ORIGINAL ARTICLE

Provisionally accepted for publication

Identifying the risk factors for carbetocin failure during caesarean section: a retrospective cohort study.

Risk factors for carbetocin failure

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DOI: 10.36129/jog.2026.267

ABSTRACT

Objective. To evaluate risk factors associated with carbetocin failure during caesarean section in a Malaysian tertiary hospital.

Materials and Methods. We conducted a retrospective cohort study between 1st of January and 30th of June 2023, including all women who received carbetocin during caesarean section at a tertiary centre in Malaysia. Carbetocin failure was defined by a composite outcome: estimated blood loss ≥1000 mL, ≥10% drop in haematocrit, ≥4 g/dL drop in haemoglobin, need for additional uterotonics, or second-line interventions. Secondary outcomes included iron supplementation, blood transfusion, and prolonged hospital stay. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of carbetocin failure, expressed as adjusted odds ratios (AOR) with 95% confidence intervals (CI).

Results. A total of 447 women received carbetocin; 191 (42.7%) experienced carbetocin failure. Multivariate analysis identified preeclampsia (AOR 3.53, 95%CI 1.02–12.21, p = 0.047), previous postpartum haemorrhage (AOR 3.71, 95%CI: 0.80–17.28, p = 0.094), and higher foetal weight (AOR 1.000, 95%CI 1.000–1.001, p = 0.017) as significant risk factors. Obesity, age, parity, and pre-existing anaemia were not significantly associated with failure. Among those with carbetocin failure, 83.8% required additional uterotonics and 26.7% developed postpartum haemorrhage.

Conclusions. Carbetocin failure following caesarean section was associated with preeclampsia, prior postpartum haemorrhage, and increased foetal weight. Obesity was not an independent predictor. These findings may support improved clinical risk stratification and highlight the need for further multicentre research.

Key words

Carbetocin; risk factors; caesarean section; postpartum haemorrhage.

Introduction

Postpartum haemorrhage (PPH) remains a primary contributor to maternal mortality in developing nations**,** with uterine atony responsible for 70-80% of the cases [1]. The current guideline recommends routine use of uterotonics immediately following childbirth to prevent PPH [2]. Oxytocin has traditionally been the first-line prophylactic agent; however, its short half-life necessitates repeated administration and cold-chain storage. Many

studies have explored carbetocin as a potential alternative, particularly in the setting of caesarean section (CS) [3]. Carbetocin is a heat-stable, synthetic oxytocin analogue with an extended half-life of 41 minutes, offering prolonged uterine contraction after a single intravenous dose, thus avoiding the need for continuous infusion.

Caesarean section is the primary setting in which carbetocin is utilised, as it is associated with a greater incidence of severe PPH and a threefold increase in the need for second-line interventions compared to vaginal birth [4]. Evidence shows that, in comparison to oxytocin, carbetocin significantly lowers blood loss, reduces reliance on additional uterotonics, and decreases the overall risk of PPH during caesarean section [5]. Despite strong evidence supporting its efficacy, global adoption remains inconsistent. Currently, only the Society for Obstetricians and Gynaecologists of Canada (SOGC) recommends it as the preferred uterotonic of choice at elective caesarean sections [6]. At the same time, many countries, including Malaysia, lack national recommendations, leaving clinicians without standardised guidelines. Although a cost-effectiveness study supported the use of carbetocin in reducing PPH and blood transfusion, its use remains inconsistent, primarily due to higher initial costs and the absence of standardised policy recommendations [7].

Although carbetocin has demonstrated superiority over oxytocin in preventing postpartum haemorrhage, it is not immune to treatment failure. Deges et al. define carbetocin failure as meeting at least one of the following criteria: a ≥10% drop in haematocrit, a ≥4 g/dL reduction in haemoglobin, an estimated blood loss of ≥1000 mL, the need for additional uterotonics, or the use of second-line interventions [8,9]. A successful response is defined as the absence of these outcomes. In this study, predictors of carbetocin failure included previous PPH, caesarean delivery during labour, cervical ripening, and higher birth weight, with a reported failure rate of 7.3%. Although obesity is a risk factor for uterine atony due to altered pharmacokinetics and impaired myometrial contractility, it did not emerge as a significant predictor of carbetocin failure in this study.

Given the absence of local data, we aim to replicate the findings of Deges et al. by evaluating the risk factors for carbetocin failure within our population. Our objectives are threefold: to characterise baseline maternal demographics of women receiving carbetocin during caesarean sections, to identify risk factors associated with its failure, and to examine whether obesity contributes to this outcome. We hypothesise that obesity may be linked to increased rates of carbetocin failure during caesarean delivery, given its established association with uterine atony and impaired myometrial contractility.

Materials and Methods

Study Design and Setting

We conducted a retrospective cohort study from 1st January 2023 until 30th June 2023, which included all women with a live fetus who gave birth via caesarean section and were administered carbetocin, regardless of the indication of caesarean section and gestational age at delivery at one tertiary care hospital. A single obstetrician reviewed the medical records for the selected period, and study data were collected from the hospital's electronic system. Following that, data entry analysis was done using the Statistical Programme for Social Sciences (SPSS) version 26.0. All patients received written consent about the risks and indications of caesarean section. As this is a retrospective study, an additional specific consent was not required. Patient data were anonymised before analysis. Permission for retrieving and collecting data was obtained from the head of the Obstetrics and Gynaecology Department and also from the hospital director.

