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THE MANAGEMENT OF SECONDARY POSTPARTUM HEMORRHAGE

K. M. Groom and T. Z. Jacobson

INTRODUCTION

Secondary postpartum hemorrhage is defined as excessive vaginal bleeding from 24 h after delivery up to 6 weeks postpartum[1]. Unlike primary postpartum hemorrhage, there is no clear definition for quantity of blood loss and this can vary from 'increased lochia' to massive hemorrhage. The diagnosis is therefore subjective, which may account for the variation in reported incidence. The reported overall incidence of secondary postpartum hemorrhage in the developed world varies from 0.47% to 1.44%[2,3].

The etiology of secondary postpartum hemorrhage is diverse and management is dependent on identifying the cause and tailoring treatment appropriately. The published work on the management of secondary is limited compared with primary postpartum hemorrhage[4]. However, with falling maternal mortality rates, there is increasing interest and attention to maternal morbidity and the important topic of management of secondary postpartum hemorrhage. The majority of cases of secondary postpartum hemorrhage are associated with minor morbidities but may still require re-admission to hospital, use of antibiotics and surgical intervention. In more extreme cases, major morbidity requiring hysterectomy, arterial ligation or radiological intervention is possible[5] and maternal death may still result from massive secondary postpartum hemorrhage despite the use of all available interventions.

ETIOLOGY OF SECONDARY POSTPARTUM HEMORRHAGE

Subinvolution/uterine atony

The major cause of secondary postpartum hemorrhage is subinvolution of the uterus. This results in failure of obliteration of blood vessels underlying the placental site, leading to prolonged bleeding. The two main causes of this are infection (see Chapter 44) and inflammation (endometritis) and retained placental tissue.

Endometritis is more common following prolonged rupture of membranes, prolonged labor, emergency Cesarean section or with a retained placenta requiring manual removal. A history of offensive lochia, maternal pyrexia and uterine tenderness is often present and retained placental tissue is more common in women with a previous history of retained placenta or if there were concerns at the time of delivery of incomplete placenta and/or membranes. It is less likely following delivery by Cesarean section. Differentiation between the two causes is often difficult and both conditions may co-exist.

Lower genital tract trauma

Missed vaginal lacerations and hematomas may present as secondary postpartum hemorrhage. These are often associated with traumatic deliveries or those requiring ventouse or forceps. They usually present within the first few days after delivery. Infected suture lines and episiotomy sites may lead to wound breakdown and result in excessive vaginal bleeding.

Placental abnormalities

Placenta accreta, increta and percreta are all known causes of massive primary postpartum hemorrhage. When managed conservatively with placental tissue left *in situ* (with or without methotrexate therapy), they can also be associated with delayed bleeding and the need for hysterectomy[6,7] (see Chapter 24).

Uterine abnormalities

Fibroids are associated with primary postpartum hemorrhage. They cause uterine enlargement and prevent involution of the uterus, therefore leading to prolonged bleeding from the placental bed. More rarely, they can be associated with secondary postpartum hemorrhage. Fibroids have usually been identified by ultrasound in the antenatal period.

Abnormalities of uterine vasculature such as arteriovenous malformations and false aneurysms may also lead to secondary postpartum hemorrhage. Arteriovenous malformations are due to an abnormal communication between an artery and vein with proliferation of each vessel with interconnecting fistula. It is believed these malformations may result from venous sinuses becoming incorporated in scars within the myometrium after necrosis of the chorionic villi. The majority are acquired after pregnancy and may result from trophoblastic disease, previous uterine curettage, uterine or cervical malignancy[8,9] or Cesarean section[10,11]. Diagnosis is made using ultrasound with color Doppler analysis.

Cesarean section wound dehiscence or surgical injury

Surgical injury to pelvic blood vessels at the time of Cesarean section[10] usually presents within 24 h. However, later presentations, in particular those causing broad ligament hematomas, have been described[5] and should be considered in women presenting acutely with signs of intra-abdominal hemorrhage. Delayed presentation of bleeding from non-union/dehiscence of the Cesarean section uterine scar has also been described. This is believed to be due to local infection at the site of uterine closure causing erosion of blood vessels. In the cases reported, this has lead to massive postpartum hemorrhage 2–3 weeks after Cesarean section and the need for subtotal hysterectomy[12]. Diagnosis of uterine dehiscence post-Cesarean section associated with infection has also been made at hysteroscopy[13], although causing less significant postpartum hemorrhage and only requiring treatment with antibiotics.

