**The Effectiveness of Oxytocin for the Prevention of Postpartum Haemorrhage: an Individual Participant Data Meta-Analysis.**

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**Author Contributions:**

AR managed the project and coordinated the collaborative process, taking primary responsibility for data collection, verification of individual patient data, data synthesis, manuscript drafting, editing and finalization. BWM, WL, CAW and MF formulated the research concept and supervised every stage of the study's implementation. MF, BWM and ADW provided clinical and editorial oversight. NA and WL provided statistical oversight. MF and MP assisted with the screening of studies, risk of bias screening and Trustworthiness in RAndomised Controlled Trials screening. All authors were involved in the decision to submit the manuscript. All contributing trial investigators supplied data and answered questions about their trials. They also had opportunities to comment on the initial scope, draft protocol and manuscript.

# **Abstract**

Background: Post-partum haemorrhage (PPH) is a common complication of labour.

Objective: To assess the effectiveness of oxytocin in comparison to no treatment for the prevention of PPH.

Selection criteria: Published and unpublished randomised controlled trials (RCTs) comparing systemic oxytocin to placebo or no intervention for the prevention of PPH were included. We did not apply language restrictions.

Search Strategy: We identified RCTs from the Cochrane network meta-analysis on uterotonics for the prevention of PPH and updated the search via: Ovid MEDLINE, Embase via Ovid, Web of Science, CENTRAL, CINAHL Plus and clinicaltrials.gov.

Data collection and analysis: An Individual participant data (IPD) meta-analysis.

Main results: Of 14 eligible RCTs, four provided IPD (n=4,304; 51.7% received oxytocin and 48.4% received placebo or no intervention). Meta-analysis of IPD showed that oxytocin decreased the risk of PPH≥500 mL (aOR 0.59; 95% CI 0.46 to 0.74) and PPH≥1000 mL (aOR 0.51; 95%CI 0.32 to 0.80).

Of ten RCTs that did not share data, seven met trustworthiness criteria while three did not. Trustworthy IPD and aggregate data from RCTs meeting trustworthiness criteria (n=6,003) showed that oxytocin significantly reduced the rate of PPH≥500 mL (aOR 0.53; 95%CI 0.45 to 0.62) and PPH≥1000 mL (aOR 0.59; 95%CI 0.48 to 0.71). Three RCTs not meeting trustworthiness criteria (n=1,027) reported a larger risk reduction of oxytocin for PPH≥500mL (aOR 0.37; 95%CI 0.03 to 4.03) and PPH≥1000mL (aOR 0.13; 95%CI 0.01 to 1.45).

Conclusions: Prophylactic oxytocin reduces the risk of PPH≥500mL and PPH≥1000mL compared to no treatment. Studies not meeting trustworthiness criteria reported a larger effect, underlining the importance of integrity assessment in MA.

Keywords**:** meta-analysis; oxytocin; postpartum haemorrhage; randomised controlled trial

**Introduction**

Postpartum haemorrhage (PPH) is the leading cause of maternal morbidity and mortality worldwide.(1) Annually, 14 million women experience PPH, resulting in 70,000 maternal deaths. The burden of PPH mortality and morbidity is concentrated in low resource settings.(1-3) PPH is traditionally defined as estimated blood loss (EBL) ≥500 mL from the genital tract during the puerperium, and complicates approximately six percent of births annually.(4) Severe PPH (EBL ≥1000 mL) complicates one to two percent of births.(5) Due to the subjective nature of estimating blood loss in labour, the definition of PPH has been updated and now includes signs of clinical shock regardless of the volume of EBL.(6)

PPH is difficult to predict and occurs frequently in women without identifiable risk factors.(6, 7) Thus preventative care with active management of the third stage of labour, including uterotonic agents to promote uterine contraction, is required.(8) There are many uterotonic agents, all with differing effectiveness and maternal side effect profiles.