This study was only conducted after obtaining ethical approval on the 11th of November 2024 from the Malaysian Medical Research and Ethics Committee (MREC) with the National Medical Research Register (NMRR) ID-24-02938-HPQ (IIR). This was done per

ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. Women with intrauterine death or fetal loss before 22 weeks, medically indicated second-trimester termination of pregnancy and women with incomplete or missing data were excluded. Carbetocin (generic name: carbetocin), administered in all cases, was manufactured by Ferring Pharmaceuticals, Switzerland.

The primary endpoint of this study is to meet at least one of the following criteria:
a) ≥10% drop in haematocrit,
b) ≥4 g/dL reduction in haemoglobin,
c) an estimated blood loss of ≥1000 mL,
d) need for an additional uterotonic agent
e) use of second-line interventions (e.g., Bakri balloon, uterine compression sutures, internal iliac artery ligation, caesarean hysterectomy).

The secondary endpoint included the need for iron supplementation (either oral or intravenous) in the postpartum period due to anaemia, extended hospitalisation resulting from PPH and/or anaemia, and the need for blood transfusion.

Sample Size

Determining an appropriate sample size is critical to ensure the reliability and validity of research findings. However, determining the population size of pregnant women administered carbetocin during caesarean sections can be challenging due to fluctuating numbers of patients who received carbetocin every month. Therefore, the sample size calculation assumes an unknown or potentially infinite population size to ensure robust statistical inference.

Parameters for Sample Size Calculation
• Margin of Error (E): 5% (0.05)
• Confidence Level (CI): 95% (corresponding to a Z-score of approximately 1.96)
• Expected Population Proportion (p): 50% (0.50) [10,11].

The sample size (n) was calculated using the formula for estimating a population proportion with an unknown or potentially infinite population size:

$$n = \frac{Z^2 . p(1-p)}{E^2}$$

Where:
• Z is the critical value corresponding to the desired confidence level (1.96 for 95% CI).
• p is the estimated proportion (0.50).
• E is the margin of error (0.05).

Based on the calculations using the specified parameters:

$$n = \frac{1.96^2 . 0.50(1-0.50)}{0.05^2}$$

$$n = \frac{3.8416.0.50(1-0.50)}{0.025}$$

$$n = \frac{0.9604}{0.025} = 384.16$$

Rounding up to the nearest whole number, the estimated sample size required for this study is approximately 385.

Statistical analysis

The analysis started with a descriptive evaluation of maternal characteristics, obstetric history, and intrapartum characteristics. Continuous variables were summarised as means with standard deviations (SD), while categorical data were expressed as frequencies and percentages. To compare groups with and without carbetocin failure, univariate analysis was performed using Chi-square tests for categorical variables and independent t-tests for continuous variables. Variables with a p-value < 0.25 in univariate testing were selected for inclusion in the multivariable model. Binary logistic regression was then applied to identify independent predictors of carbetocin failure, with the outcome variable coded as a binary measure (yes/no). Independent variables were drawn from the univariate analysis.

A backwards stepwise likelihood ratio (LR) approach was used to eliminate non-contributing variables, yielding a final model comprising only statistically significant factors. Results were presented as adjusted odds ratios (AORs) with corresponding 95% confidence intervals (CIs). Before analysis, the dataset underwent rigorous quality checks, including assessments for missing values, outliers, and data inconsistencies, to ensure robustness and accuracy of the findings. Only women with complete data for all variables relevant to the primary outcome were included. Variables with missing data were excluded.

Results

From 1st January 2023 to 30th June 2023, 8606 live births were recorded in our hospital, of which 2333 women (27.1%) underwent caesarean section. Among these, 447 women (19.2%) received carbetocin as prophylaxis during the caesarean section. Of the women administered carbetocin, 191 (42.7%) experienced carbetocin failure, 160 (83.8%) required additional uterotonics mainly due to uterine atony intraoperatively, and 51 (26.7%) developed postpartum haemorrhage (PPH). Only 9 (4.7%) required second-line surgical interventions. 140 of them (73%) did not present with estimated total blood loss ≥1000 mL after caesarean delivery.

As shown in Table 1, maternal age, BMI, obesity and ethnicity were not significantly associated with carbetocin failure. Although minor differences were noted between the success and failure groups, these demographic characteristics did not exhibit a meaningful association with the outcome. Additionally, parity, prior caesarean section, and previous PPH were not found to be independent predictors. Uterine malformation and previous myomectomy are uncommon in this cohort to draw any conclusion.

In Table 2, placenta praevia was identified as a significant predictor of carbetocin failure ($p = 0.047$). Women with diabetes mellitus on treatment, including both gestational diabetes (GDM) and pre-existing diabetes, had a lower rate of carbetocin failure compared to diabetic women not on treatment. Furthermore, preeclampsia was observed more frequently among women in the success group (8.6%) than in the failure group (1.6%), a statistically significant difference ($p = 0.001$).

