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Title: medical management of secondary postpartum haemorrhage: A prospective cohort study

Short running title: Medical management of secondary PPH

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Abstract:

Background: Secondary postpartum haemorrhage (PPH) complicates ~1% of pregnancies and can cause serious maternal morbidity.[1] However, evidence guiding optimal management is scarce and often based on case series and expert opinion.[2]

Aims: To measure the success of primary medical therapy in managing secondary PPH and to identify factors associated with need for surgical management.

Materials and methods: Postpartum patients presenting to a tertiary women's hospital Emergency Department between July 2020 and October 2021 with secondary PPH were recruited. Data from the acute presentation were collected prospectively. Antenatal and intrapartum data were collected from medical record review. The primary outcome was the success of medical management for secondary PPH, defined by the implementation of medical or expectant measures without subsequent need for surgical intervention.

Results: One-hundred and twenty patients underwent primary medical management for secondary PPH. Ninety-eight (82%) were managed successfully with medical management and 22 (18%) required surgery. Medical management involved misoprostol (n=33; 27.5%), antibiotics (n=108; 90%), and less commonly other uterotonics (n=6; 5%). Factors associated with lower rates of successful medical management included: antecedent manual removal of placenta (MROP) (OR 0.2, p=0.047), primary PPH ≥500ml (OR 0.39, p=0.048) or ≥1L (OR 0.24, p=0.009), >200ml blood loss at presentation (OR 0.17, p=0.015), increasing time post-delivery (OR 0.84, p=0.044), retained products of conception (RPOC) on ultrasound (OR 0.024, p=0.001) and vaginal birth (OR 0.27, p=0.027).

Conclusion: Medical management was highly successful. Vaginal birth, MROP, primary PPH, RPOC on ultrasound and increasing time post-delivery were associated with increased need for surgical management.

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Introduction

Secondary postpartum haemorrhage (PPH), defined by abnormal bleeding between 24 hours and 12 weeks post-partum,[3] complicates approximately 1% of pregnancies and can be a serious cause of maternal morbidity.[1] Despite this, it receives far less attention than its primary counterpart and data guiding the optimal management strategies for secondary PPH are scarce. In their 2008 Cochrane review, Alexander et al. were unable to find any randomised trials to guide care.[3] Few non-randomised studies exist to inform practice, and excluding antibiotic therapy for endometritis, much of the evidence guiding secondary PPH management is based on case series and expert opinion.[2]

Treatment options for secondary PPH include both medical and surgical modalities. Medical management includes use of uterotonics such as misoprostol, antibiotics, tranexamic acid, hormonal therapy or a combination of these.[4] Surgical management may involve evacuation of retained products, or less commonly a hysterectomy.[3] The rates of surgical management vary vastly between studies[5,6] and whilst effective, surgery is not without complications, including a significant rate of uterine perforation,[1,6] and Asherman's syndrome.[2,7]

While curettage is regularly used for secondary PPH management, it has been suggested that a trial of initial medical or expectant management may be more appropriate in some cases.[4] We are unaware of any prospective studies to date that assess whether first line medical management can prevent the need for surgical management of secondary PPH.

In this prospective trial, we aimed to determine the success rates of primary expectant or medical therapy, including the use of antibiotics, uterotonics or a combination, for the management of secondary PPH. Additionally, we aimed to identify the factors associated with successful medical management and the morbidity associated with the implementation of primary conservative measures.

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Materials and methods

This study was prospectively registered and approved by the Mercy Ethics Committee (ID number: 2020-04).

Recruitment

We conducted a prospective, observational study of patients presenting to the Emergency Department (ED) of a tertiary women's hospital, between the 1st of July 2020 and 31st of October 2021 with secondary PPH. Patients were eligible for inclusion if they presented following a delivery at gestation of >20 weeks with abnormal bleeding between 24 hours and 12 weeks postpartum and were excluded if they were under 18 years old or were managed with primary surgical management. All were managed by the treating clinician according to an institutional guideline "Management of Secondary Post-Partum Haemorrhage: ED Guideline" developed and implemented in July 2020 (Supplementary Figures 1-3).

