 43/346 versus 46/332; RR 0.85, 95% CI 0.59 to 1.23).

Invasive nonsurgical interventions: Low-certainty evidence suggests that UVI of oxytocin solution may reduce the risk of **MROP** compared with UVI of saline solution (14 trials, 1370 women; 388/702 versus 418/668; average RR 0.82, 95% CI 0.69 to 0.97). Low-certainty evidence suggests that UVI of oxytocin solution may make little or no difference to **instrumental evacuation of retained products** when compared with UVI of saline solution (four trials, 826 women; 27/420 versus 29/406; RR 0.89, 95% CI 0.56 to 1.40).

Surgical interventions (including hysterectomy): Hysterectomy was not reported as an independent outcome in the Cochrane review; however, data on hysterectomy were included in reporting of **severe maternal morbidity**. The review defined serious maternal morbidities as hysterectomy, admission to intensive care, renal or respiratory failure, and other additional surgical procedures to treat postpartum haemorrhage (PPH) other than MROP, related to the randomized interventions. Low-certainty evidence suggests that the effect of the intervention is not known considering the wide CIs for this outcome (four trials, 724 women; 0/369 versus 3/355; RR 0.14, 95% CI 0.01 to 2.69).

Procedure-related complications: It is unclear what effect UVI of oxytocin solution has on both **abdominal pain** and **hypertension following injections** when compared with injection of saline solution only, because the evidence for both outcomes was of very low certainty.

Infections: Moderate-certainty evidence suggests that UVI of oxytocin solution probably increase infections when compared with saline solution; however, the 95% CI is also compatible with an appreciable reduction in risk (three trials, 820 women; 43/417 versus 31/403; RR 1.35, 95% CI 0.87 to 2.09).

Mean blood loss: It is unclear what effect UVI of oxytocin has on mean blood loss when compared with saline solution only, because the evidence was of very low certainty.

Postpartum anaemia: The review reported three proxy outcomes relevant to consideration of postpartum anaemia. High-certainty evidence suggests that the intervention makes little or no difference to a **fall in haemoglobin level > 10% from time of randomization to first day postpartum** (one trial, 541 women; 185/274 versus 178/267; RR 1.01, 95% CI 0.90 to 1.14). However, the evidence on **haemoglobin 24–48 hours postpartum** and **haemoglobin 40–45 days postpartum** was of very low certainty.

Nausea, vomiting or shivering: Although both nausea following injection and shivering following injection were reported, the evidence was of very low certainty.

Maternal temperature ≥ 38 °C: The review reported **fever**, but the parameters were defined differently in two trials (>38 °C; > 37.5 °C on two successive occasions between 1 and 12 hours apart or one reading of more than 38 °C in the 24 hours after birth), and not defined at all in the other two trials. The available evidence suggests that UVI of oxytocin solution may increase the risk of fever when compared with saline solution alone (four trials, 707 women; 16/360 versus 9/347; RR 1.67, 95% CI 0.76 to 3.64; low-certainty evidence).

The review reported **prolonged hospitalization** (**stay in hospital for more than 2 days** was reported), and **maternal satisfaction** (**maternal dissatisfaction with third-stage management** was reported), but the evidence for both of these outcomes was of very low certainty.

The priority outcomes **maternal temperature ≥ 40 °C**, **maternal transfer**, **additional nonsurgical interventions** (for example, **external aortic compression and compression garments**), **artery embolization**, **delayed initiation of breastfeeding** and **maternal well-being** were not reported for this comparison.

Effects of UVI of oxytocin solution versus UVI of plasma expander

One small trial included in the Cochrane review reported evidence relevant to only two priority outcomes for this comparison. However, the evidence on both **additional blood loss ≥ 1000 mL** (the trial reported **blood loss > 1000 mL**) and **invasive nonsurgical interventions** (**MROP** reported) was of very low certainty.

Effects of UVI of oxytocin solution versus UVI of prostaglandin solution

Only six priority outcomes were reported for this comparison: **additional uterotonics**; **invasive nonsurgical interventions** (**MROP** reported); **procedure-related complications** (**abdominal pain reported**); **mean blood loss**; **nausea**, **vomiting or shivering** (**shivering following injection** reported); **maternal temperature ≥ 38 °C** (**fever** reported). However, the evidence for all these outcomes was of very low certainty.

