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Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A Cost-Effectiveness Analysis

Karen Pickering¹ · Ioannis D. Gallos² · Helen Williams² · Malcolm J. Price³ · Abi Merriel² · David Lissauer² · Aurelio Tobias² · G. Justus Hofmeyr⁴ · Arri Coomarasamy² · Tracy E. Roberts¹

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Abstract

Objective The objective of this study was to estimate the relative cost effectiveness for the full range of uterotonic drugs available for preventing postpartum haemorrhage (PPH).

Methods A model-based economic evaluation was constructed using effectiveness data from a network meta-analysis, and supplemented by the literature. A UK National Health Service (NHS) perspective was adopted for the analysis, which is based on UK costs from published sources. The primary outcome measure is cost per case of PPH avoided (≥ 500 mL blood loss), with secondary outcome measures of cost per case of severe PPH avoided (≥ 1000 mL) and cost per major outcome (surgery) averted also being analysed.

Results Carbetocin is shown to be the most effective strategy. Excluding adverse events, ‘ergometrine plus oxytocin’ was shown to be the least costly strategy. The incremental cost-effectiveness ratio for prevention of PPH with carbetocin compared with prevention with ‘ergometrine plus oxytocin’ was £1889 per case of PPH ≥ 500 mL avoided; £30,013 per case of PPH ≥ 1000 mL avoided; and £1,172,378 per major outcome averted. Including adverse events in the analysis showed oxytocin to be the least costly strategy. The incremental cost-effectiveness ratio for prevention of PPH with carbetocin compared with prevention with oxytocin was £928 per case of PPH ≥ 500 mL avoided; £22,900 per case of PPH ≥ 1000 mL avoided; and £894,514 per major outcome averted.

Conclusion The results suggest carbetocin, oxytocin and ‘ergometrine plus oxytocin’ could all be favourable options for being the most cost-effective strategy for preventing PPH. Carbetocin could be the preferred choice, especially if the price of carbetocin decreased. Mixed findings mean a clear-cut conclusion cannot be made as to which uterotonic is the most cost effective. Future research should focus on collecting more robust evidence on the probability of having adverse events from the uterotonic drugs, and on adapting the model for low- and middle-income countries.

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Key Points for Decision Makers

This cost-effectiveness analysis is the first analysis to analyse the relative cost effectiveness for the full range of uterotonic drugs available for preventing postpartum haemorrhage.

The results of this paper show carbetocin, oxytocin and ‘ergometrine plus oxytocin’ to all be favourable options for the prevention of postpartum haemorrhage.

A small decrease in the price of carbetocin could make it the preferred uterotonic for preventing postpartum haemorrhage.

1 Introduction

Postpartum haemorrhage (PPH) is a leading cause of maternal death worldwide [1]. PPH is defined as blood loss ≥ 500 mL from the genital tract within the first 24 h of birth [2], and maternal death is defined as the death of a woman while pregnant or within 42 days of termination of the pregnancy [3]. Uterotonic drugs administered at the birth of the baby are routinely recommended for the prevention of PPH for all women, but there is uncertainty over which uterotonic drug is best. Currently, in the UK [4] and globally [5], oxytocin is recommended for preventing PPH due to its relatively high effectiveness, relatively low incidence of adverse effects and low price.

A handful of other uterotonic drugs and combinations of uterotonic drugs are available, with properties lacking in oxytocin. For example, oxytocin requires refrigeration, which is not possible in some low- and middle-income country (LMIC) settings. Currently, misoprostol is recommended where oxytocin is unavailable [5], as misoprostol is heat stable and administration is easy, in the form of a tablet. Carbetocin is a synthetic, heat-stable version of oxytocin, with a similar side-effect profile [6, 7], which could make it a favourable alternative to oxytocin.

A few studies have compared the cost effectiveness of a single alternative uterotonic drug with standard care for the prevention of PPH [8–14]. A recent UK study found the uterotonic drug carbetocin to be cost saving compared with current practice oxytocin [15], but there are no published studies exploring more than two uterotonic drugs or any ranking of cost effectiveness for multiple uterotonic drugs.

In this paper, we report the results of a model-based economic evaluation using effectiveness data from a network meta-analysis (NMA) [16]; alongside these, data on costs and resource use were collected prospectively. The objective of this economic evaluation was to compare the relative cost effectiveness of the full range of uterotonic drugs available for the prevention of PPH, for women delivering by vaginal delivery. The risk of a woman having PPH differs depending on mode of delivery [17, 18]. Only women giving birth by vaginal delivery were included in this study. A separate analysis for caesarean section delivery is reported elsewhere [16].

2 Methods

A model was constructed to facilitate all the relevant comparisons in order to determine the most cost-effective uterotonic drug for the prevention of PPH. The analyses were carried out from the perspective of the UK National Health Service (NHS), as this was a UK-funded study. The

primary outcome measure was cost per case of PPH avoided (≥ 500 mL blood loss). Secondary outcome measures of cost per case of severe PPH avoided (≥ 1000 mL) and cost per major outcome (surgery) averted were also analysed. The results are presented in terms of the incremental cost-effectiveness ratio (ICER), namely the additional cost per case of PPH ≥ 500 mL avoided; additional cost per case of severe PPH ≥ 1000 mL avoided; and additional cost per major outcome averted.

2.1 Model Structure

A decision tree model was developed to represent the alternative strategies. The pathways of the model follow national guidelines [4, 19] and were finalised using expert opinion from within the research study team. The pathways represent, as far as possible, the clinical steps carried out in a UK hospital in the event of PPH. The clinical pathways on which the decision tree is based are presented in Fig. 1. The full model structure is available in Appendix 1.