In 2018, the Cochrane collaboration published a network meta-analysis (NMA) evaluating all uterotonics for the prevention of PPH(9), and found that the combination of oxytocin plus ergometrine, the combination of oxytocin plus misoprostol or carbetocin alone are the most effective uterotonic regimens for preventing PPH. In clinical practice, oxytocin is the most frequently used uterotonic for active third stage management due to its proven effectiveness, and relatively few maternal side effects.(10, 11)

In general, systematic reviews (SR) and meta-analyses (MA) of randomised controlled trials (RCTs) provide the highest level of evidence and certainty of a particular treatment’s effect size. However, the results of SRs and MAs are only reliable if the underlying RCTs are trustworthy. There is increasing evidence that data with compromised integrity are included in evidence synthesis within medicine(12-15), and also in obstetrics and gynaecology.(16, 17) MA with individual participant data (IPD-MA) allow assessment of the trustworthiness of RCT data. Here, we report an IPD-MA assessing the effectiveness oxytocin or the prevention of PPH.

**Methods**

This IPD-MA followed a prospectively registered protocol (PROSPERO: CRD42022348464, accessed from: https://www.crd.york.ac.uk/prospero/). Ethical approval was received from Monash University Human Research Ethics committee in compliance with the requirements of the National Statement on Ethical Conduct in Human Research, Project ID:34839.

Search Strategy and eligibility criteria

Relevant RCTs from the 2018 Cochrane NMA were included.(9) Using the same inclusion criteria, with the help from an information specialist at Cochrane, we updated the search with RCTs published between May 2018 to May 2023 (Figure S1). All RCTs, published and unpublished, comparing systemic oxytocin to placebo or no intervention for the prevention of PPH, were eligible. No limits were set on the dose of oxytocin, route of administration or the mode of delivery. No language restrictions were used. Two investigators (AR and MF) independently screened articles and disagreements were resolved by a third reviewer (MP).

Data access

We approached investigators of eligible RCTs to share IPD. Trial investigators’ contact details were obtained through the published articles or their institutional websites. IPD-MA invitations were e-mailed at least four times if there was no response. Where the corresponding authors’ contact details were unavailable or no response was obtained, attempts were made to contact other authors involved in the RCTs and co-authors were copied in. If authors were not responding to e-mails, other contact details were sought from institutional affiliations and social media platforms. Our academic contacts in particular countries were also used to contact the authors and/or their institutions who were not responding to the initial enquiries. Journal editors were contacted as the last resort for some studies.

RCT investigators who agreed to partake in this study supplied de-identified IPD. Data was requested for all women randomised, even if excluded from original trial analyses.

Quality assessment

*Studies that shared IPD*

The received data were harmonised and recoded to the pre-defined IPD-MA definitions. They were examined for missing data, error, internal consistency, consistency with the publication, and pattern of treatment allocation and data presentation, where possible.(18) Identified issues were communicated with RCT investigators for a solution.

*Studies that did not share IPD*

The Trustworthiness in RAndomised Clinical Trials (TRACT) data integrity tool(19) was used to assess the trustworthiness of studies that did not provide IPD. This checklist surveys seven domains, including governance, author group, plausibility of intervention, time frame, dropout rates, baseline characteristics and outcomes; it aims to make an objective assessment regarding a trial’s trustworthiness. If needed, we contacted authors for clarification.

*Risk of Bias assessment*

The risk of bias (RoB) was evaluated by one reviewer (AR) for all studies using the Cochrane RoB-2 tool.(20) The RCTs were categorised into ‘low’, ‘some concerns’ and ‘high’ risk of data integrity concerns. In cases where information was incomplete, clarification was sought from the trial authors. The RoB-2 scores were then compared with those from the 2018 Cochrane NMA for consistency.(9) The GRADE tool was applied by one reviewer (AR), with results compared to the 2018 Cochrane NMA.(8, 22)

#### Outcomes

Primary outcomes were PPH≥ 500 mL and severe PPH ≥1000 mL. Secondary outcomes were EBL (mL), duration of the third stage of labour (minutes), need for additional uterotonics, blood transfusion, manual removal of placenta, admission to intensive care unit (ICU), headache, nausea, vomiting, shivering, diarrhoea and pyrexia (Figure S2).

#### Data synthesis

For each outcome, an intention-to-treat analysis was performed using all available data comparing oxytocin and placebo or no intervention. In this IPD-MA, placebo or no intervention was considered the reference group for all outcomes.

Our primary analysis was a two-stage MA to synthesize the IPD. If we were unable to use a two-stage approach due to the occurrence of rare events, then a one-stage approach was used. For the two-stage method, we used multilevel mixed-effects logistic regression (a stratified intercept by study and a random treatment effect, covariates as fixed effects with a maximum likelihood estimator).(21) We tested treatment-covariate interactions for PPH using interaction terms between treatment and potential effect modifiers. Only within-trial interaction was considered to avoid ecologic bias.