Choriocarcinoma

The majority of cases of choriocarcinoma after a non-molar pregnancy present with secondary postpartum hemorrhage or irregular vaginal bleeding[14]. In addition, secondary symptoms of metastatic disease may be present. The diagnosis is made by serum β-human chorionic gonadotropin (β-hCG), histological diagnosis and radiological imaging including ultrasound, plain film X-ray and computed tomography (CT) scan.

Bleeding disorders, coagulopathies and use of anticoagulants

Women with congenital hemorrhagic disorders such as von Willebrand's disease (quantitative or qualitative deficiency of von Willebrand factor), carriers of hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency) and factor XI deficiency are at an increased risk of postpartum hemorrhage. Often, these abnormalities of the coagulation system are undetected until challenged by trauma, surgery or childbirth and so may be undiagnosed prior to pregnancy. These women are not at increased risk of antepartum hemorrhage[15] but at significant risk of both primary and secondary postpartum hemorrhage. The risk of secondary postpartum hemorrhage may be even greater than primary postpartum hemorrhage as the pregnancy-induced rise in maternal clotting factors falls after delivery. The reported incidence for secondary postpartum hemorrhage in these conditions is 20–28% for von Willebrand's disease, 11% for hemophilia carriers and 24% in factor XI deficiency[16–19]. Postpartum acquired hemophilia has also been described. This is a rare condition but can cause severe hemorrhage. It is caused by antibodies to factor VIII which partially or completely suppress factor

VIII procoagulant activity in women with previously normal levels and activity of factor VIII. Bleeding usually commences within 3 months of delivery but may be delayed for up to 12 months[15].

The use of anticoagulants in the postpartum period may also cause delayed bleeding. In particular, women using warfarin should be carefully monitored and informed of the risks of hemorrhage.

MANAGEMENT OF SECONDARY POSTPARTUM HEMORRHAGE

Evidence regarding the management of secondary postpartum hemorrhage is limited. A Cochrane review searched and assessed all randomized or quasi-randomized comparisons of drug therapies, surgical therapies and placebo or no treatment for secondary postpartum hemorrhage. Forty-five papers were identified, but none met the inclusion criteria, and the review concluded there was no evidence from randomized trials to show the effects of treatments for secondary postpartum hemorrhage[4].

The main aims of treatment are to provide basic resuscitation, establish a cause for the bleeding, and tailor the treatment (medical and/or surgical) according to the cause.

Resuscitation

Approximately 10% of cases of secondary postpartum hemorrhage will present with massive hemorrhage[20] and require immediate attention. In these cases, resuscitation should be commenced prior to establishing a cause and should include the involvement of senior staff at the earliest opportunity (see Chapter 20).

Restoration of circulating blood volume should be achieved by gaining intravenous access with two large-bore cannulae and administering intravenous fluids initially with physiological saline (up to 2 liters) and then with plasma expanders until blood is available. Blood should be obtained for full blood count, coagulation screen and cross-match. High-concentration oxygen (10–15 liters per minute) should be administered by a tight-fitting mask[21]. Close observation of vital signs including pulse, blood pressure, oxygen saturation and urine output should be maintained throughout resuscitation. Blood and blood products should be given according to blood loss, response to initial fluid administration and hemoglobin and coagulation results. If hemorrhage is life-threatening, transfusion with uncross-matched O rhesus-negative or type-specific blood may need to be considered. Identification of the cause of bleeding should then be made and further management planned accordingly.

In cases of less significant hemorrhage, basic resuscitation should be instigated as appropriate but blood transfusion may be delayed whilst establishing a cause for the bleeding.

Clinical presentation

Ninety-five percent of women present within the first month after delivery, 19% within 7 days, 41% in 8–14 days, 23% in 15–21 days and 12% in 22–28 days[2]. The amount of blood loss at presentation varies but most are hemodynamically stable. A thorough history will provide information relating to cause and should include details regarding parity, labor, mode of delivery, third-stage or puerperal complications and any relevant medical and family history. Clinical signs and symptoms at the time of presentation may include offensive lochia, abdominal cramping, uterine tenderness, pyrexia, enlarged uterus and an open cervical os.

