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Subinvolution of the placental site as the cause of hysterectomy in young woman

Olga Triantafyllidou,[1] Stavroula Kastora ,[2,3] Irini Messini,[4] Dimitrios Kalampokis[5]

[1]Reproductive Medicine Unit, Maternity Hospital Lito, Athens, Greece
[2]Department of Medicine, University of Aberdeen College of Life Sciences and Medicine, Aberdeen, UK
[3]Department of General Surgery, Aberdeen Royal Infirmary, Aberdeen, UK
[4]Department of Pathology, Maternity Hospital Lito, Athens, Greece
[5]Department of Obstetrics, Maternity Hospital Lito, Athens, Greece

Correspondence to
Dr Stavroula Kastora;
stavroula.kastora@abdn.ac.uk

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SUMMARY

Subinvolution of placental sites (SPSs) is a rare but severe cause of secondary postpartum haemorrhage (PPH). SPS is characterised by the abnormal persistence of large, dilated, superficially modified spiral arteries in the absence of retained products of conception. It is an important cause of morbidity and mortality of young women. In this study, we present a case of secondary PPH in a young woman after uncomplicated caesarean delivery who was deemed clinically unstable, and finally, underwent emergent total abdominal hysterectomy. We reviewed the literature with an emphasis on the pathophysiology of this situation. Treatment of patients with SPS includes conservative medical therapy, hysterectomy and fertility-sparing percutaneous embolotherapy.

BACKGROUND

Postpartum haemorrhage (PPH) is a major problem worldwide and it still represents a leading cause of maternal deaths.[1] The incidence of PPH is approximately 5%–20% of all deliveries, with the great percentage to be attributed to the developing countries.[1 2] It is commonly divided into two groups: primary and secondary PPH. Primary postpartum bleeding occurs within the first 24 hours after delivery, whereas secondary PPH occurs between 24 hours and 6 weeks post partum and it is not particularly associated with the way of delivery (vaginal or caesarean section). The causes of primary PPH include uterine atony, retained placenta, congenital of acquired disorders of coagulation and trauma. The most common cause of primary PPH worldwide is still uterine atony. Secondary PPH accounts only for 1% of all labours and its aetiology includes severe endometritis, retained products of conception, gestational trophoblastic disease, uterine artery pseudoaneurysm and subinvolution of the placental site (SPS).

SPS is defined as delayed or inadequate physiological closure and sloughing of the superficial modified spiral arteries at the placental site (failed process of normal involution).[3] It was reported in 1910 for the first time in the literature by Küster, and only in 1945 Rutherford and Hertig described clinical and pathological findings of 'Non-involution of the Placental Bed'.[4 5] It is difficult to estimate the precise frequency of SPS in all secondary PPH because the histopathological examination of aspiration products after uterine surgical evacuation is essential to the diagnosis. The clinical management of SPS demands immediate action with little time, due to severity of haemorrhage. In this report, we present an additional case of severe SPS in young woman, who underwent hysterectomy, as well as the review of the literature.

CASE PRESENTATION

A 34-year-old nulliparous primigravida Caucasian woman with a normal single pregnancy after ovarian stimulation and In Vitro Fertilisation (IVF) treatment due to poor ovarian reserve was admitted at 38+3 weeks of pregnancy with signs of labour. In spite of good uterine contractions, the cervical dilatation after 7 hours was only 2 cm and caesarean section was performed as a result of the failure to progress in first stage. The postpartum period was uneventful and patient was discharged with recommendations on fourth postoperative day.