All variables besides the identification variable were checked for missing values and entries outside the expected ranges. Variables that were missing >0.01% of observations were analysed separately for each dataset using the patterns chart of missing data. In the event of missing values for covariates or potential effect modifiers in any RCT, we performed multiple imputations using chained equations (ten imputed datasets) within the RCT before the MA.(22)

We performed an aggregate data MA using the same random-effects model to assess the risk of data unavailability bias of the IPD-MA. We then assessed the treatment effect using IPD and aggregate data of studies that met trustworthiness criteria. We also estimated the treatment effect from the RCTs that did not meet trustworthiness criteria.

Stata/SE version 18.0, provided by StataCorp in College Station, Texas, USA, was used for statistical analysis. The ipdmetan, meqrlogit, and meta commands within Stata were used for conducting the MA.

**Results**

Study selection and participants

We screened 196 RCTs from the Cochrane 2018 NMA, which compared uterotonics for the prevention of PPH.(9) Eleven RCTs comparing oxytocin to placebo or no intervention were eligible for inclusion. An additional systematic search, conducted by the Cochrane information specialist, identified 305 unique references; however, after abstract and full-text screening, none were eligible for inclusion. A further 470 studies were retrieved from databases, with screening identifying two additional eligible RCTs, bringing the total to 13 (see PRISMA-IPD flow diagram, Figure 1). One multicentre RCT(23) was conducted in two countries (Assiut, Egypt and Eastern Cape, South-Africa) and was reported as two separate RCTs in one publication. We considered these as two separate RCTs, thus increasing the total number of studies from 13 to 14.

Of the 14 RCT authors, two did not respond to our invitation. (24, 25) Of the 12 who responded, four agreed to participate, while eight declined. The primary reasons for declining were the unavailability of IPD, either due to the inability to retrieve the data (N=3) or because the original authors had retired (N=2) or were deceased (N=2). Other reasons for declining were being too busy to participate (N=1). A detailed summary of the included RCTs, author responses, and reasons for non-participation is provided in Table 1.

Study characteristics

Of the four studies that provided IPD, three studies provided complete IPD.(26-28) One paper reported two separate RCTs conducted in different trial centres(23),the lead trialist in one centre declined participation, while the lead trialist from the other trial centre accepted our invitation and provided IPD (Table 1).

Data veracity of the four IPD sets was tested using a recently published IPD integrity tool(18) and all four were included in our MA.(23, 26-28) Of these, one study (n=51)(26) used placebo and the other three (n=4203)(23, 27, 28) had no intervention as the control. Route and dose of oxytocin also varied: two studies administered 10 international units (IU) intramuscularly(23, 27), one administered 5IU intramuscularly(28) and one administered 5IU intravenously.(26)

Trustworthiness assessment

Of 10 RCTs that did not provide raw data, seven were regarded as low-risk of integrity concerns. Three RCT’s were considered high-risk for integrity concerns(23-25) due to previous publication retractions(29, 30), missing trial registration(25) and absent research ethics(24) (Table S5) and thus not meeting the trustworthiness criteria. For Abdel-Aleem at el., our trustworthiness concerns only related to the Egyptian part of the study. (22)

Risk of bias in included studies

All of the RCTs were identified as having ‘some concerns’ (N=7) or ‘high risk’ (N=6) of bias (Figure S3 and S4). This is predominantly due to the lack of prospective study registration, as most of the studies were conducted before the 2010 trial registration mandate and because in most RCTs assessors and patients were not blinded to the treatment allocation.

Descriptive analysis of participants

In total, 4,304 participants were randomised to prophylactic oxytocin (n=2,223; 51.7%) and placebo or no intervention (n=2,081; 48.4%).The mean maternal age was 28.5 years for oxytocin and 28.4 years for placebo or no intervention. Parity was similar between groups, 17.7% of patients were nulliparous in oxytocin arm and 19.7% in the control arm (Table S2).