As shown in Table 3, induction of labour does not directly impact carbetocin efficacy. However, cervical dilation at the time of caesarean section was greater in the failure group compared to the success group ($p = 0.036$). Furthermore, higher fetal birth weight of >4000g may contribute to carbetocin failure, due to a distended uterus, leading to the increased risk of PPH. Among the 191 women experiencing carbetocin failure, 83.8% required additional uterotonics.

As shown in Table 4, placenta previa and macrosomic babies >4000g were significantly more prevalent in the carbetocin failure group compared to the success group.

There were no statistically significant differences in pre-delivery haemoglobin (Hb) and haematocrit (Hct) values between the two groups (Hb: 11.83 ± 1.24 g/L vs. 11.75 ± 1.31 g/L, p = 0.552; Hct: 36.20 ± 3.33% vs. 35.94 ± 3.72%, p = 0.432), indicating that baseline anaemia did not appear to influence carbetocin effectiveness. Post-delivery Hb and HCT levels were not routinely measured in our centre, hence, they were excluded. They will only be measured in the event of PPH or clinical suspicion of PPH. A 20% threshold was set to balance data retention and minimise bias.

Haemoglobin and haematocrit changes were assessed within 24 hours postoperatively to capture the cumulative blood loss during and after caesarean section. Although carbetocin's half-life is only 40-60 minutes, its clinical effect is still being reflected in the overall haemostatic response following administration.

The primary endpoint of criteria (c) and (d) were designed to capture both quantitative and clinical aspects of carbetocin failure. Criteria (c) reflects measurable haemorrhage volume and criteria (d) captures cases where clinicians used additional uterotonic drugs when the uterine tone is atonic - despite an estimated blood loss of <1000 ml.

The majority of the patients (49.7%) stayed in the hospital between 4- 6 days, 33.6% stayed for less than 3 days, whereas 16.8% stayed for more than 7 days. In our cohort, 12 patients (2.7%) required blood transfusions, whereas a total of 31 patients (6.9%) received iron supplementation upon discharge.

As shown in this multivariable logistic regression analysis (Table 5), preeclampsia and previous PPH were found to be significant predictors of carbetocin failure. Higher fetal weight also emerged as a significant predictor, correlating with an increased risk of carbetocin failure.

Discussion

Our findings indicate that preeclampsia, previous PPH and higher fetal weight >4000g are significant risk factors for carbetocin failure, while obesity alone did not emerge as an independent predictor. In line with international guidelines, the avoidance of non-indicated caesarean sections remains an important preventive measure, as higher caesarean section rates are linked with increased PPH risk [12,13].

Preeclampsia is known to elevate PPH risk [14], largely due to its complex pathophysiology, which includes abnormal angiogenesis, vascular dysfunction, and impaired uteroplacental blood flow, leading to hypertension and coagulopathy [15]. Despite this, prior studies, including that by B. Nucci et al., have shown that carbetocin is both effective and safe in women with preeclampsia [16] and may also be the most effective agent in minimising blood loss and reducing the need for additional uterotonics [17,18]. These findings suggest that clinical practice at our centre aligns with the current evidence, despite preeclampsia being a risk factor.

In a cohort study by Oberg, Anna Sara et al., women with a history of one prior PPH faced nearly triple the risk of recurrence, while those with two or more prior instances had a sixfold increase, compared to women with no such history [19]. This aligns with our study, and further research is needed to specifically investigate the causes of PPH. In our cohort, 73.3% of women with carbetocin failure had an estimated blood loss of

less than 1000 mL, compared to 34.1% reported by Deges et al. This discrepancy may suggest underdiagnosis of postpartum haemorrhage (PPH) in our centre, likely due to reliance on visual estimation of blood loss, which is known to be inaccurate. Contemporary best practices recommend the use of objective methods, such as gravimetric techniques, which have been shown to improve accuracy and early recognition of significant haemorrhage. Kadri et al. noted that healthcare providers tend to underestimate postpartum blood loss by around one-third when relying on visual assessment, regardless of level of experience. [20]

Fetal macrosomia >4000g has been consistently linked with elevated PPH risk [21, 23, 24]. A key mechanism underlying this association is uterine overdistension, which impairs effective uterine contraction following delivery [22]. Furthermore, a larger placental surface area in macrosomic pregnancies may contribute to increased bleeding risk due to the greater area of placental separation [23]. As for now, there is limited research that specifically looked into the relation of fetal macrosomia with carbetocin failure, and there is room for further research.

Over the past three decades, postpartum haemorrhage (PPH) rates have risen in high-income countries, a trend that is not fully accounted for by shifts in recognised risk factors. One proposed explanation is the increasing prevalence of maternal obesity. A retrospective cohort study from New Zealand found that nulliparous women with obesity had twice the risk of PPH compared to those with a normal BMI, regardless of the mode of delivery [25]. Another study reported that obese women who experienced PPH were more frequently administered uterotonic agents, although the likelihood of requiring multiple doses was comparable to that of non-obese women [26]. However, results from other studies can be conflicting. Some studies suggest that obesity may have no association with PPH risk, or might even be protective [27–29]. To date, most trials focus on carbetocin's superiority over oxytocin rather than obesity-specific outcomes [1,3]. The lack of association between carbetocin failure and obesity in our study may reflect the drug's efficacy despite increased maternal adiposity. Notably, the prevalence of obesity and parity in our cohort was substantially higher than that reported by Deges et al., with 57.4% of women classified as obese in our study compared to 21.8% in theirs [8]. This discrepancy suggests that our analysis captures a broader representation of high-risk populations, potentially offering deeper insights into carbetocin's efficacy.