Effects of UVI of oxytocin solution versus UVI of ergometrine solution

One outcome was reported for this comparison in a single, very small trial. Evidence for **invasive nonsurgical interventions** reported as **MROP** was of very low certainty.

No other priority outcomes were reported for this comparison.

Effects of UVI of carbetocin solution versus UVI of oxytocin solution

One trial of 200 women contributed data to this comparison. It is unclear what effect UVI of carbetocin solution has on **blood loss > 500 mL** (proxy for **additional blood loss ≥ 500 mL**), **blood transfusion**, and **invasive nonsurgical interventions**: **MROP**, and **adherent placenta**, **piecemeal removal and uterine curettage** in comparison with oxytocin injection (very-low-certainty evidence).

Low-certainty evidence suggests that UVI of carbetocin solution may reduce the **use of additional uterotonics** (one trial, 200 women; 18/100 versus 69/100; RR 0.26, 95% CI 0.17 to 0.40) and may also reduce **total mean blood loss (in mL)** (measured from diagnosis of retained placenta to 2 hours postpartum) (one trial, 200 women; mean difference [MD] 98 mL lower, 95% CI 192.47 mL lower to 3.53 mL lower) when compared with oxytocin solution.

Postpartum anaemia: The review reported **postpartum haemoglobin (Hb) concentration (g/dL)** and **change in Hb concentration (g/dL)**. Low-certainty evidence suggests that carbetocin injection may increase **postpartum Hb concentration (g/dL)** (one trial, 200 women; MD 0.87 g/dL higher, 95% CI 0.08 g/dL higher to 1.66 g/dL higher) and may reduce **changes in Hb concentration (g/dL)** (one trial, 200 women; MD 0.55 g/dL lower, 95% CI 0.59 g/dL lower to 0.51 g/dL lower) when compared with oxytocin.

No other priority outcomes were reported for this comparison.

Additional considerations

A separate 2012 Cochrane review assessed the effectiveness of UVI (alone or with any uterotonic drug) for the routine management of the third stage of labour and identified nine studies (1118 women) *(2)*. Comparing UVI of normal saline plus oxytocin with UVI of saline only (six studies, 394 women), there was no evidence of difference in any of the relevant outcomes. Other comparisons included only one study for each, and there was no relevant information available for the specified review outcomes. The authors concluded that there was insufficient evidence to support the routine use of oxytocin (or other uterotonics) with normal saline via UVI for the active management of the third stage of labour until new evidence is available.

Desirable effects

How substantial are the desirable anticipated effects of UVI of oxytocin versus other UVI regimens?

Judgement

— Don't know	✓ Varies	— Trivial	— Small	— Moderate	— Large

Undesirable effects

How substantial are the undesirable anticipated effects of UVI of oxytocin versus other UVI regimens?

Judgement

✓ Don't know	— Varies	— Large	— Moderate	— Small	— Trivial

Certainty of the evidence

What is the overall certainty of the evidence on effects of UVI of oxytocin versus other UVI regimens?

Judgement

— No included studies	✓ Very low	— Low	— Moderate	— High

Additional considerations

None.

Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with UVI of oxytocin solution versus other UVI regimens for retained placenta?

Research evidence

In a review of qualitative studies evaluating "what women want" from intrapartum care, findings indicate that most women want a normal birth (with good outcomes for mother and baby) but acknowledge that medical intervention may sometimes be necessary *(high confidence) (3)*. Most women, especially those giving birth for the first time, are apprehensive about labour and birth *(high confidence)* and wary of medical interventions, although, in certain contexts and/or situations, women welcome interventions to address recognized complications *(low confidence)*. Where interventions are introduced, women would like to receive relevant information from technically competent health-care providers who are sensitive to their needs *(high confidence)*.

Findings from an update of a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and providers suggest that women do not recognize the clinical definitions of blood loss or what might be considered "normal" blood loss *(moderate confidence) (4)*. Furthermore, in some low- and middle-income countries (LMICs), women place a greater value on the expulsion of so-called "dirty blood", which they perceive as a normal cleansing process and something that should not be prevented *(moderate confidence)*.