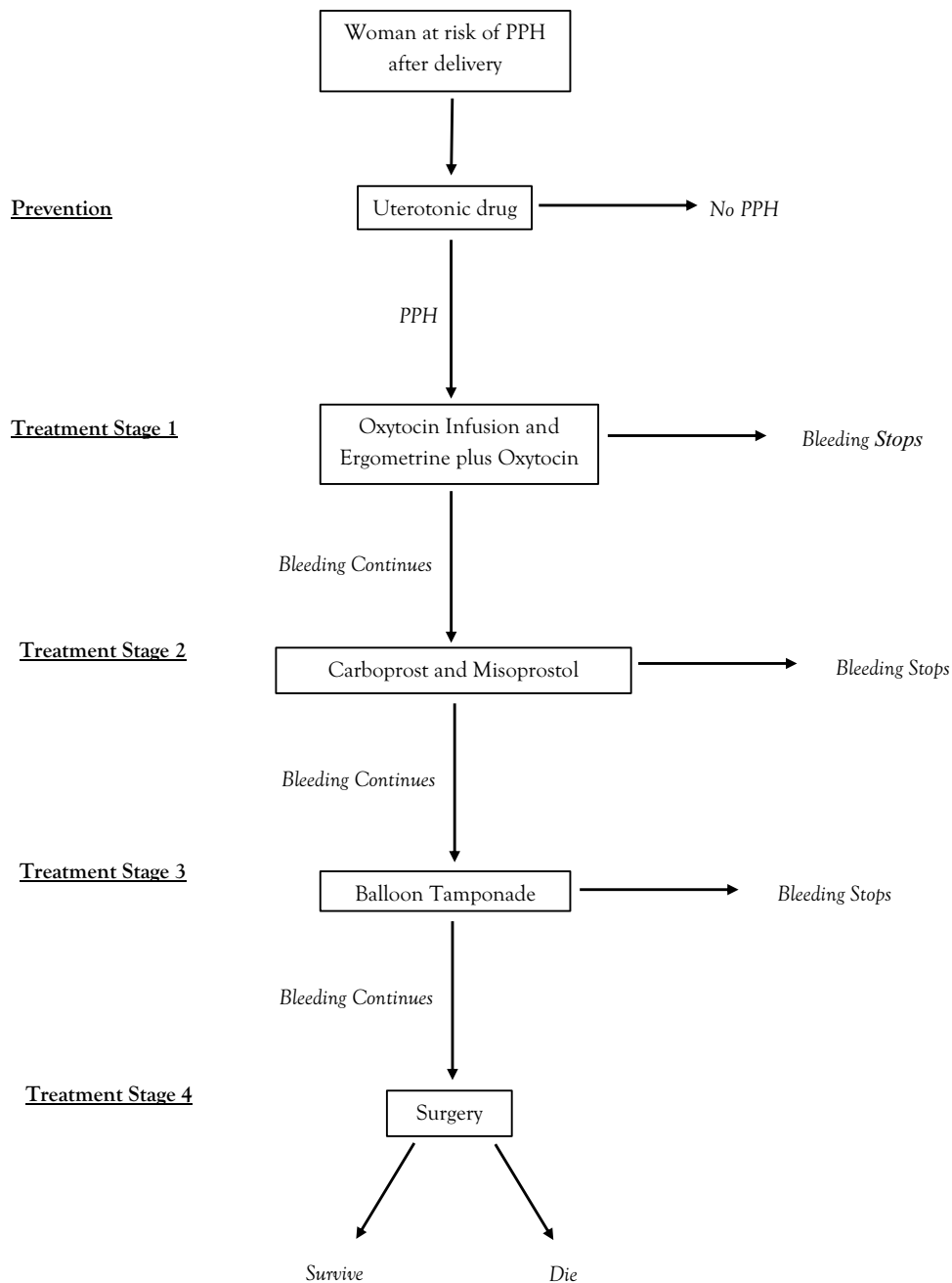
The model commences when women are approaching the third stage of labour, where the third stage of labour is defined as the period of time after the birth of the baby and before removal of the placenta and membranes [20]. At the prevention stage (Stage 0) of the model, women are given one of six active prevention strategies: carbetocin, ergometrine, ‘ergometrine plus oxytocin’, ‘misoprostol plus oxytocin’, misoprostol, and oxytocin.

It is assumed that after receiving a particular prevention strategy at stage 0, a woman will have a probability of either bleeding (PPH ≥ 500 mL) or experiencing no PPH. If a woman shows signs of continuing to bleed, she may require further treatment. Following WHO and UK guidelines [4, 5, 19], it is possible that in some cases where a uterotonic drug has been given for prevention, it will be given again as treatment for PPH.

If, after the prevention stage, a woman continues to bleed, she will follow a consecutive series of four treatments. Each one is an attempt to stop the bleeding. The stages are as follows:

0. *Prevention Stage.*
1. *Treatment Stage 1* If bleeding continues (≥ 1000 mL blood loss), the woman will be treated with a combination of two drugs: an oxytocin infusion and ‘ergometrine plus oxytocin’. (If this fails, she will enter treatment stage 2).
2. *Treatment Stage 2* If bleeding continues, the woman will be treated with two alternative drugs: carboprost and misoprostol. (If this fails, she will enter treatment stage 3).

Fig. 1 Summarised version of the clinical pathways in the model



3. *Treatment Stage 3* If bleeding continues, the woman will receive a minimally invasive balloon (balloon tamponade). (If this fails, she will enter treatment stage 4).
4. *Treatment Stage 4* If bleeding continues, a surgical procedure such as a hysterectomy will be carried out on the woman. The model allows death at this stage, but the probability of death is negligible.

2.2 Adverse Events

After receiving a drug for either prevention or treatment of PPH, a woman has a chance of having an adverse event. Adverse events considered possible in the model included nausea, vomiting, tachycardia, hypotension, hypertension, headache, fever, shivering, and abdominal pain. This is the complete list of adverse events found in the NMA.

The probability of a woman having adverse events and the associated costs were included in the models as weighted

averages. The costs are incurred after the woman has been given a uterotonic drug to prevent or treat PPH.

The third stage of labour can differ depending on mode of delivery. Given this, the current study was carried out for vaginal delivery only, which applies to the vast majority of births (75%) [21].

2.3 Effectiveness Data

The effectiveness data are presented in Table 1. The effectiveness data required for the model were based on the results of the trials sourced from the NMA [16]. The NMA was comprised of 137 studies and 87,466 women. Where necessary, data were supplemented by other published literature. No data were available in the NMA for the effectiveness of treatment stages 2, 3 and 4. These were sourced from the literature [22–25].