INVESTIGATIONS

Three weeks later, she was admitted with severe vaginal bleeding. Transvaginal ultrasound (US) examination revealed possible organised blood clots inside the uterus. There was not echogenic material suspicious for retained placenta within the endometrial cavity using the gray-scale US findings and colour Doppler US imaging was negative for the presence of internal vascular flow. Moreover, the patient did not have any sings or symptoms of inflammation (endometritis), fever, rigours, pelvic or abdominal pain. Complete blood count was normal [haemoglobin (Hb): 12.1 g/dL and platelets: 325×10^9/L, white cell count 8.500 $\times 10^9$/L, CRP 0.7 mg/L)]. Serum β-subunit of hCG gonadotropin (β-hCG) was negative and there were no signs of coagulopathy (prothrombin time, activated partial thromboplastin time, International Normalised Ratio (INR) and plasma fibrinogen levels were within normal levels. The patient was resuscitated with warm fluids and blood was sent for cross match (four units of red blood cells and four units of fresh frozen plasma). Uterine curettage was performed and 150 mL of curetted material was negative for retained placental products. Despite curettage of the endometrium, rectal misoprostol and intravenous administration of ergometrine maleate (Mitrotan, GAP), the bleeding did not cease and intrauterine tamponade was performed. Twelve hours after curettage, the patient was not stabilised, fainted and kept bleeding with gradual decline of Hb. She was tachycardic with a blood pressure of 100/65 mm Hg and her haemoglobin reached 6 g/dL. In combination with close monitoring of haemodynamics and urine output, patient's coagulation profile was repeatedly measured (prothrombin time/activated

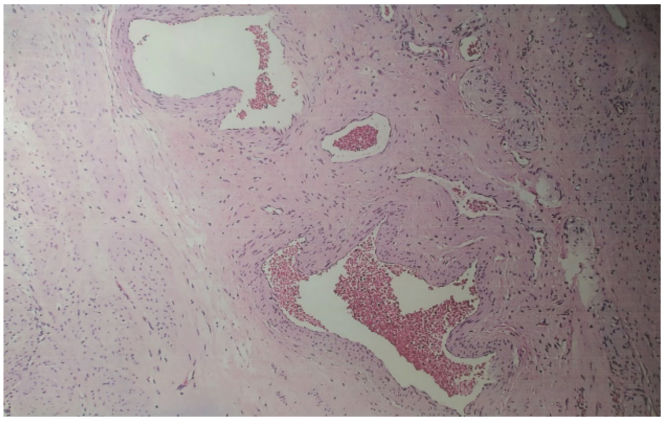

Figure 1 Subinvolution of uteroplacental arteries. Dilated, clustered, myometrial arteries with partial obliteration by thrombi (haematoxylin-eosin staining, magnification: ×400.

partial thromboplastin time increased until 12.6 s /41.4 s, respectively, and fibrinogen level was 1.7 g/L).

TREATMENT

The patient was given four units of packed red blood cells and four units of fresh frozen plasma, however abdominal US re-examination revealed an enlarged uterus with the accumulation of blood around the intrauterine tampon. Pelvic CT and MRI imaging with contrast did not reveal a pathological cause of bleeding. Given that the patient was deemed clinically unstable, an emergency total abdominal hysterectomy was performed without further imaging such as angiography. Histopathological examination of uterus identified large thrombus in the endometrial cavity and the typical findings of subinvoluted placental bed vessels. Microscopic sections of myometrium revealed large, dilated superficial myometrial blood vessels with thickened walls at the placental implantation site indicative of SPS (figure 1). There was no evidence of retained products of conception or inflammation of the decidua neither in the curettage material nor in the removed uterus. The diagnosis of SPS was made.

OUTCOME AND FOLLOW-UP

The neonate was delivered safely without complications and was admitted in the neonate ward for a day of observations given the maternal complications. Ovaries were spared during the total abdominal hysterectomy in view of preserving maternal ovarian fertility with the further possibility of surrogacy.

DISCUSSION

PPH is a serious obstetric problem, one of the leading causes of maternal mortality and morbidity. Secondary PPH is less frequently addressed, partly, due to the majority of patients who are treated medically on an outpatient basis, without hospitalisation. SPS is an important cause of secondary PPH and it should be considered in patient with severe PPH, due to its association with life-threatening haemorrhage. SPS is diagnosed by excluding other causes of persistent secondary postpartum haemorrhagic vaginal discharge. These include endometritis, retained products of placenta, gestational trophoblastic disease and coagulopathy. The diagnosis of SPS can be confirmed only histologically as it happened in our case. Excluding all above-mentioned diagnosis by clinical, US examination, laboratory tests and histology of curetted products, the diagnosis of PPH remained unknown until the final histopathological examination of uterus. However, Petrovitch *et al*[6] in their study mentioned that the suspicion of this situation may done through the sonographic characteristics of the pathological vessels. Placental site subinvolution may be suspected in US examination in the infrequent case where hypoechoic tortuous vessels are visible along the inner third of the myometrium.[6] Pulsed wave doppler US then might indicate increased peak systolic velocity (PSV; >0.83 m/s; normal 0.22 m/s 3 days post partum, falling to 0.10 m/s after 6 weeks). The increased vascularity areas may correlate with the placental implantation site documented by predelivery. However, these findings are not always pathognomonical and may overlap with congenital or acquired arteriovenous malformations or retained products of conception.