The same review highlighted women's need for information about PPH, ideally given during antenatal care *(moderate confidence)*, and the importance of kind, clinically competent staff with a willingness to engage in shared decision-making around PPH management *(moderate/low confidence)*. In addition, it was found that women are concerned about feelings of exhaustion and anxiety (at being separated from their babies) following PPH, as well as the long-term psychological effects of experiencing PPH and the negative impact this may have on their ability to breastfeed *(moderate/low confidence)*.

Additional considerations

None.

Judgement

—	—	✓	—
Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

Balance of effects

Does the balance between desirable and undesirable effects favour UVI of oxytocin solution or other UVI regimens?

Judgement

—	✓	—	—	—	—	—
Don't know	Varies	Favours other UVI regimens	Probably favours other UVI regimens	Does not favour either	Probably favours UVI of oxytocin solution	Favours UVI of oxytocin solution

Resources

How large are the resource requirements (costs) of UVI of oxytocin versus other UVI regimens for retained placenta

Research evidence

The Cochrane review on UVI for retained placenta did not prespecify any cost or economic outcomes. A literature search did not identify any cost-effectiveness studies related to this intervention.

Additional considerations

This intervention requires items (uterotonic solution, needle, syringe, normal saline, gloves) that are typically available in adequately equipped hospital settings. Performing this intervention would be considered part of the expertise of skilled health personnel.

Main resource requirements

Resource	Description
Staff	Uterotonic solution administered via UVI by skilled health-care personnel.
Training	Training to administer injections, and to monitor and manage expected and unexpected side-effects, is part of standard maternity staff training. However, additional training would be required if this intervention is to be introduced in settings where it has not previously been available.
Supplies	Indicative costs: ■ Oxytocin per 10 IU: US$ 0.22–1.19 *(5,6)* ■ Carboprost per 250 μg: US$ 23.84 *(7)* ■ Misoprostol per 200 μg: US$ 0.09–0.52 *(5)* ■ Ergometrine per 500 μg: US$ 1.97 *(7)* ■ Carbetocin per 100 μg: US$ 13.10 –25.60 *(8–11)* ■ Plasma expander: Dextran 70 6% in normal saline, 20 mL: US$ 0.20 *(12)* ■ Needle and syringe: approximately US$ 0.07 *(6)*7 ■ Normal saline – median price of USD$1 per litre *(12)* ■ Gloves.
Equipment and infrastructure	Oxytocin cold chain storage and transport costs: Cost per birth: possibly US$ 0.84 in a low-resource setting *(13)*.
Time	Minimal
Supervision and monitoring	Supervision and monitoring to ensure appropriate use, stock availability and quality.

Resources required

Judgement

✓	—	—	—	—	—	—
Don't know	Varies	Large costs	Moderate costs	Negligible costs or savings	Moderate savings	Large savings

Certainty of the evidence on required resources

What is the certainty of the evidence on costs?

Judgement

✓	—	—	—	—
No included studies	Very low	Low	Moderate	High

Cost-effectiveness

Judgement

✓	—	—	—	—	—	—
Don't know	Varies	Favours other UVI regimens	Probably favours other UVI regimens	Does not favour either	Probably favours UVI of oxytocin solution	Favours UVI of oxytocin solution

Equity

What would be the impact of UVI of oxytocin solution versus UVI of other regimens for treatment of retained placenta on health equity?

Research evidence

No direct evidence was identified.

Additional considerations

The 2015 World Health Organization (WHO) *State of inequality* report indicates that women who are poor, least educated and who reside in rural areas have lower coverage of health interventions and worse health outcomes than more advantaged women *(14)*. Therefore, reducing maternal morbidity due to PPH could have a positive impact on health equity and improve outcomes among disadvantaged women. Reducing the need for MROP or curettage to treat retained placenta (which may require transfer to a higher level of care) would probably reduce inequities for women giving birth in primary health facilities.