The NMA reported relative probabilities. For the health economic analysis, absolute probabilities were required. This required transforming the relative probabilities by using one main comparator. Oxytocin was deemed a suitable main comparator in the base case because it is currently recommended for prevention of PPH in the UK [4], and because the NMA revealed a large number of studies comparing

oxytocin with an alternative strategy, so data around the oxytocin strategy was considered to be the most robust.

The main clinical outcomes from the NMA were defined by blood loss ≥ 500 mL and ≥ 1000 mL. It was assumed that preventing PPH ≥ 500 mL meant non-progression beyond Stage 0 in the model, and correspondingly preventing PPH ≥ 1000 mL meant treatment at Stage 1 of the model, but no further treatment had been given.

Given all women in the model are exposed to prevention and treatment for PPH, the probability of death in the model is zero.

The probabilities of experiencing adverse events were sourced from the NMA [16]. Full details are presented in Appendix 2. The data for adverse events was not complete, and so assumptions were required to complete the dataset (see Sect. 2.5.2).

2.4 Resource Use and Costs

The study uses UK unit costs, as the current study is hosted and funded by UK research money. All costs sourced are reported in 2016 UK prices, having been appropriately inflated if necessary [26]. Key costs are presented in Table 2.

Delivery costs [27] were incurred at the start of the model. Standard practice dosage and routes of administration

Table 1 Effectiveness data

Item	Description	Probability of success ^a	Standard error ^b	Lower 95% CI (%)	Upper 95% CI (%)	Source
Prevention	Oxytocin	0.908	0.009	0.891	0.925	Gallos et al. [16]
Prevention	Carbetocin	0.944	0.288	0.883	0.974	Gallos et al. [16]
Prevention	Ergometrine plus oxytocin	0.936	0.101	0.908	0.958	Gallos et al. [16]
Prevention	Ergometrine	0.891	0.140	0.830	0.933	Gallos et al. [16]
Prevention	Misoprostol plus oxytocin	0.931	0.144	0.892	0.958	Gallos et al. [16]
Prevention	Misoprostol	0.899	0.078	0.861	0.929	Gallos et al. [16]
Treatment Stage 1	Oxytocin	0.977	0.003	0.971	0.997	Gallos et al. [16]
Treatment Stage 1	Carbetocin	0.988	0.756	0.932	0.244	Gallos et al. [16]
Treatment Stage 1	Ergometrine plus oxytocin	0.982	0.105	0.972	0.895	Gallos et al. [16]
Treatment Stage 1	Ergometrine	0.973	0.342	0.935	0.658	Gallos et al. [16]
Treatment Stage 1	Misoprostol plus oxytocin	0.981	0.176	0.966	0.824	Gallos et al. [16]
Treatment Stage 1	Misoprostol	0.970	0.060	0.958	0.940	Gallos et al. [16]
Treatment Stage 2	Carboprost	0.840	0.016	0.755	0.887	Butwick et al. [24]
Treatment Stage 3	Balloon tamponade	0.840	0.016	0.775	0.888	Doumouchtsis et al. [22]
Treatment Stage 4	Surgery ^c	0.994	0.0006	0.85	1.00	Knight [23]

^aProbabilities of success are absolute probabilities converted from relative probabilities from the network meta-analysis (NMA), relative to the oxytocin arm. Oxytocin was deemed most suitable as the main comparator in the base case. The NMA revealed a large number of studies comparing oxytocin with an alternative strategy, so data around the oxytocin strategy was considered to be the most robust

^bStandard errors shown are the standard errors for their respective relative probabilities. Where no standard errors for probabilities were provided in the literature estimates, they were calculated as a tenth of one minus its value [33]

^cThe effectiveness of treatment stage 4 (surgery) was based on a literature estimate for hysterectomy. Different surgical procedures can be carried out to treat postpartum haemorrhage (PPH) (laparotomy, B-Lynch suturing technique [brace suture]), but as a hysterectomy is the procedure usually used as a life-saving measure for PPH [23, 25], the source was considered appropriate

Table 2 Table of costs

Item	Drug/treatment	Unit cost (£)	Other information	Sources
Delivery costs	Delivery costs associated with vaginal delivery	1826.04 ^a	per delivery. See Appendix 3 for breakdown of calculation	NHS reference costs [27]
Uterotonic drug	Oxytocin	0.91	per 10 IU, intramuscularly	British National Formulary [29]
Uterotonic drug	Misoprostol	0.17	per 200 µg tablet	National Electronic Drug Tariff [28]
Uterotonic drug	Ergometrine	1.50	per 500 µg, intramuscularly	British National Formulary [29]
Uterotonic drug	Ergometrine + oxytocin	1.57	per 500 µg (ergometrine) + 5 IU, intramuscularly (oxytocin)	British National Formulary [29]
Uterotonic drug	Misoprostol plus oxytocin	1.08	per person (cost of misoprostol + cost of oxytocin)	British National Formulary [29], National Electronic Drug Tariff [28]
Uterotonic drug	Carbetocin	17.64	per 100 µg, intramuscular	British National Formulary [29]
Treatment for PPH	Oxytocin infusion	0.91	per 10 IU, infusion	British National Formulary [29]
Treatment for PPH	Carboprost	18.2	per 250 µg, intramuscular	British National Formulary [29]
Treatment for PPH	Balloon tamponade	1280.42 ^a	Per procedure	NHS reference costs [27]
Treatment for PPH	Postpartum surgery	3780.40 ^a	Per procedure	NHS reference costs [27]
Treatment for PPH	Blood transfusion	171.84–163.63 ^a	Per unit £171.84 (1st unit), £163.63 (subsequent units)	National Institute for Health and Care Research [31]
Hospital stay	Excess bed days	440.49 ^a	Per excess day in hospital. The figure is a weighted average of all excess bed-day costs for a vaginal delivery (normal or assisted) within an inpatient setting (see Appendix 5)	NHS reference costs [27]
Adverse event	Nausea	28.50 ^a	Per event. Cyclizine (50 mg, twice, IV injection) and ondansetron (4 mg twice, IM)	British National Formulary [29]
Adverse event	Vomiting	442.05 ^a	Per event. Prochlorperazine (12.5 mg 3 times daily, IM) with IV fluids – 24 h	NHS reference costs [27], British National Formulary [29]
Adverse event	Hypertension	630.55 ^a	Per event. Labetalol (200 mg over 24 h) and nifedipine (20 mg over 24 h, orally)	NHS reference costs [27], British National Formulary [29]
Adverse event	Headache	0.66 ^a	Per event. Paracetamol and codeine for 24 h	British National Formulary [29]
Adverse event	Tachycardia	440.49 ^a	Per event. Observation over 24 h	NHS reference costs [27]
Adverse event	Hypotension	440.49 ^a	Per event. IV fluids and observation over 24 h	NHS reference costs [27]
Adverse event	Fever	443.04 ^a	Per event. Paracetamol and IV antibiotics with fluids. Observation over 24 h, including a blood culture, high vaginal swab, full blood count and CRP test	NHS reference costs [27], British National Formulary [29]
Adverse event	Shivering	440.49 ^a	Per event. Observation over 24 h	NHS reference costs [27]
Adverse event	Abdominal pain	0.25 ^a	Per event. Paracetamol and oral morphine for 24 h	British National Formulary [29]