Normal postpartum loss may continue beyond 6 weeks in up to 25% of women, especially if breast-feeding[20] and the first period may be heavy, prolonged and painful as a result of an anovulatory cycle. Women should be given this information during normal postpartum care to avoid unnecessary concern and presentation for medical investigation.

Investigations

Baseline blood tests should include full blood count, coagulation studies, C-reactive protein, a group and hold specimen and serum β-hCG. Vaginal swabs should be taken at the time of examination for aerobic as well as anaerobic bacterial growth, including swabs from episiotomy or vaginal tear sites. In women with signs of infection, a mid-stream urine specimen

should be collected and, if maternal temperature is > 38°C, blood cultures should be taken.

Ultrasound imaging of the pelvis should be considered if there are concerns of retained placental tissue. If this is within 7–14 days of delivery, interpretation may be difficult as remaining blood clots may appear as mixed echogenic material in a similar manner to retained tissue. The use of duplex color Doppler helps to improve diagnostic accuracy in differentiating clot and tissue[22], as retained placental tissue will often maintain a blood supply unlike necrotic decidua and clot[23].

The over-diagnosis of retained placental tissue on ultrasound may lead to unnecessary surgical intervention and its potential complications. However, ultrasound does have significant benefits, as it has a good negative predictive value and therefore is helpful in excluding a diagnosis of retained placental tissue. Neill and colleagues assessed 53 women undergoing ultrasound for secondary postpartum hemorrhage. Definitive diagnosis of retained placental tissue was either made histologically or, in those women managed conservatively, absence of retained tissue was assumed if bleeding diminished within 1 week. They demonstrated the diagnostic value of ultrasound assessment to have a positive predictive value of 46% (95% confidence interval (CI) 31–70%), a negative predictive value of 96% (95% CI 88–100%), with a sensitivity of 93% (95% CI 80–100%) and a specificity of 62% (95% CI 48–79%)[24]. This study also suggested that a standardized approach to reporting an ultrasound investigation of secondary postpartum hemorrhage would be helpful. This is shown in Table 2.

Additional imaging should also be considered for specific causes of secondary postpartum hemorrhage such as plain chest film and CT scanning for metastases in cases of choriocarcinoma, magnetic resonance imaging (MRI) for placenta accreta[25,26] and angiography for intractable bleeding of unknown origin[10].

Treatment

The majority of cases of secondary postpartum hemorrhage are due to subinvolution of the uterus caused by uterine infection and/or retained placental tissue. Initial management

Table 1 Causes of secondary postpartum hemorrhage

Subinvolution of the uterus – retained placental tissue and/or endometritis, fibroid uterus
Lower genital tract lacerations/hematoma
Surgical injury
Dehiscence of Cesarean section scar
Vascular abnormality – arteriovenous malformation
Placental abnormality – placenta accreta, percreta and increta
Choriocarcinoma
Coagulapathies, bleeding disorders, use of anticoagulants

Table 2 A proposed standardized system for reporting postpartum ultrasound scan. Adapted from Neill *et al.*, 2002[24]

1. Normal endometrial cavity
2. Endometrial cavity containing fluid only
3. Endometrial cavity enlarged (anteroposterior (AP) depth > 1 cm). Maximum AP dimensions noted
4. Endometrial cavity containing echogenic foci. Dimensions of largest foci noted. Doppler evaluation of blood flow in foci

Table 3 The management of secondary postpartum hemorrhage

Medical	*Surgical*
Oxytocics	Uterine evacuation
Prostaglandins	Uterine tamponade balloon
Antibiotics	Uterine compression sutures
Tranexamic acid	Hysterectomy
Vasopressin	Pelvic arterial ligation
Clotting factor concentrates	
Chemotherapy	*Radiological*
Oral contraceptive pill	Selective arterial embolization

should include resuscitation as discussed above, the use of uterotonic agents, administration of antibiotics and consideration of surgical evacuation of the uterus.