Furthermore, placenta praevia did not appear to contribute to carbetocin failure, as haemorrhage in these cases is primarily linked to placental location rather than uterine atony. This distinction underscores the need to differentiate between causes of PPH when evaluating uterotonic effectiveness.

The strength of our study is the analysis of the risk factors of Carbetocin failure among the Malaysian population. To the best of our knowledge, no studies have reported on the risk factors of Carbetocin failure, particularly in this Southeast Asian region. This may aid in refining clinical risk assessment and uterotonic strategies.

Interpretation of our results requires consideration of a few limitations. It is worth noting that all the caesarean sections were performed by medical officers and specialists with varying years of experience. Some practitioners could be more prone to additional uterotonics out of habit. The retrospective and monocentric nature of our study makes it difficult to extrapolate and compare the results with the available literature. Nevertheless, it allows us to evaluate the risk factors for carbetocin failure.

It is also possible that a small number of patients who received Carbetocin during the study period were not included in our analysis due to human error of being omitted from documentation, potentially underestimating the true sample size.

Our sample size (n=447) may have been too small to uncover a clinically relevant carbetocin failure rate after caesarean section based on composite criteria, or to detect statistically significant effects of maternal and obstetric variables as potential risk factors.

Conclusions

This study provides the first data on carbetocin failure predictors in a Malaysian obstetric population, whereby pre-eclampsia, previous postpartum haemorrhage and higher fetal weight >4000g were identified as key contributors.

Although obesity was not found to be an independent predictor within our cohort, its complex association with postpartum haemorrhage merits further investigation in larger, multicentre studies.

Compliance with ethical standards

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline.

Authors contribution

C.K.L. – conceptualisation, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualisation, writing – original draft, writing – review & editing.
R.B.R. – conceptualisation, formal analysis, project administration, supervision, validation, visualisation, writing – original draft, writing – review & editing.
F.B.M.Y. – conceptualisation, project administration, resources, supervision, writing – review & editing.

Acknowledgement

The authors would like to thank the Director-General of Health Malaysia for permission to undertake and publish this study.

Funding

Self-funded.

Study registration

National Medical Research Register (NMRR) ID-24-02938-HPQ (IIR).

Disclosure of interest

The authors declare that they have no conflict of interest for this study.

Ethical Approval

This study was conducted after obtaining ethical approval from the Medical Research and Ethics Committee (MREC).

Informed consent

All patients received written consent about the risks and indications of caesarean section.

Data sharing

All data were collected using subject IDs and saved in soft copy on a computer protected by a password. The research data was stored on a secure server hosted at Google Cloud Platform, with data encrypted to prevent unauthorised access. Password protection was enforced, with access limited to the corresponding author only.

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Table 1: Maternal Demographics and Obstetric History

Characteristic		Success (n=256)	Failure (n=191)	P-value
Age (years)		31.44 ± 5.50	32.05 ± 5.97	0.267
BMI (kg/m²)		31.80 ± 6.57	31.90 ± 6.32	0.882
Obesity	BMI ≥ 30	143, 55.9%	114, 59.7%	0.418
	BMI < 30	113, 44.1%	77, 40.3%	
Ethnicity	Malay	253, 98.8%	188, 98.4%	0.717
	Non-Malay	3 , 1.2%	3 , 1.6%	
Parity		2.79 ± 1.91	2.61 ± 1.73	0.316
Previous CS		80 (31.3%)	47 (24.6%)	0.123
Previous Myomectomy		1 (0.4%)	0 (0%)	0.387
Previous PPH		11 (4.3%)	6 (3.1%)	0.527
Uterine Malformation		0 (0.0%)	1 (0.5%)	0.246

Data are presented as mean ± SD or n (%) unless otherwise specified. A p-value <0.05 was considered statistically significant.

Table 2: Medical Comorbidities in Pregnancy

Comorbidity	Success (n=256)	Failure (n=191)	P-value
Diabetes not on treatment	53 (20.7%)	55 (28.8%)	**0.048***
Diabetes on Treatment	64 (25%)	33 (17.3%)	0.064
Preeclampsia	22 (8.6%)	3 (1.6%)	**0.001***
Chronic Hypertension	13 (5.1%)	11 (5.8%)	0.752
Pulmonary Embolism	1 (0.4%)	1 (0.5%)	0.835
Uterine Fibroid	3 (1.2%)	6 (3.1%)	0.143
Pregnancy-Induced Hypertension	9 (3.5%)	6 (3.1%)	0.828
Placenta Previa	18 (7.0%)	24 (12.6%)	**0.047**
Others	22 (8.6%)	8 (4.2%)	0.215