CRP C-reactive protein, IM intramuscularly, IV intravenous, PPH postpartum haemorrhage

^aDuring the probabilistic sensitivity analysis, a gamma distribution was fitted to model uncertainty. Because only a point estimate was available in the literature, the widest possible uncertainty was explored [33, 34]

were identified for each uterotonic drug (see Table 2), via the study team, and unit costs were taken from published sources [28, 29]. The total cost for the balloon tamponade procedure was £1280.42 (Table 2) [27]. A hysterectomy cost was £3780.40 (Table 2) [27]. It was assumed that a woman requiring treatment at Stage 4 (surgery, having already had

a failed attempt at balloon tamponade) will remain in theatre throughout Stages 3 and 4. In order to avoid duplication of some costs by summing these procedures, women who ultimately required the more serious intervention of hysterectomy incurred only half of the cost for a balloon tamponade.

The assumed lengths of hospital stay were based on blood loss and are based on real data from Birmingham Women's Hospital, UK, and supplemented by published literature [30] (Appendix 4). The associated cost attached to an extra day in hospital was £440.49 (Table 2).

Treatments for adverse events in their worst case were sought via expert opinion, which consisted of a team of five obstetricians. The experts' opinions were put forward and debated and discussed until consensus was reached to which they could all comply. The obstetricians were part of the research team.

Other resource implications and costs would be associated with blood transfusion [31]. Based on expert opinion, two units of blood were assumed to be given to women reaching treatment Stage 3 and an additional two units of blood were assumed to be given to women reaching treatment Stage 4 of the models.

A full breakdown of how unit costs were calculated is provided in the Appendices (Appendix 3 and Appendix 5).

2.5 Assumptions

In addition to those already described, several assumptions were required in order to develop a workable model. These are described below. All assumptions were agreed and finalised within the clinical research team prior to the analysis.

2.5.1 Model Structure

1. No routine uterotonic drug for PPH has been administered to women prior to them entering the model.
2. All prevention strategies (Stage 0) are followed by the same stages of treatment (Stages 1–4), except for where misoprostol is given for prevention, either alone or as part of a combination drug. Following expert opinion, misoprostol may not be given for treatment if it has already been given for prevention of PPH. In the case where misoprostol has been given for prevention, and the patient requires Stage 2 treatment (carboprost and misoprostol), the patient will forgo the misoprostol and only receive carboprost. Misoprostol is not replaced by another drug or form of treatment.
3. After 'no PPH', 'bleeding stops' and 'survive' pathways, women will return to full health.
4. A chance of death can only occur after treatment Stage 4.
5. All births are assumed to take place in an obstetric unit, where appropriate treatment for PPH is readily available should the women require it. This is true of 87% of births in the UK [21].
6. The model runs for the immediate postpartum period only.

2.5.2 Adverse Events

1. Based on the evidence from the NMA and pharmacological knowledge, it was assumed that the adverse event profile of carbetocin and oxytocin is similar. Similarly, the adverse event profile of 'ergometrine plus oxytocin' was assumed to be similar to ergometrine, and the adverse event profile of 'misoprostol plus oxytocin' to be similar to misoprostol alone.
2. If data were missing for carbetocin, but available for oxytocin, then the probability for the adverse event was based on oxytocin. This reasoning was applied to other similar uterotonic agents.
3. If data were missing for both uterotonic agents with the same adverse events profile (e.g. data were missing for both carbetocin and oxytocin), then an average of the probabilities available for that side effect was used. Ergometrine is commonly known to be associated with a high level of all side effects, with the exceptions of fever and shivering. So uterotonic drugs containing ergometrine were removed from the averaging process, apart from when considering fever and shivering. Misoprostol is commonly known to be associated with fever and shivering [32], so uterotonic drugs containing misoprostol were removed from the averaging process for these adverse events.

2.5.3 Cost and Resource Use

1. Costs for uterotonic drugs were assumed to be standard across the model. That is, they are assumed to carry the same cost, regardless of whether they are given for prevention or treatment.
2. Costs for administration of treatment (i.e. staff time) were assumed to be included in delivery costs and excess bed-day costs. Administration costs were assumed to be broadly captured by the cost of delivery (Appendix 3). No extra staff costs were therefore attached to treatment costs of PPH.
3. An outcome of death assumed no excess bed-day costs.
4. The effectiveness of treatments used for adverse events were assumed to be 100% successful.
5. The cost of treatment for adverse events, as a weighted average, was attached to every outcome of the model, except death. That is, unless a woman died, she would incur costs for treatment for adverse events, based on the probability that an adverse event occurs.

2.6 Analysis

Two alternative analyses were carried out. Because of the multiple missing data for adverse events, analysis was carried out including and excluding adverse events. Each

analysis was carried out for the following three outcome measures:

- (a) Cost per case of PPH ≥ 500 mL avoided.
- (b) Cost per case of PPH ≥ 1000 mL avoided.
- (c) Cost per major outcome averted, where a major outcome refers to treatment stage 4 of the model (surgery).