Data collection

Participant details were de-identified, collected, and managed using REDCap electronic data capture tools.[8,9] Data from the acute presentation and management were collected prospectively; demographic, antenatal and intrapartum data were collected by medical record and birthing outcome database review. Subsequent investigation or management within 12 weeks postpartum, including re-presentations, admissions, additional ultrasounds (USS) or surgical procedures were also collected via medical record review and recorded in the REDCap database.

Outcomes

Our primary outcome was to determine the success of medical management for secondary PPH. Successful management was defined by the implementation of medical or expectant measures without subsequent requirement for surgical intervention. Secondary outcomes consisted of the rates of complications associated with medical management of secondary PPH including: number of

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re-presentations, number of re-presentations with estimated blood loss (EBL) >500ml, number of re-presentations requiring further medical management, number and duration of admissions required, number of days until resolution (defined as the number of days between initial presentation and final review), hysterectomy, high dependency unit (HDU) or intensive care unit (ICU) admission and the need for blood or iron transfusion. As an additional secondary outcome, an exploratory analysis was undertaken to determine patient characteristics, including demographics, antenatal and intrapartum factors, and details of the acute ED presentation that were associated with successful medical management.

Statistical analysis

Analysis was conducted according to a pre-defined statistical plan. Stata/BE v17 (StataCorp, College Station, TX, USA) was used to undertake the statistical analyses.

Patient characteristics and details of the acute presentation and management were summarised with counts and relative frequencies, median (interquartile range, IQR) or mean ± SD depending on the type and distribution.

Complications of medical management were compared between the unsuccessful and successful medical management groups. Continuous variables are presented as medians (with IQR, minimum and maximums) and compared between outcome groups using the Wilcoxon rank-sum test. Categorical variables are presented as counts (with relative frequencies) and compared between outcome groups using Fisher's exact test.

Exploratory analyses of factors associated with successful medical management were examined independently using a series of univariable logistic regression models; data are presented as odds ratios with corresponding 95% confidence intervals and p-values. We examined a range of patient characteristics, including demographic, antenatal and intrapartum factors, and acute ED presentation details. The potential association for each considered factor was explored individually,

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with the results provided for all factors irrespective of their statistical significance. Due to the small sample size, we did not attempt to construct a multivariable model.

Results

Over the 16-month period, 120 patients who underwent primary medical or expectant management for secondary PPH were recruited. This represented 1.6% of 7669 (4563 vaginal/instrumental deliveries, 3106 caesarean sections) women that delivered in our institution over this time frame. During this period an additional five patients were consented that underwent primary surgical management; and were subsequently excluded from the analysis.

Patient characteristics

Patient demographics are summarized in Table 1. The mean (SD) age was 32±5 years. Sixty-nine (58%) patients were primiparous, 48 (40%) presented post caesarean, and 72 (60%) following vaginal birth, of which 29 (40%) had been instrumental vaginal deliveries. The placenta was delivered by manual removal (MROP) in 7 (6%) cases and 14 (13%) placentas were incomplete or piece-meal at delivery. Delivery was complicated by a primary PPH in 48 (40%) patients.

The median (IQR) time post-delivery to ED presentation was 18 days (12, 37) (Supplementary Table 1). At the initial ED presentation, the EBL was <50 ml in 68 (58%) cases, 50-200ml in 40 (34%) cases, and >200ml in 10 (8%) cases. In addition to abnormal bleeding, 39 (33%) patients presented with abdominal pain, 10 (8%) were tachycardic (HR >100bpm), 4 (3%) hypotensive (systolic blood pressure <100mmHg) and 2 (2%) patients were febrile (temperature >37.5°C).