Data are presented as n (%) unless otherwise specified. A p-value <0.05 was considered statistically significant. The others consist of hepatitis B or C infection (1.1%), hyperthyroidism (1.3%) and bronchial asthma (4.3%)

Table 3: Delivery & Labour Characteristics, Neonatal Factors and Hematological Outcomes

Characteristic		Success (n=256)	Failure (n=191)	P-value
Gestational age	Pre-term (<37 Weeks)	59 (23.0%)	33 (17.3%)	0.136
	Term (≥37 Weeks	197 (77%)	158 (82.7%)	
Induced labour		102 (39.8%)	70 (36.6%)	0.492
Type of CS (Emergency)		75.8%	78.0%	0.581
Labour Duration (hours)		3.07 ± 4.01	3.28 ± 4.23	0.605
Oxytocin in labour		93 (36.3%)	65 (34.0%)	0.615
Cervical Dilation (cm)		2.49 ± 2.70	3.05 ± 2.94	**0.036**
Type of anaesthesia	General	8 (3.1%)	12 (6.3%)	0.140
	Spinal - Epidural	248 (96.9%)	179 (93.7%)	
Estimated blood loss	< 1000cc	256 (100%)	140 (73.3%)	
Average Baby Weight (gram)		2993.86 ± 716.37	3164.24 ± 664.25	**0.011**
Hb pre delivery (g/L) (mean ± SD)		11.83 ± 1.24	11.75 ± 1.31	0.552

Hct pre delivery (%) (mean ± SD)	36.20 ± 3.33	35.94 ± 3.72	0.432

Data are presented as mean ± SD or n (%) unless otherwise specified. A p-value <0.05 was considered statistically significant.

Table 4: Indications for Caesarean Section and Carbetocin Failure Status

Indication for CS	Success (n=256)	Failure (n=191)	Total (%)
Fetal distress	63 (24.6)	51 (26.7)	114 (25.5)
Poor progress	28 (10.9)	27 (14.1)	55 (12.3)
Failed IOL	33 (12.9)	14 (7.3)	47 (10.5)
Placenta previa	18 (7.0)	26 (13.6)	44 (9.8)
Macrosomic baby >4000g	22 (8.6)	22 (11.5)	44 (9.8)
Fetal malpresentation	22 (8.6)	8 (4.2)	30 (6.7)
Multiple pregnancy	18 (7.0)	11 (5.7)	29 (6.4)
Maternal request	14 (5.5)	9 (4.7)	23 (5.1)
Previous scars	16 (6.3)	6 (3.1)	22 (4.9)
Preeclampsia	11 (4.3)	3 (1.6)	14 (3.1)
Secondary arrest	5 (2.0)	6 (3.1)	11 (2.5)
Others	7 (2.7)	7 (3.7)	14 (3.1)

The others consist of 2 previous scars (0.2%), abruptio placenta (0.4%), chorioamnionitis (0.2%), cord prolapse (0.4%), history of myomectomy (0.2%), history of OASIS (0.2%), paraplegia post MVA (0.2%) and prolonged 2nd stage (1.1%).

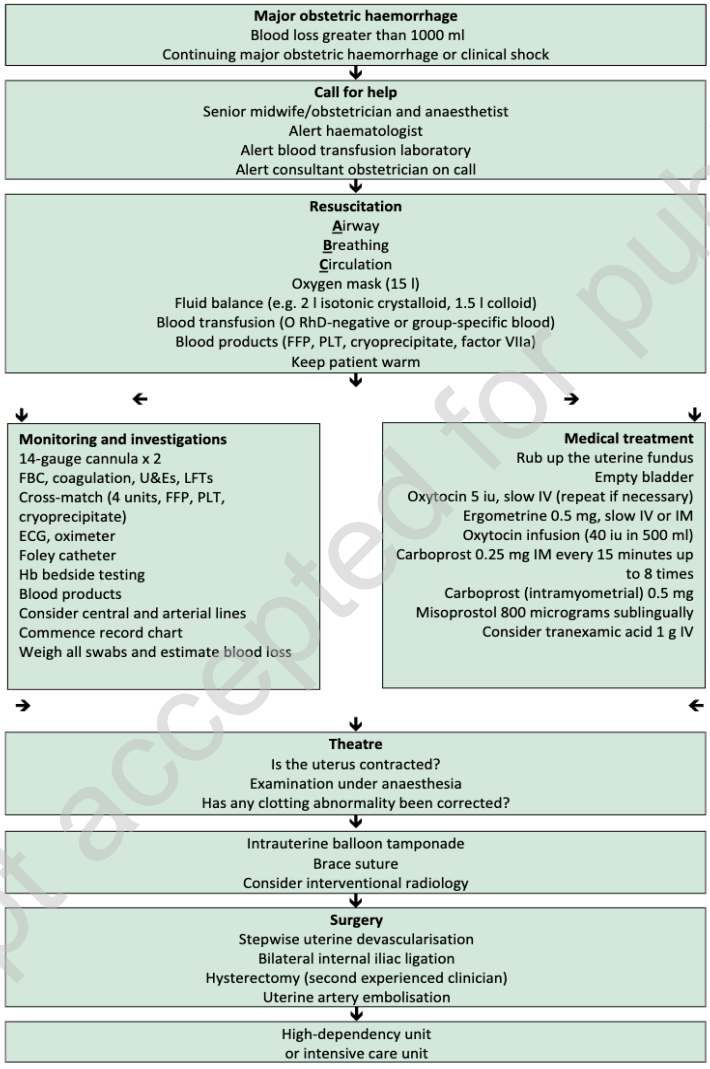
Table 5: Final Predictors of Carbetocin Failure