Uterotonic agents

Syntocinon can be administered as an intravenous or intramuscular bolus (10 units) or in combination with ergometrine (Syntometrine®)

1 ampoule as an intramuscular injection. This can be followed by a syntocinon infusion (40 units in 500 ml normal saline at an infusion rate of 125 ml/h). Prostaglandin $F_{2\alpha}$ (Haemabate®/ Carboprost) can be given by intramuscular injection at a dose of 250 μg every 15 min, up to a total of 2 mg (i.e. 8 doses). Misoprostol can also be given as an alternative prostaglandin (400–800 μg orally or rectally).

Antibiotics

Endometritis is likely to play a significant role in many cases of secondary postpartum hemorrhage and the majority of women are prescribed antibiotics. In a 3-year study of almost 20 000 women, 132 women (0.69%) had a secondary postpartum hemorrhage and 97% of these were treated with antibiotics[2]. However, only three-quarters of these women had microbiological specimens collected and a positive culture was obtained in only 13.5%. In a similar observational study of 83 women with secondary postpartum hemorrhage, 45% presented with pyrexia, and 64 had bacteriological swabs taken, of which only 12.5% were positive. Organisms identified included group B streptococcus, bacteroides, E. coli, Clostridium perfringens and Lancefield group D streptococcus. Despite the lack of evidence to support the presence of a specific bacterial pathogen, 92% of the women received antibiotics[3]. Recommended choices of antibiotic treatment include amoxycillin with clavulanic acid (Augmentin®)[27] and a combination of amoxycillin, metronidazole and gentamicin[3]. Endometritis is a major contributor to subinvolution of the uterus. Although infection may not be confirmed in a large population of cases, we recommend that antibiotics are always given for secondary postpartum hemorrhage (see Chapter 44).

Uterine evacuation

Examination under anesthetic and surgical evacuation of the uterus should be considered if retained placental tissue is suspected clinically or after ultrasound examination. This has good reported success rates, with bleeding stopping promptly in all 72 women undergoing evacuation of the uterus for secondary postpartum hemorrhage in one study, despite only 36% having proven histological evidence of retained tissue[3]. This study was unable to find any clear association with presence or absence of retained tissue at the time of evacuation and day of onset of bleeding or morbidity at the time of secondary postpartum hemorrhage. However, retained tissue was more likely if membranes were incomplete at delivery, primary postpartum hemorrhage had occurred or if secondary postpartum hemorrhage was judged to be heavy or moderate (compared with light) in volume[3]. The use of ultrasound prior to surgical evacuation of the uterus does not appear to significantly alter the chances of histological diagnosis confirming retained tissue. In one study, 33% of those with no preoperative scan had retained placental tissue compared to 37% following a scan[2].

Retained placental tissue is likely to be associated with infection and, therefore, broad-spectrum intravenous antibiotics should be given in conjunction with surgical evacuation. As serum concentrations of most antibiotics peak 1 h after intravenous administration, these should be administered just prior to surgery[20]; however, in women who are hemodynamically stable, it may be appropriate to give 12–24 h of antibiotic cover prior to consideration of surgery[1]. At the time of surgery, uterotonic agents such as syntocinon, ergometrine and prostaglandins may be given to aid uterine contractility and control hemorrhage.

There is no clear evidence to support which method of evacuation should be used. Manual removal of tissue, use of a suction catheter and sharp curettage with a metal curette have all been described[2]. The risk of uterine perforation is much higher in uterine evacuation postpartum and may be even further increased if associated with endometritis. Hoveyda and colleagues describe uterine perforation in three of 85 women undergoing the procedure for secondary postpartum hemorrhage. These were performed from 4 days to 28 days after delivery with both a suction and metal curette. In all cases, the procedures were performed by senior medical staff. One woman went on to require a hysterectomy, but the other two were managed conservatively[2]. Perforation after Cesarean section is more likely and, as these women have a lower risk of retained placental tissue, surgical

evacuation in these cases should be very carefully considered.

Additional complications include the risk of Asherman's syndrome. There is limited evidence to ascertain if this risk is increased for postpartum uterine evacuation; however, in a large study of intrauterine adhesions, 21.5% of cases had a postpartum curettage as a preceding event[28]. The need for a second procedure due to incomplete evacuation of retained tissue may also occur[2]. Hysterectomy may be required to control bleeding in up to 5% of cases[20].