Management and outcomes

Ninety-eight (82%) patients were successfully treated with medical or expectant management and 22 (18%) required subsequent surgery. Medical management most often involved misoprostol (n=33; 27.5%), antibiotics (n=108; 90%) or a combination of both, and less commonly other

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uterotonics (syntocinon or ergometrine, n=6; 5%). Nine women were managed expectantly with a "watch and wait" approach and were not prescribed medical treatment (Supplementary Table 2).

There were 81 re-presentations to hospital following discharge, from 56 (47%) patients. Of these, 28 presentations required further medical management, and 2 patients re-presented with an EBL >500ml, both of whom required subsequent surgery. Eighteen patients required admission to hospital following their initial presentation to ED and six additional patients were admitted following further re-presentations. Of those admitted, the median (IQR) duration of admission was 3 (2,3) days. The median (IQR) number of days until resolution of symptoms was 1 (0, 3). No patients required a hysterectomy or ICU admission. One woman was admitted to the HDU (1%), 2 (2%) required blood transfusions, and 3 (3%) received iron transfusions. Failed medical management was associated with a higher incidence of re-presentations, subsequent medical management, hospital admissions, blood transfusions and iron transfusions, compared with patients who were successfully treated medically (Table 2).

Factors associated with success of medical management

Factors associated with lower rates of successful medical or expectant management included: MROP at vaginal delivery, primary PPH of ≥500ml or ≥1L and increasing EBL post-delivery, >200ml blood loss at ED presentation, increasing time post-delivery at ED presentation and confirmed retained products of conception (RPOC) on USS (all $p<0.05$) (Table 3). Secondary PPH following caesarean section, compared to vaginal delivery and instrumental, was associated with higher rates of successful medical management (OR 3.67, 95%CI 1.16, 11.63, $p=0.027$). Age, parity, gestation at delivery, placental and membrane status at delivery and tachycardia or hypotension at ED presentation showed no evidence of being associated with the success of medical management.

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Discussion

To our knowledge this is the first prospective study to evaluate whether medical and expectant management for abnormal postpartum bleeding can prevent the need for surgery. Overall, non-surgical management predominantly with antibiotics, with or without misoprostol, was highly successful for the management of secondary PPH with 82% of patients avoiding surgery. Complications associated included re-presentation to hospital in 43%; half of which required further medical treatment and two cases with heavy bleeding >500ml EBL. Twenty percent of patients required admission, including one to HDU. Blood products were required in 2% and iron transfusions in 3% of patients. No patients required a hysterectomy or ICU admission. We also identified several factors associated with lower success rates of medical management, including vaginal birth, MROP, primary PPH (and increasing EBL at birth), RPOC on USS, EBL >200ml at presentation and increasing time post-delivery.

Previously, curettage was the treatment of choice for secondary PPH, with earlier studies describing 60-88%[5,10,11] of patients managed surgically. In the postpartum period, uterine instrumentation is associated with higher complication rates. The rates of uterine perforation have been estimated at approximately 1.5-4%[6,12] for postpartum curettage, compared to 0.05% in early trimester dilation and curettage for miscarriage.[13] In addition, rates of Asherman's syndrome are not insignificant and pose a risk to future fertility.[7] More recently, small retrospective studies by Shiel et al. and Feigenberg et al. reported symptom resolution in 93% and 76% of patients respectively following conservative management,[6,14] more consistent with our cohort. However, larger cohort data pertaining to the safety and efficacy of medical management are lacking, and as our results demonstrate, medical management is not entirely without morbidity which must also be considered. Fifty-six patients re-presented to ED following medical or expectant management. A proportion of these were planned reviews as per the institutional guideline (Supplementary Figures 1-3), however, 23 patients required further medical management and two patients re-presented with heavy

bleeding (EBL>500ml) that required emergency surgical management. In addition to the impacts on physical health, added admissions and medical treatments during the postnatal period has the potential to disrupt this important time for breastfeeding, newborn bonding and perinatal mental health.