2.6.1 Analysis 1

Analysis 1 was a deterministic analysis of the relative cost effectiveness for a range of uterotonic drugs for the prevention of PPH for vaginal delivery. This analysis excludes any information on adverse events. The results are presented as ICERs.

2.6.2 Analysis 2

Analysis 2 was a deterministic analysis similar to Analysis 1, but adverse events were included in this analysis.

2.6.3 Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) was carried out to explore the uncertainty of the model input data. In PSA, distributions are assigned to all uncertain model parameters, and by drawing randomly from these distributions, a large number (10,000) of mean cost and effectiveness estimates are generated. These estimates are used jointly to form an empirical distribution of the differences in cost and effectiveness of interventions. A normal distribution was fitted to absolute probabilities, and a beta distribution was fitted to model uncertainty in relative probabilities used in the model [33]. There is no uncertainty around unit costs so no distribution was fitted. Resource use is uncertain and so costs including resource use have a confidence interval. Only point estimates for uncertain costs were available in the literature, and in these cases a gamma distribution was fitted, and the widest possible uncertainty applied [33, 34]. The PSA was carried out for Analysis 2, based on the outcome measure of ‘cost per case of PPH ≥ 500 mL avoided’ only.

The majority of the carbetocin trials included in the NMA consist of a small sample population [16]. Carbetocin is the most effective strategy, and is known to have a favourable adverse event profile, similar to oxytocin [6, 7]. However, carbetocin has a much higher unit cost than the other uterotonic drugs. A threshold analysis was therefore carried out to see the effect on the results if the price of carbetocin was lowered.

3 Results

We report the results for the separate analyses according to the outcome upon which the analysis was based (outcome measures a, b, c). The results of the analyses are summarised in Table 3.

3.1 Analysis 1

Deterministic analysis exploring the relative cost effectiveness for a range of uterotonic drugs for the prevention of PPH for vaginal delivery. Adverse events are excluded from this analysis.

- (a) ‘Ergometrine plus oxytocin’ is the least costly prevention strategy with an average cost of £2538 per woman (Table 3). The strategy in which carbetocin is given as the uterotonic drug for prevention is the most effective, and ‘ergometrine plus oxytocin’ is the second most effective strategy. All other prevention strategies are dominated by ‘ergometrine plus oxytocin’, as they are both more costly and less effective than ‘ergometrine plus oxytocin’. The estimated ICER for prevention with carbetocin compared with prevention with ‘ergometrine plus oxytocin’ was £1889 per case of PPH ≥ 500 mL avoided. This means that every additional case of PPH ≥ 500 mL avoided by using carbetocin over ‘ergometrine plus oxytocin’, costs an extra £1889 (Table 3).
- (b) For the outcome in terms of PPH ≥ 1000 mL avoided, the results in an ICER for prevention with carbetocin compared with prevention with ‘ergometrine plus oxytocin’ was £30,013 per case of PPH ≥ 1000 mL avoided (Table 3).
- (c) For the outcome measure of major outcome averted, the ICER for prevention with carbetocin compared with prevention with ‘ergometrine plus oxytocin’ was £1,172,378 per major outcome averted (Table 3).

3.2 Analysis 2

Adverse events are included in this analysis.

- (a) Oxytocin is the least costly prevention strategy with an average cost of £2618 per woman (Table 3). Carbetocin is the most effective strategy, and oxytocin is the fourth most effective strategy. All other prevention strategies are dominated by carbetocin as the strategy of carbetocin is relatively more effective and less costly. The ICER for prevention with carbetocin compared with prevention with oxytocin was estimated to be £928 per case of PPH ≥ 500 mL avoided.

Table 3 Summary of results

	Cost per average woman (£)	PPH (≥ 500 mL) avoided		PPH (≥ 1000 mL) avoided		Major outcome averted	
		Effectiveness	ICER ^a (£)	Effectiveness	ICER ^a (£)	Effectiveness	ICER ^a (£)
Analysis 1 (excluding adverse events)							
Ergometrine + oxytocin	2538	0.936		0.998843		0.999970	
Carbetocin	2551	0.944	1889	0.999301	30,013	0.999982	1172,378
Misoprostol + oxytocin	2539	0.931	Dominated	0.998843	Dominated	0.999966	Dominated
Oxytocin	2545	0.908	Dominated	0.998668	Dominated	0.999946	Dominated
Misoprostol	2548	0.899	Dominated	0.997859	Dominated	0.999924	Dominated
Ergometrine	2551	0.891	Dominated	0.996982	Dominated	0.999926	Dominated
Analysis 2 (including adverse events)							
Oxytocin	2618	0.908		0.997859		0.999945	
Carbetocin	2650	0.944	928	0.999301	22,900	0.999982	894,514
Ergometrine + oxytocin	2662	0.936	Dominated	0.998843	Dominated	0.999970	Dominated
Ergometrine	2752	0.891	Dominated	0.997082	Dominated	0.999925	Dominated
Misoprostol + oxytocin	2762	0.931	Dominated	0.998668	Dominated	0.999966	Dominated
Misoprostol	2772	0.899	Dominated	0.996982	Dominated	0.999923	Dominated

In general, results are given to 3 decimal places. Where rounding resulted in identical effectiveness ratios, effectiveness ratios are given to 6 decimal places

All costs are rounded to nearest £

PPH postpartum haemorrhage

^aICER: incremental cost-effectiveness ratio expressed as the additional cost per additional case of PPH (≥ 500 mL) avoided

- (b) For the outcome in terms of PPH ≥ 1000 mL avoided, the ICER for prevention with carbetocin compared with prevention with oxytocin was £22,900 per case of PPH ≥ 1000 mL avoided.
- (c) For the outcome measure of major outcome averted, the ICER for prevention with carbetocin compared with prevention with oxytocin was £894,514 per major outcome averted.

is lowered from £17.64 to £3.88, carbetocin becomes the dominant strategy (least costly and most effective).

In Analysis 2, the leading strategies are carbetocin and oxytocin. Lowering the price of carbetocin made no difference to the results in this analysis, because the results were most sensitive to adverse events. The low costs attached to adverse events for oxytocin, compared with the adverse events of carbetocin, resulted in oxytocin always being a leading strategy.