Judgement

✓	—	—	—	—	—	—
Don't know	Varies	Reduced	Probably reduced	Probably no impact	Probably increased	Increased

Acceptability

Is UVI of oxytocin acceptable to key stakeholders?

Research evidence

No direct evidence relating to the acceptability of UVI for the treatment of retained placenta from either women or providers was identified.

Additional considerations

Intravenous oxytocin is widely used internationally and in a range of resource settings (low to high) *(4)*. Some uterotonics (such as carbetocin) may not be available in all settings.

Findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment by women and health-care providers has provided indirect evidence in relation to oxytocin use in the postpartum period *(4)*. Findings indicate that providers recognize the benefits of using oxytocin to prevent PPH and hasten the delivery of the placenta *(moderate confidence)*. However, in some LMIC settings, providers hold the perception that the intravenous oxytocin may actually cause retained placenta when administered preventatively or may contribute to PPH when given to induce labour *(moderate confidence)*. In rural LMIC settings where access to health facilities may be limited, community-based health providers (usually traditional birth attendants) prefer to use traditional techniques (massage) and herbal medicines to treat retained placenta *(moderate confidence)*. There were no findings from studies of women's perceptions relating to the acceptability of oxytocin.

Judgement

✓ Don't know	— Varies	— No	— Probably No	— Probably Yes	— Yes

Feasibility

Is UVI of oxytocin solution for treatment of retained placenta feasible to implement?

Research evidence

No direct evidence relating to the feasibility of using UVI of an uterotonic for the treatment of retained placenta from either women or providers was identified. However, intravenous oxytocin is widely used internationally and in a range of resource settings (low to high) *(4)*.

Additional considerations

Indirect findings from a qualitative systematic review exploring perceptions of PPH prevention and treatment among women and health-care providers suggest that resource constraints may influence effective use of oxytocin for retained placenta, particularly in LMICs *(high confidence) (4)*. Inconsistent supplies and concerns about oxytocin storage in areas with limited/inconsistent electricity hinder utilization, and a lack of experienced staff to administer the injection limits use in certain contexts *(high confidence)*. In a wide variety of settings, health-care providers feel they need more training in third-stage management as well as specific training on when/how to administer oxytocin *(high confidence)*.

This intervention requires items (needle, syringe, normal saline, gloves) that are typically available in adequately equipped hospital settings. Performing this intervention would be considered part of the expertise of skilled health personnel. Injectable oxytocin is already widely available in a range of resource settings (low to high) and has multiple applications (such as for PPH prevention and treatment as well as labour induction). Oxytocin (10 IU in 1 mL for injection) is listed in the *WHO model list of essential medicines (15)*.

Judgement

— Don't know	— Varies	— No	— Probably No	✓ Probably Yes	— Yes

Summary of judgements table

Desirable effects	— Don't know	✓ Varies		— Trivial	— Small	— Moderate	— Large
Undesirable effects	✓ Don't know	— Varies		— Large	— Moderate	— Small	— Trivial
Certainty of the evidence	— No included studies			✓ Very low	— Low	— Moderate	— High
Values				— Important uncertainty or variability	— Possibly important uncertainty or variability	✓ Probably no important uncertainty or variability	— No important uncertainty or variability
Balance of effects	— Don't know	✓ Varies	— Favours other UVI regimens	— Probably favours other UVI regimens	— Does not favour either	— Probably favours UVI of oxytocin	— Favours UVI of oxytocin
Resources required	✓ Don't know	— Varies	— Large costs	— Moderate costs	— Negligible costs or savings	— Moderate savings	— Large savings
Certainty of the evidence on required resources	✓ No included studies			— Very low	— Low	— Moderate	— High
Cost-effectiveness	✓ Don't know	— Varies	— Favours other UVI regimens	— Probably favours other UVI regimens	— Does not favour either	— Probably favours UVI of oxytocin	— Favours UVI of oxytocin
Equity	✓ Don't know	— Varies	— Reduced	— Probably reduced	— Probably no impact	— Probably increased	— Increased
Acceptability	✓ Don't know	— Varies		— No	— Probably No	— Probably Yes	— Yes
Feasibility	— Don't know	— Varies		— No	— Probably No	✓ Probably Yes	— Yes