In the absence of randomised trials and evidence-based guidelines, determining the optimal management strategy for patients with secondary PPH is difficult, and relies heavily on the clinical judgment of the treating team. To appropriately guide clinicians, treatment protocols must consider the vast spectrum of secondary PPH presentations. Diagnosis is subjective, based on the patient and clinician's perception of "abnormal bleeding", and presentation can range from mildly increased lochia to life-threatening bleeding. Furthermore, at time of presentation, determining the cause of secondary PPH clinically can be challenging. The aetiology includes endometritis and RPOC, as well as rarer causes such as pseudoaneurysms of the uterine artery, arterio-venous malformations or coagulopathies,[4] which are not easily differentiated clinically. USS is commonly employed to differentiate the causes of secondary PPH. However, predicting RPOC on USS has varying success, with case series reporting wide variation in sensitivities and specificities.[15] An audit of 200 cases of postpartum curettage found 77% of participants had evidence of RPOC on USS pre-operatively, but this was confirmed on histology in only 40%.[12] There is limited evidence to direct clinicians regarding USS features that should mandate surgical evacuation, and those suggesting expectant or medical approaches are appropriate. In this study, treatment was predominantly with antibiotics (90%), and 27.5% of participants received misoprostol. Uterotonics were rarely administered (4%). Nine women were expectantly managed, each of whom were systemically well with minimal bleeding. In two cases the bleeding was thought to be a return of normal menses. These patients were managed expectantly at the discretion of the treating clinician, due to the minimal blood loss and low suspicion for endometritis or retained products of conception. None of these women required surgical management.

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Our findings suggest it may be possible to predict which patients with secondary PPH will be successfully treated medically and assign treatment accordingly. Vaginal birth, antecedent MROP and RPOC on USS, indicate an increased likelihood that RPOC is the underlying cause of secondary PPH and therefore a reciprocal increase in the likelihood of requiring surgical management. Patients that presented later in the postpartum period, particularly 30 or more days postpartum, and those with a secondary PPH of >200ml were also more likely to require surgery. We hypothesise these cases were unlikely due to endometritis alone (in the absence of RPOC); with endometritis being less likely when more remote from birth, and more likely associated with smaller volume bleeding. Additionally, clinicians may have a lower threshold to operate in the setting of larger volume blood loss. An USS was not performed on all patients that presented with secondary PPH, and the decision for imaging to be performed was based on the severity of symptoms as well as time post-delivery. RPOC on USS was associated with an increased likelihood of requiring surgical management, however this finding may be affected by selection bias as the patients with heavier bleeding were more likely to be scanned. In contrast, abnormal postpartum bleeding following caesarean section, which is less likely to be associated with RPOC, particularly given standard protocols of checking the endometrial cavity prior to closure of the myotomy, and more likely to be caused by endometritis, is more responsive to medical management with antibiotics. Furthermore, in participants presenting post caesarean section, medical management with misoprostol may offer limited additional benefit to antibiotics and may be over-prescribed. While there is little risk of harm involved the use of misoprostol, side effects of GI upset, and abdominal pain are common and should be considered. Stratifying patients based on these factors may identify a cohort of patients with secondary PPH who are safe to be treated medically or expectantly, thus avoiding the risks associated with surgery.

During the recruitment period an additional five patients were recruited that presented to ED with secondary PPH but underwent primary surgical management and were subsequently excluded from analysis. These patients all presented at ≥6 weeks postpartum, had confirmed RPOC on USS of ≥12ml in volume and were consented for primary surgical management at the discretion of the treating

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clinician. It is unknown whether they would have been successfully managed medically, however from interpreting our study results, their success rate with medical therapy alone would likely have been reduced.