3.3 Sensitivity Analysis

3.3.1 Probabilistic Sensitivity Analysis (PSA) of Analysis 2

The cost-effectiveness acceptability curve (CEAC) shows the probability that each intervention is cost effective, compared with the alternative, for a range of values of the maximum acceptable ceiling ratio [35]. As the willingness-to-pay (WTP) per PPH ≥ 500 mL avoided tends to infinity, the probability that carbetocin is cost effective compared with oxytocin tends to 95%. The difference in probabilities over the WTP reflects some uncertainty in the model. The CEAC for leading strategies carbetocin and oxytocin is presented in Fig. 2.

3.3.2 Threshold Analysis (Lowering the Price of Carbetocin)

The results of the threshold analysis are presented in Table 4.

In Analysis 1, the leading strategies are carbetocin and 'ergometrine plus oxytocin'. When the price of carbetocin

3.3.3 Additional One-Way Sensitivity Analyses

Additional one-way sensitivity analyses were conducted that changed the cost of treatment stage 4 (surgery) and the effectiveness of treatment stage 2 (carboprost). These are not reported as they showed no difference to the results.

4 Discussion

This study explores the relative cost effectiveness for the full range of uterotonic drugs at preventing PPH in all women having a vaginal delivery. In this study, limited data around adverse events meant that two analyses were required: one analysis excluding adverse events (Analysis 1), and a second analysis including adverse events, using best available data supplemented by assumptions (Analysis 2).

Both analyses show that carbetocin is the most effective prevention strategy.

Fig. 2 Cost-effectiveness acceptability curve between prevention strategies oxytocin and carbetocin, using distributions around the accuracy data

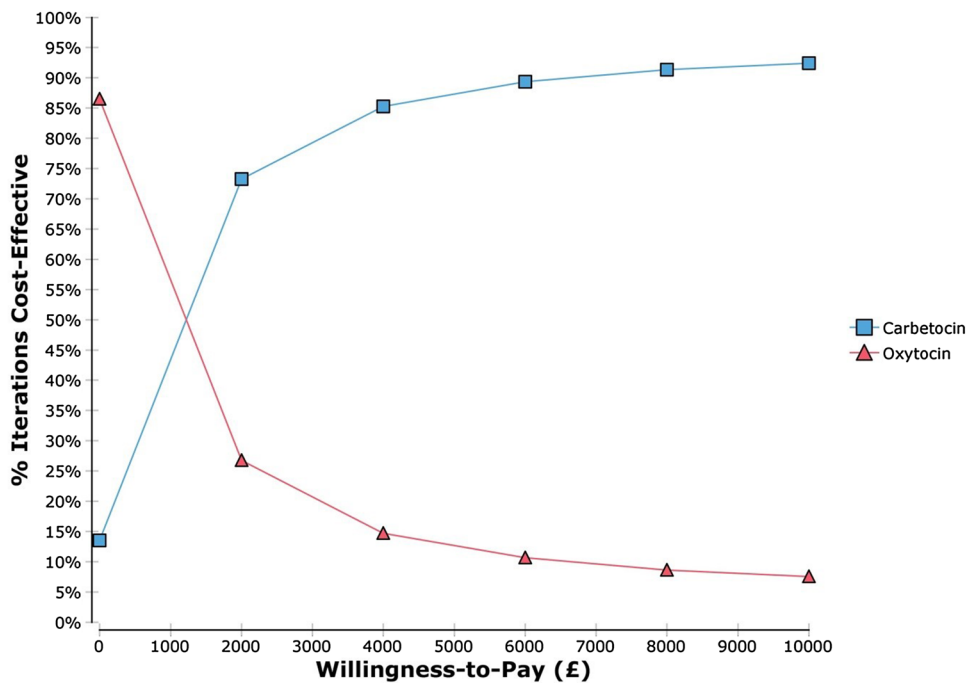


Table 4 Threshold analysis: altering the price of carbetocin

	Other prevention strategies not dominated	Price at which carbetocin becomes dominant strategy (least costly and most effective) (£)
Analysis 1	Ergometrine plus oxytocin	3.88
Analysis 2	Oxytocin	Carbetocin never dominates oxytocin

In Analysis 1, ‘ergometrine plus oxytocin’ is the least costly prevention strategy, and the ICER for prevention with carbetocin compared with prevention with ‘ergometrine plus oxytocin’ was estimated to be £1889 per case of PPH \geq 500 mL avoided; £30,013 per case of PPH \geq 1000 mL avoided; and £1,172,378 per major outcome averted.

In Analysis 2, oxytocin is the least costly prevention strategy. The respective ICERs for prevention with carbetocin compared with prevention with oxytocin was estimated to be £928 per case of PPH \geq 500 mL avoided; £22,899.57 per case of PPH \geq 1000 mL avoided; and £894,514 per major outcome averted.

The leading strategies across both analyses were carbetocin, oxytocin and ‘ergometrine plus oxytocin’.

‘Ergometrine plus oxytocin’ and carbetocin were the leading strategies in Analysis 1, where no adverse events were included. However, there are reservations around the use of ergometrine for the prevention of PPH because of its relatively higher prevalence of adverse events and its known correlation with an increased risk of stroke [36], which is strongly associated with hypertension. The threshold analysis showed lowering the cost of carbetocin to £3.88 per dose would make carbetocin the dominant strategy. But, as a result of the relatively high prevalence of adverse events for ergometrine, in

reality carbetocin is likely to perform relatively better than suggested in Analysis 1 and in the threshold analysis.

In Analysis 2 (adverse events included), oxytocin and carbetocin were the leading strategies. The threshold analysis (lowering the cost of carbetocin) showed no effect here, displaying that oxytocin was a leading strategy in this analysis because of its favourable adverse events profile, relative to the other uterotonic drugs. Overall, in Analysis 2, the costs associated with adverse events from oxytocin were lower than the costs associated with adverse events from carbetocin. The adverse events data for carbetocin were incomplete. It is unclear how robust these limited data are on adverse events associated with carbetocin. In this study, the adverse events attached to carbetocin are shown to be worse than adverse events attached to oxytocin. However, in the published literature, carbetocin is found to have a similar adverse events profile to oxytocin [6, 7], and so in reality, carbetocin is likely to perform slightly better than suggested in Analysis 2.