In view of these significant complications, women should always be fully counselled of the risks and informed consent obtained prior to the procedure. Surgery should be performed by experienced senior medical staff.

Other surgical procedures

In the event of a large secondary postpartum hemorrhage, other surgical procedures may need to be considered. This includes cases of bleeding from an infected placental bed or placental abnormality such as placenta accreta, bleeding from retained placental tissue not controlled with uterine evacuation, non-union/dehiscence of Cesarean section scar, bleeding from a surgical injury or uncontrolled bleeding from a lower genital tract laceration.

Insertion of an intrauterine tamponade balloon, such as the Bakri[29] or Rüsch balloon[30], has been successfully described for treatment of primary postpartum hemorrhage and may be considered in cases of secondary postpartum hemorrhage due to uterine subinvolution/atony once retained placental tissue has been excluded (see Chapters 28 and 29). Laparotomy may also be required which allows further investigation into the cause of bleeding and treatment by the use of surgical compression sutures, hysterectomy and pelvic arterial ligation as appropriate.

The B-Lynch brace suture is well described for the treatment of primary postpartum hemorrhage[31] and has now been reported in 72 cases of secondary postpartum hemorrhage (B-Lynch C, personal communication, August 2005). The use of a surgical compression suture may avoid the need for hysterectomy in women wishing to conserve fertility.

Within an Australian population with an overall incidence of secondary postpartum hemorrhage of 1.44% over 15 years, only nine cases required hysterectomy (0.9%)[3]. However, in a subgroup of women with massive intractable obstetric hemorrhage, two out of seven with secondary postpartum hemorrhage required hysterectomy. In one of these cases, hysterectomy was performed 7 days after delivery due to intractable bleeding from lower genital tract laceration but maternal death still resulted. The second case had further morbidity following her hysterectomy for secondary postpartum hemorrhage with bleeding from wound disunion and sepsis and required bilateral hypogastric artery ligation 14 days after delivery[5]. Hysterectomy in such situations carries significant risks but can be life-saving and should be considered early in cases of massive hemorrhage, whether primary or secondary.

Pelvic artery ligation may also be considered for cases of massive secondary postpartum hemorrhage uncontrolled by medical and simple surgical measures. Lédée and colleagues report the use of bilateral hypogastric artery ligation in 49 of 61 cases of intractable hemorrhage; this includes four out of seven cases of secondary postpartum hemorrhage, all of which were successful at arresting bleeding[5] (see Chapter 32). As with primary postpartum hemorrhage, arterial ligation should be performed by an experienced surgeon and his/her involvement should be considered whilst planning a laparotomy in such cases.

Selective arterial embolization

Pelvic angiography to assess the internal iliac artery, uterine artery and its vaginal branches is a helpful tool in the assessment of ongoing hemorrhage (Figure 1). It also allows the introduction of embolization agents to arrest bleeding (see Chapter 30).

Pelage and colleagues studied 14 women presenting with uncontrollable secondary postpartum hemorrhage at a mean of 16 days after delivery. Six women (43%) had delivered by Cesarean section and the remainder by spontaneous vaginal delivery. Eight women had evidence of endometritis (57%), with four of those associated with histologically proven retained
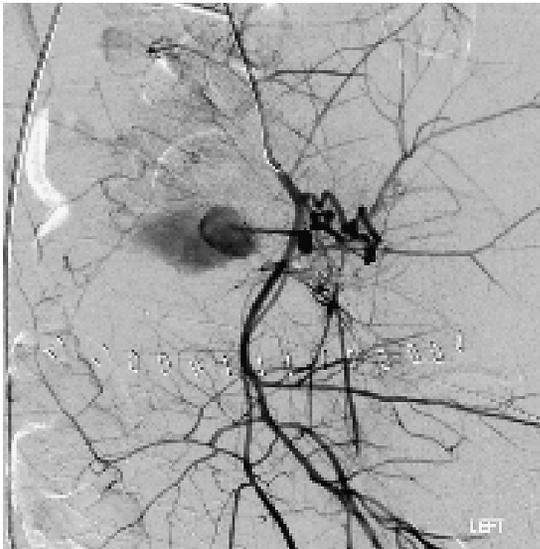
Figure 1 Angiogram demonstrating brisk hemorrhage from false aneurysm prior to embolization