Factors	Odds Ratio (AOR)	95% Confidence Interval	P-value
Preeclampsia	3.53	1.02 – 12.21	0.047
Previous PPH	3.71	0.80 – 17.28	0.094
Higher Fetal Weight >4000g	1.000	1.000 – 1.001	0.017

Appendix 1
Royal College of Obstetricians and Gynaecologists (RCOG) 2016 – Green-top Guideline No. 52

Appendix III: A flow chart of the different steps for the management of major PPH

Resuscitation, monitoring, investigation and treatment should occur simultaneously



Abbreviations: ECG electrocardiogram; **FBC** full blood count; **FFP** fresh frozen plasma; **Hb** haemoglobin; **IV** intravenous; **IM** intramuscular; **LFTs** liver function tests; **PLT** platelets; **PPH** postpartum haemorrhage; **RhD** rhesus D; **U&Es** urea and electrolytes.

Appendix 2
World Health Organization (WHO) 2025 - Consolidated guidelines for the prevention, diagnosis and treatment of postpartum haemorrhage

Summary list of recommendations for the prevention, diagnosis and treatment of postpartum haemorrhage

Context	Recommendation	Category of recommendation
Antenatal interventions to prevent postpartum haemorrhage	**1.** Full blood count testing is the recommended method for diagnosing anaemia in pregnancy. In settings where full blood count testing is not available, on-site haemoglobin testing with a haemoglobinometer is recommended over the use of the haemoglobin colour scale as the method for diagnosing anaemia in pregnancy.[a] **Revalidated**	Context-specific recommendation
	2. Daily oral iron and folic acid supplementation with 30 mg to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid is recommended for pregnant women to prevent maternal anaemia, puerperal sepsis, low birth weight and preterm birth.[a] **Revalidated**	Recommended
	3. Intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2800 µg (2.8 mg) of folic acid once weekly is recommended for pregnant women to improve maternal and neonatal outcomes if daily iron is not acceptable due to side-effects, and in populations with an anaemia prevalence among pregnant women of less than 20%.[a] **Revalidated**	Context-specific recommendation
	4. Intravenous iron therapy is recommended over oral iron therapy for women with iron-deficiency anaemia during pregnancy when oral iron cannot be used or is not tolerated, or there is a clinical need to correct the anaemia rapidly, provided the woman can be monitored for prompt identification of anaphylaxis. **New**	Context-specific recommendation

[a] Integrated from the *WHO recommendations on antenatal care for a positive pregnancy experience.*

Context	Recommendation	Category of recommendation
Intrapartum interventions to prevent postpartum haemorrhage	**5.** For women in the second stage of labour, techniques to reduce perineal trauma and facilitate spontaneous birth (including perineal massage, warm compresses and a hands-on guarding of the perineum) are recommended, based on a woman's preferences and available options. **Updated**	Recommended
	6. Routine or liberal use of episiotomy is not recommended for women undergoing spontaneous vaginal birth.[b] **Revalidated**	Not recommended
Postpartum interventions to prevent postpartum haemorrhage	**7.** The use of a quality-assured uterotonic is recommended for the prevention of postpartum haemorrhage during the third stage of labour for all births. To effectively prevent postpartum haemorrhage, only ***one*** of the following uterotonics should be used: oxytocin, carbetocin and misoprostol, as outlined in the specific recommendations below: **7.1** Oxytocin (10 IU, intramuscularly/intravenously) is recommended for the prevention of postpartum haemorrhage for all births. **7.2** Carbetocin (100 µg, intramuscularly/intravenously) is recommended for the prevention of postpartum haemorrhage for all births; the heat-stable carbetocin formulation is recommended in settings where cold chain cannot be guaranteed. **7.3** Misoprostol (either 400 µg or 600 µg, orally) is recommended for the prevention of postpartum haemorrhage for all births. **Updated**	Recommended
	8. In situations where women giving birth vaginally already have intravenous access, the intravenous administration of 10 IU oxytocin – diluted and administered slowly over 1 to 2 minutes – is recommended in preference to intramuscular administration. **Edited**	Context-specific recommendation
	9. Uterotonic options that are not recommended for the prevention of postpartum haemorrhage include ergometrine/methylergometrine, fixed-dose combination of oxytocin and ergometrine, and injectable prostaglandins, as outlined in the specific recommendations below: **9.1** Ergometrine/methylergometrine is not recommended for the prevention of postpartum haemorrhage. **9.2** Fixed-dose combination of oxytocin and ergometrine (5 IU/500 µg, intramuscularly) is not recommended for the prevention of postpartum haemorrhage. **9.3** Injectable prostaglandins (carboprost or sulprostone) are not recommended for the prevention of postpartum haemorrhage. **Updated**	Not recommended
	10. In settings where multiple uterotonic options are available, oxytocin (10 IU, intramuscularly/intravenously) is the recommended uterotonic agent of choice for the prevention of postpartum haemorrhage for all births. **Updated**	Recommended