Synthesis of results

*Primary outcomes: IPD-MA*

Oxytocin use was associated with a significant decrease in the rate of PPH ≥500 mL (4 RCTs, n=4,304, 16.0% vs 22.8%, aOR 0.59; 95% CI 0.46 to 0.74; p = 0.514; Figure 2). Similarly, oxytocin was associated with a significant decrease in the rate of PPH ≥1000 mL (4 RCTs, n=4,304, 3.0% vs 5.7%, aOR 0.51; 95% CI 0.32 to 0.80; p=0.835; Figure 3).

Oxytocin use was associated with a significantly decrease in the average EBL (4 RCTs, n=2,083, mean difference (MD) 56.54 mL, 95% CI -98.52 to -14.55; Table S3). Oxytocin was associated with a decreased duration of third stage by 11 seconds (3 RCTs, n=2,033, 95% CI -0.77 to 0.39; Table S3). Oxytocin use was associated with a decrease in additional uterotonic use (2 RCTs, n=171, risk ratio (RR) 0.74, 95% CI 0.21 to 2.66; Table S3), and blood transfusion requirement (2 RCTs, n=31, RR 0.96, 95% CI 0.24 to 3.93; Table S3), although these findings were not significant.

Analysis of most maternal adverse effects was limited due to small sample sizes; two studies reported maternal headache, finding that oxytocin is associated with a non-significant increased risk of headache (n=96; RR 6.5, 95% CI 0.35 to 119; Table S3).

Combining IPD with aggregate data of studies that met trustworthiness criteria

Analysis of studies meeting trustworthiness criteria (IPD and aggregate data) showed that oxytocin use decreased the risk of PPH ≥500 mL by 46% (10 RCTs, n=7634, aOR 0.54; 95% CI 0.46 to 0.64; p= 0.489, Figure 2). RCTs that did not meet trustworthiness criteria reported a 63% decreased risk of PPH ≥500 mL (2 RCTs, n=1027, aOR 0.37; 95% CI 0.03 to 4.03; p=0.514, Figure 2). Analysis of all data (n=7,030) suggested that oxytocin decreased the risk of PPH ≥500 mL by 47% (12 RCTs, n=8661, aOR 0.53; 95% CI 0.45 to 0.62; p=0.489, Figure 2).

Regarding severe PPH≥1000mL, analysis of studies meeting trustworthiness criteria (IPD and aggregate data) showed that oxytocin use was associated with a decreased the risk of PPH ≥1000 mL by 41% (9 RCTs, n=7,624, aOR 0.59; 95% CI 0.48 to 0.71; p=0.612, Figure 3). RCTs that did not meet our trustworthiness criteria were associated with 87% decreased risk of PPH ≥1000 mL (3 RCTs, n=1,157, aOR 0.13; 95% CI 0.01 to 1.45; p=0.835, Figure 3). Analysis of all data suggested that oxytocin significantly decreased the risk of PPH ≥1000 mL by 42% (12 RCTs, n=8,781, aOR 0.58; 95% CI 0.47, 0.71; p=0.530, Figure 3).

Regarding EBL, studies meeting trustworthiness criteria (IPD and aggregate data) showed that oxytocin use decreased average blood loss by 76mL (10 RCTs, n=7738, MD -75.9, 95% CI -112.97 to -38.87; Table S4). One RCT not meeting trustworthiness criteria reported EBL, showing that oxytocin significantly decreased blood loss by 124mL (n=76, MD 123.90; 95% CI -174.88 to -72.92, Table S4).(25) Analysis of all data suggested that oxytocin use significantly decreased EBL by 81mL (11 RCTs, n=7814, MD -80.89; 95% CI -115.21 to -46.57, Table S4).

Regarding the length of third stage of labour, studies meeting trustworthiness criteria (IPD and aggregate data) showed that oxytocin use was associated with reduced length of the third stage of labour (7 RCTs, n=6231, MD -0.54 minutes, 95% CI -1.25 to 0.16, Table S4). One study that did not meet our trustworthiness criteria showed that oxytocin decreased the length of third stage by 8 minutes (1 RCT, n=130, MD -8.12 minutes; 95% CI -9.72 to -6.52, Table S4). (24) Analysis of all RCTs suggested that oxytocin decreased length of third stage by 2 minutes (8 RCTs, n=6361, MD -1.82 minutes; 95% CI -4.59 to 0.96, Table S4).