This study is limited by its observational nature. There are currently no randomised controlled trials to assess secondary PPH management, and future trials of larger sample size assessing the efficacy of treatment modalities are needed. Our study was conducted at a single institution and re-presentations, admissions, or surgical management at different institutions were not reported. In addition, while many women preferentially attend our small women's-specific ED in the initial weeks postpartum, a cohort of women may present to their GP for management of abnormal bleeding in the postpartum period, and these data was not collected. Additionally, while recruitment was prospective, retrospective medical record review was relied on for antenatal and intrapartum data, some of which was incomplete. Factors such as previous history of PPH, MROP or curettage procedures may be important variables but were not analysed due to inadequate data. In this population 58% of patients were estimated to have <50ml of blood loss at acute presentation and 97% were hemodynamically stable, so success rates of medical management may not be generalisable to a higher acuity population.

Non-surgical management is a safe and effective management strategy for many patients suffering secondary PPH. We have identified several risk-factors associated with either success or failure of medical management. Additional large observational studies and randomised trials to further test the association of these clinical features with resolution of symptoms using medical management would further guide decision-making for this patient group.

Tables

Table 1: Patient demographics, antenatal history, intrapartum factors (n=120)

Table 1

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	Number (%)		Number (%)
Age, mean (SD)	32 (5)	**Mode of placental delivery**[‡]	
Gravidity		Controlled cord traction	59 (50)
1	46 (38)	Manual removal of placenta	7 (6)
2	38 (32)	Fundal pressure	2 (2)
3	19 (16)	Physiological	2 (2)
4 +	17 (14)	Delivered by caesarean section	49 (41)
Parity		**Membrane status**[§]	
1	69 (58)	Complete	53 (50)
2	36 (30)	Incomplete	9 (8)
3	10 (8)	Ragged	45 (42)
4+	5 (4)	**Placenta status**[¶]	
Previous caesarean section	20 (17)	Complete	101 (88)
Two or more previous caesarean sections	5 (4)	Incomplete	3 (3)
Gestation of delivery[†]		Piece-meal	11 (10)
<32 weeks	7 (6)	**Prolonged rupture of membranes (>18 hours)**[††]	11 (9)
32 to 36+6 weeks	16 (13)	**Precipitate labour (< 2 hours)**[‡‡]	20 (29)
≥37 weeks	96 (81)	**Prolonged third stage (>30 minutes)**[§§]	3 (4)
Onset of labour		**Estimated blood loss at delivery**	
Spontaneous	46 (38)	0-499ml	72 (60)
Induced	42 (35)	500ml-999ml	28 (23)
No labour	32 (27)	>1L	20 (17)
Mode of delivery		**Infant feeding**[¶¶]	
Vaginal	43 (36)	Breast or expressed breast milk	65 (56)
Ventouse	15 (13)	Mixed feeding	40 (34)
Forceps	14 (12)	Formula feeding	8 (7)
Caesarean	48 (40)	Other	3 (3)

SD indicates standard deviation; [†]Missing data in 1 (home birth, unknown gestation), n=119; [‡]Missing data in 1, n=119; [§]Missing data in 13, n=107; [¶]Missing data in 5, n=115; [††]Missing data in 3, n=117; [‡‡]Vaginal birth only (72), missing data in 2, n=70; [§§]Vaginal birth only (72), missing data in 3, n=69; [¶¶]Missing data in 4, n=116

Table 2: Outcomes and complications of management

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Table 2			
	Successful medical management (n=98)	**Unsuccessful medical management (required subsequent surgical management) (n=22)**	**p value**
Number of re-presentations[†], median (IQR) [min, max]	0 (0,1) [0,3]	1 (1,2) [0,4]	<.001
Number of re-presentations with EBL >500ml, median (IQR) [min, max]	0 (0,0) [0,0]	0 (0,0) [0,1]	.003
Number of re-presentations requiring further medical management, median (IQR) [min, max]	0 (0,0) [0,2]	1 (0,1) [0,2]	<.001
Number of admissions required, median (IQR) [min, max]	0 (0,0) [0,1]	1 (0,1) [0,2]	<.001
Duration of admissions required (days), median (IQR) [min, max]	2 (1,3) [1,5]	3 (2,4) [2,5]	0.16
Number of days until resolution, median (IQR) [min, max]	0 (0,3) [0,82]	6.5 (2,19) [0,65]	<.001
Hysterectomy, n (%)	0 (0%)	0 (0%)	-
HDU admission, n (%)	1 (1%)	0 (0%)	-
ICU admission, n (%)	0 (0%)	0 (0%)	-
Blood transfusion, n (%)	0 (0%)	2 (9%)	0.032
Iron transfusion, n (%)	0 (0%)	3 (14%)	0.005

[†]Note: number of re-presentations also includes planned reviews in the Emergency Department as per the institutional guideline.