Large uteroplacental arteries that were modified for pregnancy by the extravillous trophoblasts remain patent past the immediate postpartum period, failing to undergo the normal process of involution. The incidence of PPH from subinvolution is most common in the second week post partum.[7] The precise incidence of severe secondary PPH was estimated by Dossou *et al*.,[8] who described the distribution of the different causes of severe secondary PPH after 26 023 deliveries. The incidence of severe secondary PPH was very low, only 0.23% (n: 60/26 023). Subinvolution of the placental bed was noted in 13.3% of the patients, while the placental retention was the most common cause of haemorrhages (30.0%). In contrast with clinical doctors, veterinaries are more familial with this condition, as SPS is the major cause of vaginal discharge in canines, occurring in 10%–20% of postpartum bitches from 6 weeks post partum onwards.[9]

In terms of pathophysiology, normal physiological changes in spiral arteries happened during the pregnancy. From early gestation (6–9 weeks), extravillous cytotrophoblasts invade the decidual part of the maternal spiral arteries, replacing the endothelium and it is completed in second trimester when the endothelial lining of the artery is completely replaced. This process causes vascular remodelling with destruction of the musculoelastic medial tissues of the arteries which are replaced by fibrinoid material.[10] These changes play an important role during pregnancy providing an adequate uteroplacental arterial flow. It is well known that altered remodelling of the spiral arteries cause preeclampsia. From this point of view, the SPS vessels can represent the opposite end of a spectrum of abnormal interactions found in preeclampsia.[11]

In the third trimester, physiologic mechanism of involution of altered uteroplacental vessels begins, as the endovascular cytotrophoblast is replaced by maternal-derived endothelial cells.[7] Uteroplacental arteries undergo thrombosis and shrinkage of the placental site. Contraction of the uterine smooth muscle also contributes to mechanical shrinkage and involution of these vessels and the uterus revert to the nonpregnant state.[12] In subinvolution of the placental implantation site, the normal remodelling of the uteroplacental arteries during the third trimester is either delayed or inadequate, resulting in the persistence of low-resistance dilated vessels with increased flow.[3] In SPS, the uterus is grossly enlarged. Histologically, subinvoluted placental bed vessels in the superficial myometrium are large, patent and dilated, with intravascular thrombosis (figure 1). Their walls in microscopic section are distorted and thickened due to deposition of hyaline with partial absence of the endothelial lining.[3 13]

The exact pathogenesis of SPS is still unknown. There are some factors that may play a role in this process. Sasagawa *et al*,[14] was the first who suggest that immunological patterns are essential for the mechanism of normal involution of uteroplacental arteries, but this study did not explain the exact pathophysiology of subinvolution of these arteries. Later, Andrew *et al*[15] found

the absence of deposition of immunoglobulins (IgG, IgA, IgM) and complement proteins (C1q, C3d, C4) in the walls of subinvoluted vessels. Another theory of pathophysiology of subinvolution consist of the increased expression of bcl-2 oncoprotein, which is associated with inhibition of apoptosis and prolonged cell survival in subinvoluted placental bed vessels.[16] Bcl-2 oncoprotein is normally not detected in the uteroplacental arteries during the third trimester of pregnancy, however, can be identified in involution and, more strongly, in subinvolution of the placental bed vessels. The review of the literature also revealed the involvement of some nuclear factors identified in controlling human trophoblast invasion, such as Signal Transducer and Activator of Transcription factors (STATs), Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ), homeobox genes or Wingless and Int-1 (WNT)-dependent transcription factors.[17] These factors may contribute to the pathogenesis of pregnancy diseases with abnormal placentation or failed trophoblast differentiation. Epithelial markers such as Troma 1 and CAM 5.2 almost always highlight the trophoblasts while placental alkaline phosphatase, human placental lactogen and epithelial membrane antigen are not pathognomonical.[18]