**Discussion**

Main Findings

This IPD-MA shows that oxytocin administered intramuscularly or intravenously immediately after birth is effective for the prevention of PPH ≥500 mL and PPH ≥1000 mL. Assessment of IPD and aggregate data from studies that met trustworthiness criteria indicated a reduction of PPH ≥500 mL of approximately 50%. The three RCTs that did not share data and did not meeting trustworthiness criteria indicated a much larger reduction of approximately 63%. For PPH ≥1000 mL, the estimated reduction was 49% based on RCTs meeting trustworthiness criteria versus 87% for RCTs not meeting our trustworthiness criteria.

Strengths and Limitations

One of the major strengths of this study was the large sample size, with a total of four RCTs, totalling 4,304 participants; 2,223 (51.7%) participants received oxytocin and 2,081 (48.4%) received no intervention or placebo. Data was received from three large trials, increasing the external validity as our findings were unlikely to be driven by one RCT.

The IPD-MA study design provided the platform for a collaborative process between the primary research team and trial investigators. This allowed for accurate and reliable investigation and validation of the raw data.(13) IPD-MA pools trial data, providing higher statistical power and more accurate treatment effect calculations. The data sets were coded for standardisation, allowing for more uniform analysis and true comparison between the studies.

The trustworthiness assessment of RCTs was performed though data replication for IPD and, for studies that did not contribute IPD, the TRACT tool.(19) To decrease the mis-categorisation of RCTs, multiple investigators agreed upon the final TRACT assessment and author response to our IPD invitations was considered.

Our study also has several limitations. IPD was only available for four of the 14 RCTs. Many of the identified RCTs were conducted many years ago; authors of seven studies had either passed away, retired or were unable to locate their data. Due to limited data, secondary outcomes (including manual placenta removal, ICU admission, vomiting and pyrexia) could not be assessed and subgroup analyses (mode of birth, risk of PPH, health care setting and dosage, regimen and route of oxytocin administration) were unable to be performed.

Our assessment of trustworthiness may inherently involve some degree of subjectivity. While the TRACT checklist(19) and other similar tools in this field(31, 32) are relatively new, increased experience in identifying trustworthiness issues will help improve standardization.(33) Nonetheless, the lack of response from many authors to our data requests is concerning. Regardless of whether data are intentionally fabricated or fail to meet trustworthiness standards, unreliable data should not be included in MAs that guide clinical practice.(34)

Interpretation

The Cochrane NMA performed in 2018(9) reported a 39% reduction in PPH ≥500 mL with oxytocin use when compared to placebo or no intervention. In parallel, our IPD showed a 41% decrease. For severe PPH ≥1000 mL, both the NMA and the IPD indicated a 39% decrease.

Our results confirm that oxytocin is an effective intervention for the prevention of PPH. While our study has confirmed a long-established hypothesis that oxytocin is more effective than no intervention, our study was worthwhile as it is the first IPD-MA to assess oxytocin versus no intervention and to consider the trustworthiness of these studies.

Including only high-quality and trustworthy data in meta-analysis are key to elucidating the true treatment effect size. A recent IPD-MA(35) with IPD of RCTs assessing tranexamic acid for PPH prevention limited the inclusion criteria to RCTs with a sample size above 500 patients, this included only five RCTs and excluded more than 30 smaller RCTs. Indeed, the effect of tranexamic acid was, although still there, much lower than estimated in previous meta-analysis of aggregate data.(36)

When the Cochrane NMA(9) was published no screening tool was applied to ensure the integrity of included RCTs. Given the high impact nature of the Cochrane NMA informing global guideline development(37-39) and the recent recognition of compromised data integrity(16, 40, 41) the trustworthiness of these RCTs must be interrogated.

The Cochrane NMA concluded that the highest ranked uterotonics were ergometrine plus oxytocin, misoprostol plus oxytocin and carbetocin alone. However, since this NMA was published at least one of these RCTs has been retracted(42), two have current expressions of concern(43-45) and many more have concerning features, including many RCTs conducted after 2010 which were not registered.(46-48)

**Conclusion**

This IPD-MA confirms that oxytocin is more effective than no intervention for the prevention of PPH and is associated with improved maternal safety outcomes. RCTs that did not meet our trustworthiness criteria were found to exaggerate the therapeutic benefit of oxytocin, elucidating the importance of integrity assessment in MA.

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