Summary of findings table

Question: UVI of oxytocin solution compared with UVI of saline solution for management of retained placenta
Setting: Hospital (Argentina, Denmark, Hong Kong, India, Italy, Malaysia, Netherlands, Pakistan, Uganda, United Kingdom)
Reference: Kumar N, Jahanfar S, Haas DM, Weeks AD. UVI for management of retained placenta. Cochrane Database Syst Rev (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of oxytocin solution	UVI of saline solution	Relative (95% CI)	Absolute (95% CI)		
MATERNAL DEATH												
5	randomized trials	not serious	not serious	not serious	very seriousa,b	none	1/398 (0.3%)	0/384 (0.0%)	**RR 2.93** (0.12 to 71.59)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
ADDITIONAL BLOOD LOSS ≥ 500 ML												
6	randomized trials	not serious	not serious	not serious	not serious	none	132/453 (29.1%)	129/434 (29.7%)	**RR 0.98** (0.80 to 1.20)	**6 fewer per 1000** (from 59 fewer to 59 more)	⨁⨁⨁⨁ HIGH	CRITICAL
ADDITIONAL BLOOD LOSS ≥ 1000 ML												
4	randomized trials	not serious	not serious	not serious	seriousa	none	37/391 (9.5%)	33/375 (8.8%)	**RR 1.08** (0.70 to 1.68)	**7 more per 1000** (from 26 fewer to 60 more)	⨁⨁⨁◯ MODERATE	CRITICAL
BLOOD TRANSFUSION												
7	randomized trials	not serious	not serious	not serious	seriousc	none	64/493 (13.0%)	58/481 (12.1%)	**RR 1.08** (0.78 to 1.49)	**10 more per 1000** (from 27 fewer to 59 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of oxytocin solution	UVI of saline solution	Relative (95% CI)	Absolute (95% CI)		
ADDITIONAL UTEROTONICS												
4	randomized trials	not serious	not serious	not serious	serious[d]	none	43/346 (12.4%)	46/332 (13.9%)	**RR 0.85** (0.59 to 1.23)	**21 fewer per 1000** (from 57 fewer to 32 more)	⨁⨁⨁◯ MODERATE	CRITICAL
INVASIVE NONSURGICAL INTERVENTIONS – MANUAL REMOVAL OF THE PLACENTA												
14	randomized trials	very serious[e]	not serious	not serious	not serious	none	388/702 (55.3%)	418/668 (62.6%)	**RR 0.82** (0.69 to 0.97)	**113 fewer per 1000** (from 194 fewer to 19 fewer)	⨁⨁◯◯ LOW	CRITICAL
SURGICAL INTERVENTIONS: SURGICAL EVACUATION OF RETAINED PRODUCTS OF CONCEPTION												
4	randomized trials	serious[f]	not serious	not serious	serious[c]	none	27/420 (6.4%)	29/406 (7.1%)	**RR 0.89** (0.56 to 1.40)	**8 fewer per 1000** (from 31 fewer to 29 more)	⨁⨁◯◯ LOW	CRITICAL
PROCEDURE-RELATED COMPLICATIONS – ABDOMINAL PAIN												
1	randomized trials	serious[g]	not serious	not serious	very serious[a,h]	none	1/11 (9.1%)	0/7 (0.0%)	**RR 2.00** (0.09 to 43.22)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
PROCEDURE-RELATED COMPLICATIONS: HYPERTENSION FOLLOWING INJECTION												
1	randomized trials	serious[g]	not serious	not serious	very serious[i]	none	0/32 (0.0%)	0/28 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
INFECTION												