PPH is a leading cause of maternal death worldwide [1]; however, in the model no one died, because women were assumed to follow a series of treatments in an attempt to stop bleeding. There is a small risk of death if the woman reaches treatment stage 4 (surgery), but the surgical procedure would

stop the bleeding, so any risk of death is associated with complications arising from surgery.

A strength of this analysis is that it is the first model-based economic evaluation to compare the cost effectiveness of six different active strategies for preventing PPH. By using effectiveness data from an NMA, it is ensured that the pooled effectiveness data is a good reflection of the effectiveness of the prevention strategies, as opposed to a randomised control trial that may have several biases attached.

A limitation is that data were missing from the NMA. Attempts were made to make missing probabilities as accurate as possible, and the impact of adverse events was explored in the PSA. There is some uncertainty around the accuracy of the length of hospital stay data, as this was collected from only one hospital, because it was not available from the NMA. It was beyond the scope of the paper to analyse comparisons for different dosages of uterotonic drugs or different routes of administration. A further limitation is that the outcomes of the study are in natural units as quality-of-life information was not available in this analysis. This makes the results difficult to interpret as there is no explicit acceptable cost-effectiveness threshold.

This study takes the perspective of the UK NHS and, based on secondary data, it is not possible to present a wider perspective. The study may be generalizable to other high-income country settings where available resources and relative costs are similar to the UK. The results of this study may not be generalizable to some LMIC settings where resources are limited. However, rates of morbidity and mortality from PPH are much higher in LMICs [37], and this information is highly relevant for LMIC settings. Future research could adapt this model and its use of the effectiveness data, which relates to globally synthesised data, in the meta-analysis to carry out a cost-effectiveness analysis from an LMIC perspective. The choice of uterotonic drugs used in such an analysis should be considered as well as the availability of resources. For example, oxytocin requires cold chain storage, which may not be feasible in some LMIC settings.

Van der Nelson et al. [15] recently published a study exploring the cost effectiveness of carbetocin versus oxytocin for the prevention of PPH, but for caesarean section only, and presented a lower mean cost per woman compared with the current analysis. We cannot directly compare the results of this study and the results of the study by van der Nelson et al. because this study is for vaginal delivery only and van der Nelson et al. considers caesarean section only. Delivery costs are included in this study but not included in van der Nelson et al., which may be a contributing factor in the relatively lower mean cost per woman found in van der Nelson et al. Adverse events are also not included in van der Nelson's model, which may be an additional contributing factor to the lower mean cost per woman.

Since the network meta-analysis was carried out, evidence was published showing that tranexamic acid is an effective *treatment* for PPH [38]. This study is concerned

with the *prevention* of PPH and thus including tranexamic acid as a treatment in each prevention strategy of the model is unlikely to impact on the relative cost effectiveness of the prevention strategies.

5 Conclusion

Given WHO and UK guidelines recommend uterotonic drugs for the prevention of PPH, the results of this study suggest that UK current practice (oxytocin), carbetocin and 'ergometrine plus oxytocin' are the preferred strategies based on their relative cost effectiveness. Because of its high effectiveness and low incidence of adverse events, carbetocin could be the favoured uterotonic, especially if the price of carbetocin was reduced. Mixed findings across the analyses means that the findings of this study are insufficient on their own to dictate changes in practice. Future research should focus on gaining more concrete evidence on the adverse events attached to uterotonic drugs, as the model was sensitive to the costs applied to adverse events. Future research should also focus on adapting this model structure for LMICs, where rates of mortality and morbidity from PPH are much higher.

Data Availability Statement All data is in the public domain and available in the forthcoming Health Technology Assessment (HTA) monograph, or in published literature, as cited in the paper.

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Compliance with Ethical Standards

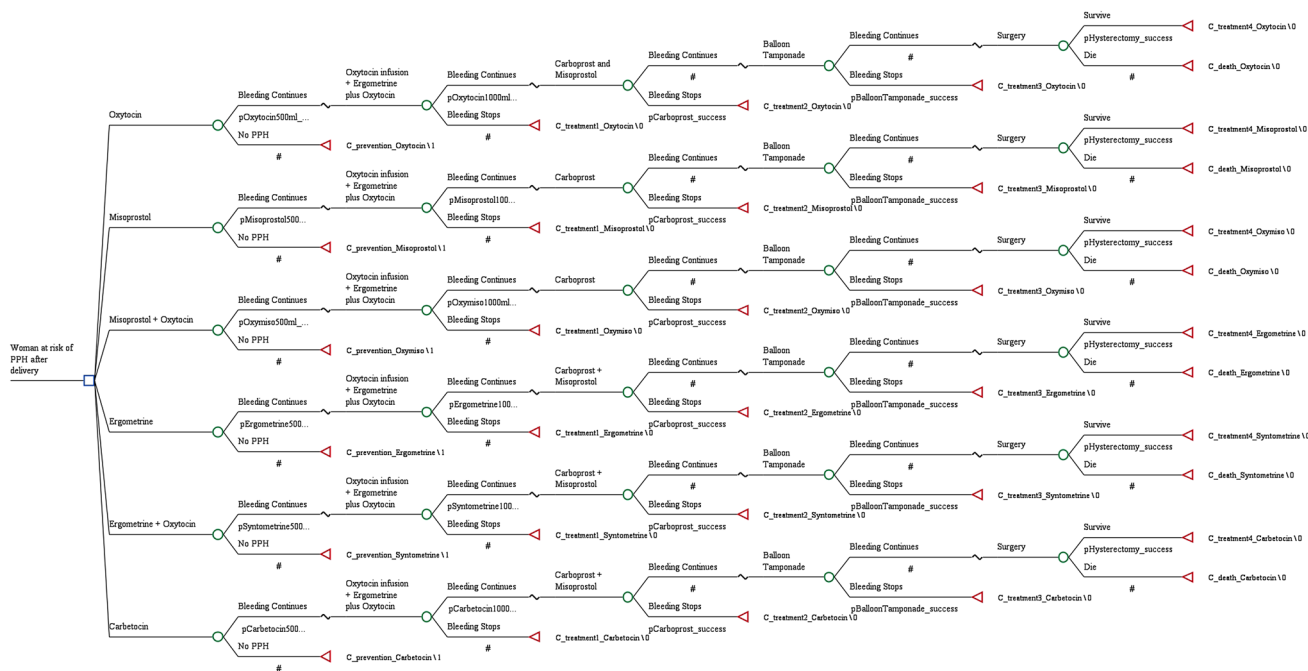
Conflicts of interest All authors Karen Pickering, Ioannis D. Gallos, Helen Williams, Malcolm J. Price, Abi Merriel, David Lissauer, Aurelio Tobias, Prof. G. Justus Hofmeyr, Prof. Arri Coomarasamy, and Prof. Tracy E. Roberts declare no competing interests.