[b] Integrated from the *WHO recommendations on intrapartum care for a positive pregnancy experience.*

Context	Recommendation	Category of recommendation
	11. Heat-stable carbetocin (100 µg intramuscularly/intravenously) is the recommended choice for the prevention of postpartum haemorrhage in settings where the oxytocin cold chain cannot be consistently maintained. If heat-stable carbetocin is not available, misoprostol (400 µg or 600 µg, orally) can be used as an alternative. **Updated**	Context-specific recommendation
	12. The administration of misoprostol (400 µg or 600 µg, orally) by community health workers and lay health workers is recommended for the prevention of postpartum haemorrhage in settings where skilled health personnel are not present to administer injectable uterotonics. **Updated**	Context-specific recommendation
	13. In settings where women give birth outside a health facility and in the absence of skilled health personnel, a strategy of antenatal distribution of misoprostol to pregnant women for self-administration is recommended for the prevention of postpartum haemorrhage, only with targeted monitoring and evaluation.[c] **Revalidated**	Context-specific recommendation
	14. Tranexamic acid is not recommended for the prevention of postpartum haemorrhage at vaginal birth. **New**	Not recommended
	15. Tranexamic acid is not recommended for the prevention of postpartum haemorrhage at caesarean birth. **New**	Not recommended
	16. In settings where skilled birth attendants are available, controlled cord traction is recommended for vaginal births if the health care provider and the woman consider a small reduction in blood loss and a small reduction in the duration of the third stage of labour as important.[d] **Revalidated**	Context-specific recommendation
	17. In settings where skilled birth attendants are unavailable, controlled cord traction is not recommended.[b] **Revalidated**	Not recommended
	18. Cord traction is the recommended method for the removal of the placenta in caesarean section.[b] **Revalidated**	Recommended
	19. Early cord clamping (<1 minute after birth) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation. **Revalidated**	Not recommended
	20. Sustained uterine massage is not recommended as an intervention to prevent postpartum haemorrhage in women who have received prophylactic oxytocin.[b] **Revalidated**	Not recommended

[c] Integrated from the *WHO recommendation on advance misoprostol distribution to pregnant women for prevention of postpartum haemorrhage.*

[d] Integrated from the *WHO recommendations for the prevention and treatment of postpartum haemorrhage.*

Context	Recommendation	Category of recommendation
Diagnosis of postpartum haemorrhage	**21.** For all women giving birth, routine objective measurement of postpartum blood loss is recommended to improve the detection and prompt treatment of postpartum haemorrhage. Methods to objectively quantify blood loss, such as calibrated drapes for women having vaginal birth, can achieve this.[e] **Revalidated**	Recommended
	22. To identify women at risk of adverse outcomes from postpartum bleeding and initiate first-response treatment, it is recommended to use the following criteria: objectively measured blood loss threshold of ≥300 mL with any abnormal haemodynamic sign (pulse >100 bpm, shock index >1, systolic blood pressure <100 mmHg, or diastolic blood pressure <60 mmHg), or objectively measured blood loss of ≥500 mL, whichever occurs first within 24 hours after birth, and with particular vigilance during the first 2 hours. **New**	Recommended
	23. Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women.[f] **Revalidated**	Recommended
First-response treatment of postpartum haemorrhage	**24.** Intravenous oxytocin is the recommended uterotonic drug for the treatment of postpartum haemorrhage.[b] **Revalidated**	Recommended
	25. If intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin, the use of intravenous ergometrine, oxytocin and ergometrine fixed-dose combination, or a prostaglandin drug (including sublingual misoprostol, 800 µg) is recommended.[b] **Revalidated**	Recommended
	26. Uterine massage is recommended for the treatment of postpartum haemorrhage.[b] **Revalidated**	Recommended
	27. Early use of intravenous tranexamic acid (within 3 hours of birth) in addition to standard care is recommended for women with postpartum haemorrhage following vaginal birth or caesarean section.[g] **Edited**	Recommended
	28. Isotonic crystalloids are recommended in preference to colloids for intravenous fluid resuscitation of women with postpartum haemorrhage.[b] **Edited**	Recommended

[e] Integrated from the *WHO recommendations on the assessment of postpartum blood loss and use of a treatment bundle for postpartum haemorrhage.*

[f] Integrated from the *WHO recommendations for the prevention and treatment of postpartum haemorrhage.*

[g] Integrated from the *WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage.*