3	randomized trials	not serious	not serious	not serious	serious[j]	none	43/417 (10.3%)	31/403 (7.7%)	**RR 1.35** (0.87 to 2.09)	**27 more per 1000** (from 10 fewer to 84 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of oxytocin solution	UVI of saline solution	Relative (95% CI)	Absolute (95% CI)		
SERIOUS MATERNAL MORBIDITY (HYSTERECTOMY, ADMISSION TO INTENSIVE CARE, RENAL OR RESPIRATORY FAILURE, AND OTHER ADDITIONAL SURGICAL PROCEDURES TO TREAT PPH OTHER THAN MANUAL REMOVAL OF PLACENTA, RELATED TO THE RANDOMIZED INTERVENTIONS)												
4	randomized trials	not serious	not serious	not serious	very serious[a,b]	none	0/369 (0.0%)	3/355 (0.8%)	**RR 0.14** (0.01 to 2.69)	**7 fewer per 1000** (from 8 fewer to 14 more)	⨁⨁◯◯ LOW	CRITICAL
MEAN BLOOD LOSS (ML)												
5	randomized trials	serious[f]	serious[k]	not serious	very serious[l]	none	143	131	-	**MD 13.56 lower** (118.83 lower to 91.71 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
POSTPARTUM ANAEMIA - FALL IN HAEMOGLOBIN LEVEL > 10% FROM TIME OF RANDOMIZATION TO FIRST DAY POSTPARTUM												
1	randomized trials	not serious	not serious	not serious	not serious	none	185/274 (67.5%)	178/267 (66.7%)	**RR 1.01** (0.90 to 1.14)	**7 more per 1000** (from 67 fewer to 93 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
POSTPARTUM ANAEMIA - HAEMOGLOBIN 24-48 HOURS POSTPARTUM, G%												
1	randomized trials	serious[m]	not serious	not serious	very serious[n]	none	85	82	-	**MD 0.1 lower** (0.76 lower to 0.56 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
POSTPARTUM ANAEMIA - HAEMOGLOBIN 40-45 DAYS POSTPARTUM, G%												
1	randomized trials	serious[m]	not serious	not serious	very serious[n]	none	47	44	-	MD 0.1 higher (0.58 lower to 0.78 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
NAUSEA FOLLOWING INJECTION												
1	randomized trials	serious[g]	not serious	not serious	very serious[o]	none	0/32 (0.0%)	0/28 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT
SHIVERING FOLLOWING INJECTION												
1	randomized trials	serious[g]	not serious	not serious	very serious[o]	none	0/32 (0.0%)	0/28 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of oxytocin solution	UVI of saline solution	Relative (95% CI)	Absolute (95% CI)		
FEVER												
4	randomized trials	not serious	not serious	not serious	very serious[b,p]	none	16/360 (4.4%)	9/347 (2.6%)	RR 1.67 (0.76 to 3.64)	17 more per 1000 (from 6 fewer to 68 more)	⨁⨁◯◯ LOW	CRITICAL
PROLONGED HOSPITALIZATION (STAY AT HOSPITAL MORE THAN TWO DAYS)												
1	randomized trials	serious[g]	not serious	not serious	very serious[l]	none	19/94 (20.2%)	20/90 (22.2%)	RR 0.91 (0.52 to 1.59)	20 fewer per 1000 (from 107 fewer to 131 more)	⨁◯◯◯ VERY LOW	IMPORTANT
MATERNAL DISSATISFACTION WITH THIRD-STAGE MANAGEMENT												
1	randomized trials	very serious[q]	not serious	not serious	very serious[l]	none	6/18 (33.3%)	8/18 (44.4%)	RR 0.75 (0.33 to 1.72)	111 fewer per 1000 (from 298 fewer to 320 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **RR**: risk ratio; **MD**: mean difference; **PPH**: postpartum haemorrhage; **UVI**: umbilical vein injection