EBL indicates estimated blood loss; HDU, high dependency unit; ICU, intensive care unit and IQR, interquartile range

Table 3: Factors potentially associated with the probability of successful medical management

Table 3			
Factor	**Odds ratio (OR)[†]**	**95% confidence interval (CI)**	**p- value**
Age (per year)	0.98	0.90, 1.07	0.66
BMI (per kg/m^2)	1.04	0.96, 1.13	0.36
BMI			
<30 kg/m^2	(ref)		

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≥30 kg/m^2	1.23	0.43, 3.51	0.70
Parity			
Primiparity	(ref)		
Multiparous	2.26	0.82, 6.27	0.12
Gestation at delivery (per week)	0.93	0.77, 1.10	0.38
Gestation at delivery			
<37 weeks	(ref)		
≥37 weeks	0.61	0.16, 2.26	0.46
Mode of Delivery			
Vaginal / instrumental	(ref)		
Caesarean section	3.67	1.16, 11.63	0.03
Mode of Delivery			
Vaginal	(ref)		
Instrumental	0.795	0.270, 2.339	.68
Caesarean section	3.333	0.960, 11.568	.058
Mode of placenta delivery (vaginal deliveries)			
CCT / Dublins / Physiological third stage	(ref)		
MROP	0.20	0.04, 0.98	0.05
Mode of placenta delivery			
CCT / Dublins / Physiological third stage / MROP	(ref)		
Caesarean	2.82	0.96, 8.26	0.06
Placental status at delivery			
Complete	(ref)		
Incomplete / piece-meal	0.51	0.14, 1.80	0.29
Membrane status at delivery			
Complete	(ref)		
Incomplete	1.42	0.16, 12.97	0.76
Ragged	0.71	0.25, 2.03	0.52
EBL at birth (per 100ml)‡	0.92	0.85, 0.99	0.03
Primary PPH			
<500ml	(ref)		
≥500ml	0.39	0.15, 0.99	0.05
Primary PPH			

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<1000ml	(ref)		
≥1000ml	0.24	0.09, 0.70	0.01
Quantification of blood loss at presentation			
<50ml	(ref)		
50-200ml	0.81	0.28, 2.34	0.70
≥200ml	0.17	0.04, 0.71	0.02
Time post-delivery of presentation (per week)	0.84	0.71, 1.00	0.04
Time post-delivery of presentation			
1-14 days	(ref)		
15-28 days	0.44	0.12, 1.58	0.21
29+ days	0.32	0.10, 1.01	0.05
Tachycardia at any presentation			
Heart rate ≥100bpm	0.72	0.18, 2.87	0.64
Heart rate <100bpm	(ref)		
Hypotension at any presentation			
Systolic blood pressure ≤100 mmHg	0.56	0.14, 2.32	0.43
Systolic bloods pressure >100 mmHg	(ref)		
Confirmed RPOC on USS (in those with USS only)			
Yes	0.02	0.003, 0.20	0.001
No / Equivocal	(ref)		

†Odds ratios are obtained from univariable logistic regression models. Each factor was examined independently.

‡Analysed as continuous variable, scaled per 100mls of estimated blood loss

BMI indicates body mass index; CCT, controlled cord traction; EBL, estimated blood loss; MROP, manual removal of placenta; PPH, postpartum haemorrhage; RPOC, retained products of conception and USS, ultrasound

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