Context	Recommendation	Category of recommendation
	29. A standardized and timely approach to the management of postpartum haemorrhage, comprising an objective assessment of blood loss and use of a treatment bundle supported by an implementation strategy, is recommended for all women having a vaginal birth. The care bundle for first-line treatment of postpartum haemorrhage should include rapid institution of uterine massage, administration of an oxytocic agent and tranexamic acid, intravenous fluids, examination of the genital tract and escalation of care.[a] **Revalidated**	Recommended
	30. Administration of a uterotonic agent is recommended for the treatment of retained placenta after vaginal birth only in the presence of postpartum haemorrhage. **Updated**	Context-specific recommendation
	31. Routine antibiotic prophylaxis is recommended for women undergoing manual removal of the placenta. **Updated**	Recommended
	32. Umbilical vein injection of oxytocin is recommended for the treatment of retained placenta only in the context of rigorous research.[b] **Revalidated**	Research-context recommendation
Treatment of refractory postpartum haemorrhage	**33.** Bimanual uterine compression is recommended as a temporizing measure until appropriate care is available for the treatment of postpartum haemorrhage due to uterine atony after vaginal birth.[j] **Edited**	Context-specific recommendation
	34. External aortic compression is recommended as a temporizing measure until appropriate care is available for the treatment of postpartum haemorrhage due to uterine atony after vaginal birth.[c] **Edited**	Context-specific recommendation
	35. Non-pneumatic anti-shock garment is recommended as a temporizing measure until appropriate care is available for the treatment of postpartum haemorrhage.[c] **Edited**	Context-specific recommendation

[a] Integrated from the *WHO recommendations on the assessment of postpartum blood loss and use of a treatment bundle for postpartum haemorrhage.*

[b] Integrated from the *WHO recommendation on umbilical vein injection of oxytocin for the treatment of retained placenta.*

[j] Integrated from the *WHO recommendations for the prevention and treatment of postpartum haemorrhage.*

Context	Recommendation	Category of recommendation
	36. Uterine balloon tamponade is recommended for the treatment of postpartum haemorrhage due to uterine atony after vaginal birth in women who do not respond to standard first-line treatment, provided the following conditions are met: • Immediate recourse to surgical intervention and access to blood products is possible if needed. • A primary postpartum haemorrhage first-line treatment protocol (including the use of uterotonics, tranexamic acid, intravenous fluids) is available and routinely implemented. • Other causes of postpartum haemorrhage (retained placental tissue, trauma) can be reasonably excluded. • The procedure is performed by health personnel who are trained and skilled in the management of postpartum haemorrhage, including the use of uterine balloon tamponade. • Maternal condition can be regularly and adequately monitored for prompt identification of any signs of deterioration.[a] **Revalidated**	Context-specific recommendation
	37. Uterine packing with plain gauze or gauze impregnated with haemostatic agent(s) is not recommended for the treatment of postpartum haemorrhage. **Updated**	Not recommended
	38. If other measures have failed and if the necessary resources are available, the use of uterine artery embolization is recommended as a treatment for postpartum haemorrhage due to uterine atony.[b] **Revalidated**	Context-specific recommendation
	39. If bleeding does not stop in spite of treatment using uterotonics and other available conservative interventions (e.g. uterine massage, balloon tamponade), the use of surgical interventions is recommended.[b] **Revalidated**	Recommended
	40. Cell salvage is recommended for the treatment of postpartum haemorrhage only in the context of rigorous research. **New**	Research-context recommendation
	41. For women experiencing acute or ongoing postpartum haemorrhage, the decision to initiate transfusion of blood products should be based on the underlying risk, continuous clinical and haematological assessments, and clear protocols for optimizing their use. **New**	Recommended

[a] Integrated from the *WHO recommendation on uterine balloon tamponade for the treatment of postpartum haemorrhage.*

[b] Integrated from the *WHO recommendations for the prevention and treatment of postpartum haemorrhage.*

Context	Recommendation	Category of recommendation
Supportive care after postpartum haemorrhage	**42.** Oral iron supplementation, either alone or in combination with folic acid, may be provided to postpartum women for 6–12 weeks after delivery for reducing the risk of anaemia in settings where gestational anaemia is of public health concern.[a] **Revalidated**	Context-specific recommendation
	43. Intravenous iron therapy is recommended over oral iron therapy for women with iron-deficiency anaemia after birth when oral iron cannot be used or is not tolerated or there is a clinical need to treat women with severe iron-deficiency anaemia rapidly, provided staff are trained to evaluate and manage anaphylactic reactions. **New**	Context-specific recommendation
Health systems interventions for postpartum haemorrhage	**44.** The use of formal protocols by health facilities for the prevention, diagnosis and treatment of postpartum haemorrhage is recommended.[b] **Edited**	Context-specific recommendation
	45. The use of formal protocols for referral of women to a higher level of care is recommended for health facilities.[b] **Revalidated**	Context-specific recommendation
	46. The use of simulations of postpartum haemorrhage treatment is recommended for pre-service and in-service training programmes.[b] **Revalidated**	Context-specific recommendation
	47. Monitoring the use of uterotonics after birth for the prevention of postpartum haemorrhage is recommended as a process indicator for programmatic evaluation.[b] **Revalidated**	Context-specific recommendation

[a] Integrated from the *WHO guideline on iron supplementation in postpartum women.*

[b] Integrated from the *WHO recommendations for the prevention and treatment of postpartum haemorrhage.*