[a] Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.
[b] Few events.
[c] Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection.
[d] Wide CI crossing the line of no effect, and including appreciable reduction in risk with oxytocin injection.
[e] Majority of pooled effect provided by studies at high risk of bias for this outcome.
[f] Majority of pooled effect provided by study (or studies) at moderate risk of bias.
[g] One study contributing data, at moderate risk of bias.
[h] Small sample size, few events.
[i] Small sample size. No events, not estimable.
[j] Wide CI crossing the line of no effect, and appreciable increase in risk with oxytocin injection.
[k] Severe statistical heterogeneity (I^2>60%).
[l] Wide CI including both appreciable reduction and appreciable increase in risk with oxytocin injection, and small sample size.
[m] All pooled effect from studies with moderate risk of bias.
[n] Single study with small sample size. Effect is not clinically meaningful.
[o] Single study with small sample size, no events, not estimable.
[p] Wide CI crossing the line of no effect and including appreciable increase in risk with oxytocin injection.
[q] One study contributing data, at high risk of bias.

Question: UVI of oxytocin solution compared with UVI of plasma expander for management of retained placenta
Setting: Hospital (Finland)
Reference: Kumar N, Jahanfar S, Haas DM, Weeks AD. UVI for management of retained placenta. Cochrane Database of Systematic Reviews (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of oxytocin solution	UVI of plasma expander	Relative (95% CI)	Absolute (95% CI)		
BLOOD LOSS > 1000 ML DURING THIRD STAGE OF LABOUR												
1	randomized trials	very serious[a]	not serious	not serious	very serious[b]	none	8/68 (11.8%)	5/41 (12.2%)	**RR 0.96** (0.34 to 2.75)	**5 fewer per 1000** (from 80 fewer to 213 more)	⨁◯◯◯ VERY LOW	
INVASIVE NONSURGICAL INTERVENTIONS – MANUAL REMOVAL OF THE PLACENTA												
1	randomized trials	very serious[a]	not serious	not serious	very serious[c]	none	49/68 (72.1%)	22/41 (53.7%)	**RR 1.34** (0.97 to 1.85)	**182 more per 1000** (from 16 fewer to 456 more)	⨁◯◯◯ VERY LOW	

CI: confidence interval; **RR**: risk ratio; **UVI**: umbilical vein injection

[a] Single study with high risk of bias.
[b] Small sample size, few events. Wide CI including both appreciable benefit and appreciable harm with oxytocin injection.
[c] Small sample size. Wide CI including both appreciable benefit and appreciable harm with oxytocin injection.

Question: UVI of prostaglandin solution compared with UVI of oxytocin solution for management of retained placenta
Setting: Hospital (Egypt, Hong Kong, Israel, Pakistan)
Reference: Kumar N, Jahanfar S, Haas DM, Weeks AD. UVI for management of retained placenta. Cochrane Database of Systematic Reviews (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of prostaglandin solution	UVI of oxytocin solution	Relative (95% CI)	Absolute (95% CI)		
ADDITIONAL UTEROTONICS												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	6/10 (60.0%)	5/11 (45.5%)	RR 1.32 (0.58 to 3.00)	**145 more per 1000** (from 191 fewer to 909 more)	⨁◯◯◯ VERY LOW	CRITICAL
INVASIVE NONSURGICAL INTERVENTIONS - MANUAL REMOVAL OF THE PLACENTA												
4	randomized trials	very serious[c]	not serious	not serious	serious[d]	none	21/87 (24.1%)	38/86 (44.2%)	**Average RR 0.55** (0.36 to 0.84)	**199 fewer per 1000** (from 283 fewer to 71 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
PROCEDURE-RELATED COMPLICATIONS - ABDOMINAL PAIN												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	3/10 (30.0%)	1/11 (9.1%)	**RR 3.30** (0.41 to 26.81)	**209 more per 1000** (from 54 fewer to 1000 more)	⨁◯◯◯ VERY LOW	CRITICAL
MEAN BLOOD LOSS (ML)												
1	randomized trials	serious[a]	not serious	not serious	very serious[e]	none	10	11	-	Average MD 19 lower (118.19 lower to 80.19 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
SHIVERING FOLLOWING INJECTION												
1	randomized trials	very serious[f]	not serious	not serious	very serious[b]	none	1/30 (3.3%)	0/30 (0.0%)	**RR 3.00** (0.13 to 70.83)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of prostaglandin solution	UVI of oxytocin solution	Relative (95% CI)	Absolute (95% CI)		
FEVER												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	1/10 (10.0%)	1/11 (9.1%)	**RR 1.10** (0.08 to 15.36)	**9 more per 1000** (from 84 fewer to 1000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **RR**: risk ratio; **MD**: mean difference; **UVI**: umbilical vein injection

[a] Single study at moderate risk of bias.
[b] Small sample size, few events. Wide CI including both appreciable benefit and appreciable harm with prostaglandins.
[c] Majority of pooled effect from studies at high risk of bias.
[d] Small sample size.
[e] Very small sample size, single study.
[f] Single study at high risk of bias.