SPS is an important and clinically elusive, diagnosis, as this mechanism responsible for an idiopathic and not iatrogenic cause of postpartum uterine bleeding.[18] Farley and Kohlmeier[19] described the death of a 19-year-old woman in USA due to SPS. Eight days after delivery, her husband brought her to the emergency room pulseless and without respirations. The diagnosis of SPS usually is under-recognised and made by excluding other causes of persistent secondary PPH. The sonographic features of subinvolution of the placental site, through visualising the low-resistance vessels present along the inner third of the myometrium can assist in the diagnosis of SPS.[6] Pulsed wave Doppler sonography may confirm an increased PSV with a low-resistance waveform which, given that high flow sonographic findings are commonly a result of true arteriovenous vascular malformations (AVMs), that may be acquired (eg, iatrogenic trauma leading to scar tissue and AVM formation) or congenital (eg, developmental vascular defects leading to a bed of abnormal arterio-venous communications).[20–25] While SPS diagnosis is only solidified via histological analysis, a high degree of suspicion from the clinical history such as abnormal uterine bleeding or recurrent loss of pregnancy may prompt the clinician to request imaging. Contrast-enhanced MRI scans could confirm the marked vascular dilatation of the uterine wall, helping us to suspect SPS before the hysterectomy.[23 24] Angiography is considered the gold standard in AVM and possibly SPS diagnosis. SPS symptomatology may increase under hormonal changes such as menstruation or pregnancy, which may raise further suspicion.[25]

The management of subinvolution of the placental site with bleeding in symptomatic patients remains controversial. It is an emergent situation and full work-up should be performed to exclude any other possible cause of secondary PPH, as well as an immediate stabilisation of the patient before the development of disseminated intravascular coagulopathy. In most cases, curettage is performed to exclude retained placental products even if US examination fails to reveal visible abnormality. Conservative approach with uterine tamponade using gauze or various balloons (Bakri) and uterotonic treatment is acceptable. However, surgical treatments such as ligation of the uterine vessels and hysterectomy are considered as standard therapies.[26 27] According to the literature, percutaneous embolisation of the uterine artery is considered as an alternative therapy of SPS before hysterectomy.[4 26–28] This procedure provides fertility preservation, but requires special equipment and ready team of medical experts. Therefore, even these days, unfortunately, not in all hospitals arterial embolization can be performed.

In conclusion, SPS is one of the rare but important cause of secondary PPH and as other AVMs, it may coexist with other causes of PPH such as retained Products Of Conception (POC).[29] This condition is likely under recognised by gynaecologist due to the absence of specific diagnostic criteria, as in our case. Only excluding other forms of delayed PPH and after failed curettage and conservative therapy, the diagnosis of SPS should be included in the differential diagnosis. MRI scan with contrast can indicate the focal areas of uterine hypervascularity. However, the histological confirmation of dilated, clustered, myometrial arteries, partially occluded by thrombi is done only after the urgent hysterectomy.

Learning points

- The incidence of postpartum haemorrhage from subinvolution is most common in the second week post partum. Subinvolution of the placental bed was noted in 13.3% of 26.023 patients, while the placental retention was the most common cause of haemorrhages (30.0%).
- The exact molecular mechanism of the pathogenesis of subinvolution of placental site is still unknown but theories include increased local expression of bcl-2 oncoprotein, absence of deposition of immunoglobulins and complement proteins in the walls of subinvoluted vessels, STATs, PPAR-γ, homeobox genes and WNT-dependent transcription factor deregulation.
- Unfortunately, subinvolution still remains a histological diagnosis and no imaging or other markers are available to identify patients' prior major complications arise.

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ORCID iD

Stavroula Kastora http://orcid.org/0000-0003-4470-5267

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