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Author contributions AC was the principal investigator of the study. IDG, HW, TR, MP and JGH were co-investigators of the study. In addition, AM and DL provided clinical input into the model assumptions, and AT carried out the statistical analysis for the meta-analysis used in this study. KP and TR wrote the paper. KP carried out the health economic analysis and TR supervised the health economic analysis. All authors reviewed the manuscript. AC will act as the overall guarantor.

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Appendix 1



Appendix 2: Probability of adverse events for each prevention strategy

Prevention strategy	Probability of adverse event (standard errors in parenthesis)								
	Nausea	Vomiting	Hypertension	Headache	Tachycardia	Hypotension	Fever	Shivering	Abdominal Pain
Oxytocin	0.039 (0.005)	0.010 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.020 (0.003)	0.071 (0.007)	0.134 (0.043)
Misoprostol plus oxytocin	0.270 (0.891)	0.039 (0.255)	*	*	*	*	0.090 (0.229)	0.261 (0.246)	*
Misoprostol	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	*	0.002 (1.630)	0.105 (0.162)	0.271 (0.140)	0.127 (0.158)
Ergometrine plus oxytocin	0.081 (0.202)	0.043 (0.099)	0.059 (0.633)	0.072 (0.294)	0.040 (0.551)	*	0.020 (0.336)	0.087 (0.282)	0.149 (0.245)
Ergometrine	0.106 (0.226)	0.042 (0.148)	0.172 (0.814)	0.129 (0.412)	*	*	0.020 (0.303)	0.097 (0.265)	0.172 (0.464)
Carbetocin	0.028 (0.341)	0.010 (0.305)	0.030 (0.808)	0.054 (0.382)	0.074 (0.498)	*	*	*	0.099 (0.307)

Source: Gallos et al. [16]

*Means data is missing

Appendix 3: Breakdown of delivery costs

Setting	Activity	National average unit cost (£)	Sources
<i>Vaginal delivery (normal and assisted)</i>			
Elective inpatient	1362	2038.40	NHS Reference Costs [27] ^a
Non-elective long stay	139,514	2634.20	NHS Reference Costs [27] ^a
Non-elective short stay	223,663	1322.60	NHS Reference Costs [27] ^a
Day case	77	418.51	NHS Reference Costs [27] ^a
Total	364,616	1826.95	
Minus average UK standard practice for preventing and treating postpartum haemorrhage (PPH) (oxytocin 10 IU, intramuscular injection)		0.91	British National Formulary [29]
Total cost of delivery		1826.04	

NB Delivery costs are calculated for all levels of co-morbidities and complications. It is assumed therefore, that the costs for any other complications other than PPH are included in the delivery costs

The values in bold are the costs used in the economic analysis

^aNational average unit costs are weighted averages of the NHS reference costs for vaginal delivery (normal and assisted) without a postpartum surgical intervention in all inpatient settings. The types of delivery include: Normal Delivery with CC Score 0–2+, Normal Delivery, with Epidural or Induction, with CC Score 0–2+, Assisted Delivery with CC Score 0–2+, Assisted Delivery, with Epidural or Induction, with CC Score 0–2+ (where CC stands for complications and comorbidities)

Appendix 4: Mean length of hospital stay

Blood loss (mL)	Stage of model	Mean length of hospital stay (days)	Sources
<500	No PPH after prevention stage	1.57	BWH ^a
≥ 500	Bleeding stops after treatment stage 1	2.2	BWH ^a
≥ 1000	Bleeding stops after treatment stage 2	2.6	BWH ^a
≥ 1500	Bleeding stops after treatment stage 3	3	BWH ^a
	Bleeding stops after treatment stage 4	6	Glaze et al. [30]

Table shows mean length of hospital stay for each stage of the decision tree model

Data was real data obtained from Birmingham Women's Hospital (BWH). The data were collected from BWH for 2000 patients over a 3 month period (March–May 2016). The data were retrieved through K2 Medical Systems™: Athena™ Maternity Information System

Appendix 5: Breakdown of excess bed day costs

Setting	Activity	National average unit cost (£)	Sources
<i>Vaginal delivery (normal and assisted)</i>			
Elective inpatient excess bed days	173	432.56	1
Non-elective excess bed days	58,278	440.51	1
Total	58,451	440.49	

Sourced from NHS Reference Costs (2014–2015) [27]. National average unit costs are weighted averages of the NHS reference costs for excess bed days associated with vaginal delivery (normal and assisted). The types of delivery include: Normal Delivery with CC Score 0–2+, Normal Delivery, with Epidural or Induction, with CC Score 0–2+, Normal Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 0–2+, Normal Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 0–2+, Normal Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 0–2+, Assisted Delivery with CC Score 0–2+, Assisted Delivery, with Epidural or Induction, with CC Score 0–2+, Assisted Delivery, with Epidural and Induction, or with Post-Partum Surgical Intervention, with CC Score 0–2+, Assisted Delivery, with Epidural or Induction, and with Post-Partum Surgical Intervention, with CC Score 0–2+, Assisted Delivery, with Epidural, Induction and Post-Partum Surgical Intervention, with CC Score 0–2+ (where CC stands for complications and comorbidities)

The value in bold is the cost used in the economic analysis

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