Question: UVI of oxytocin solution compared to UVI of ergometrine solution for management of retained placenta
Setting: Hospital (Egypt)
Reference: Kumar N, Jahanfar S, Haas DM, Weeks AD. UVI for management of retained placenta. Cochrane Database of Systematic Reviews (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of oxytocin solution	UVI of ergometrine solution	Relative (95% CI)	Absolute (95% CI)		
INVASIVE NONSURGICAL INTERVENTIONS – MANUAL REMOVAL OF THE PLACENTA												
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	7/26 (26.9%)	17/27 (63.0%)	**RR 0.43** (0.21 to 0.86)	**359 fewer per 1000** (from 497 fewer to 88 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR**: risk ratio; **UVI**: umbilical vein injection

[a] Single study at moderate risk of bias.
[b] Small sample size, few events.

Question: UVI of carbetocin solution compared with UVI of oxytocin solution for management of retained placenta
Setting: Hospital (Egypt)
Reference: Kumar N, Jahanfar S, Haas DM, Weeks AD. UVI for management of retained placenta. Cochrane Database of Systematic Reviews (in press).

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of carbetocin solution	UVI of oxytocin solution	Relative (95% CI)	Absolute (95% CI)		
BLOOD LOSS > 500 ML												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	3/100 (3.0%)	10/100 (10.0%)	**RR 0.30** (0.09 to 1.06)	**70 fewer per 1000** (from 91 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
BLOOD TRANSFUSION												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	1/100 (1.0%)	7/100 (7.0%)	**RR 0.14** (0.02 to 1.14)	**60 fewer per 1000** (from 69 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL
ADDITIONAL UTEROTONICS												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	18/100 (18.0%)	69/100 (69.0%)	**RR 0.26** (0.17 to 0.40)	**511 fewer per 1000** (from 573 fewer to 414 fewer)	⨁⨁◯◯ LOW	CRITICAL
INVASIVE NONSURGICAL INTERVENTIONS - MANUAL REMOVAL OF THE PLACENTA												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,c]	none	9/100 (9.0%)	17/100 (17.0%)	**RR 0.53** (0.25 to 1.13)	**80 fewer per 1000** (from 128 fewer to 22 more)	⨁◯◯◯ VERY LOW	CRITICAL
INVASIVE NONSURGICAL INTERVENTIONS - ADHERENT PLACENTA, PIECEMEAL REMOVAL AND UTERINE CURETTAGE												
1	randomized trials	serious[a]	not serious	not serious	very serious[b,e]	none	2/100 (2.0%)	5/100 (5.0%)	**RR 0.40** (0.08 to 2.01)	**30 fewer per 1000** (from 46 fewer to 50 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	UVI of carbetocin solution	UVI of oxytocin solution	Relative (95% CI)	Absolute (95% CI)		
MEAN TOTAL BLOOD LOSS (ML)												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	100	100	-	**MD 98 lower** (192.47 lower to 3.53 lower)	⨁⨁◯◯ LOW	IMPORTANT
POSTPARTUM ANAEMIA - POSTPARTUM HAEMOGLOBIN CONCENTRATION, G/DL												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	100	100	-	**MD 0.87 higher** (0.08 higher to 1.66 higher)	⨁⨁◯◯ LOW	IMPORTANT
POSTPARTUM ANAEMIA - CHANGE IN HAEMOGLOBIN CONCENTRATION, G/DL												
1	randomized trials	serious[a]	not serious	not serious	serious[d]	none	100	100	-	**MD 0.55 lower** (0.59 lower to 0.51 lower)	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; **RR**: risk ratio; **MD**: mean difference

[a] All of pooled effect from single trial at moderate risk of bias.
[b] Small sample size, and few events.
[c] Wide CI crossing the line of no effect and including appreciable reduction in risk with carbetocin injection.
[d] Small sample size.
[e] Wide CI including both appreciable reduction and appreciable increase in risk with carbetocin injection.

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