Figure 2 Angiogram after embolization

placental tissue; a further four women had genital tract lacerations, and the remaining two had no obvious cause for bleeding. Basic resuscitation with use of medical treatments and/or uterine curettage were performed. Angiography found no extravasation in eight women, active bleeding in three women from uterine and vaginal vessels, a false uterine artery aneurysm in two women, and evidence of an arteriovenous fistula in one woman. Pledgets of absorbable gelatin sponge were introduced to embolize both uterine arteries in 12 women. Unilateral embolization of a false aneurysm and an arteriovenous fistula were performed for the other two women. External bleeding disappeared immediately, and hemodynamic stability and correction of coagulopathy were obtained for all cases. There were no general or local complications[10].

One of the authors (T.J.) recently managed a case of massive secondary postpartum hemorrhage presenting 4 days after a Cesarean section. An emergency subtotal hysterectomy was performed with good initial results. Two hours later, vaginal bleeding restarted. There was no evidence of significant coagulopathy. Pelvic angiography was performed and a bleed from a false aneurysm related to a middle branch of the

anterior division of the left internal iliac artery was identified (Figure 1). The vessels were embolized with four coils. There was immediate cessation of bleeding and the patient's vital signs normalized (Figure 2). The patient made a good recovery despite needing 24 units of blood during the postpartum hemorrhage. Subsequent histology of the uterus showed acute inflammation and subinvolution of the placental bed.

Other measures

In cases of massive hemorrhage unsuccessfully treated with surgical measures, the use of intravenous tranexamic acid[32], recombinant factor VIIa[33] and local vasopressin[34] have been reported for primary postpartum hemorrhage. There are no reports of their use in secondary postpartum hemorrhage but, if available, it may be appropriate to consider their use in combination with other therapies and resuscitative support.

Chemotherapy

The mainstay of treatment for choriocarcinoma is chemotherapy. A low-risk chemotherapy regimen includes the use of methotrexate with folinic acid rescue on a 2-weekly cycle[35].

Medium- and high-risk regimens include the use of etopside, methotrexate, actinomycin, vincristine, cyclophosphomide and 6-mercapto-purine[36,37]. Women with choriocarcinoma are most appropriately treated through specialist trophoblastic disease referral centers[14].

Coagulopathies

Women with inherited coagulation disorders such as von Willebrand's disease and carriers of hemophilia A and B are likely to bleed postpartum if maternal clotting factors are low (< 50 IU/dl). Prophylactic administration of desmopressin (DDAVP) and clotting factor concentrates may prevent postpartum hemorrhage[15]. The aim is to raise factor levels above 50 IU/dl during labor and delivery and maintain these for up to 5 days after delivery. In the event of postpartum hemorrhage[15], replacement of deficient clotting factors should be made and identification and treatment of the cause be instigated. Management should be in close liaison with hematologists and specialist hemophilia centers as available. In cases of prolonged or intermittent secondary postpartum hemorrhage[15], the use of tranexamic acid (a fibrinolytic inhibitor)[38] or combined oral contraceptive pill has been reported[15].

Hemorrhage from postpartum acquired hemophilia is treated acutely with factor VIII (either human, porcine) or recombinant factor VIIa[15]. Immunosuppressive drugs such as corticosteroids, cyclophosphamide and azathioprine may be used to accelerate the disappearance of factor VIII inhibitors, although complete remission is likely to occur spontaneously with time.

Reversal of bleeding due to anticoagulants should follow normal protocols. Vitamin K should be considered in women with uncontrolled bleeding secondary to warfarin use and protamine sulfate may be considered if hemorrhage results from the use of heparin, although this has a much shorter half-life.

Secondary postpartum hemorrhage is an important cause of maternal morbidity and mortality. Basic resuscitation followed by investigation and treatment of the specific cause of hemorrhage are essential. The diverse nature of its etiology and often acute presentation make research in the form of a randomized controlled trial difficult. However, particularly for the treatment of hemorrhage due to uterine infection and/or retained placental tissue, this should be achievable and would provide valuable information to further our understanding of the management of secondary postpartum hemorrhage.

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