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Decidual Bleeding as a Cause of Spontaneous Hemoperitoneum in Pregnancy and Risk of Preterm Birth

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Abstract
Background: Spontaneous hemoperitoneum in pregnancy (SHiP) is a rare, life-threatening event, particularly relevant to women with endometriosis or deciduosis. ***Methods:*** To determine the type of lesions leading to SHiP, a literature search was conducted among all published SHiP cases. From a total of 1,339 publications, information on pathological findings at the bleeding site with histological data was found in 24 case reports (16 pregnant, 8 postpartum). ***Results:*** Among pregnant women (81% primigravida), 75% had a diagnosis of endometriosis and 25% of deciduosis. Among postpartum women (38% primiparous), 63% had a diagnosis of deciduosis and 25% of endometriosis. In all cases except one, decidual cells, with or without glandular structures, were present at the bleeding site. Decidual vessels were described in 7 cases and all exhibited vascular changes, including distension of the lumen, medial disorganization, or loss of vascular integrity. These vessels were significantly different from arteries seen in the secretory endometrium, showing that structural modifications take place during the initial stage of the remodelling of placental bed spiral arteries. ***Conclusions:*** During pregnancy, a link seems to exist between ectopic decidualization, particularly that occurring in endometriotic foci, and occurrence of SHiP. In addition, subclinical decidual bleeding may be a potential risk factor for preterm labour.

Introduction

Recent reports focused attention on the rare, yet life-threatening occurrence of spontaneous hemoperitoneum in pregnancy (SHiP). This may be particularly relevant to women with endometriosis or deciduosis if they are undergoing in vitro fertilization (IVF) treatment. This dramatic complication has been associated with high perinatal morbidity and even mortality, but the trigger of the spontaneous bleeding has not been established [1, 2]. Although the aetiology of SHiP remains unknown and may be multifactorial, several theories have been proposed to explain the rare complication (Table 1). The early reports describing

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Table 1. Hypotheses formulated in the literature on the cause of spontaneous hemoperitoneum in pregnancy

– Sudden increases in venous pressures associated with muscular activity, defecation, coughing, lifting, or coitus [3]
– Tortuous path of the uterine and ovarian veins, their lack of valves and their distension with elevated intraluminal pressure, although the presence of some additional vascular defect was postulated [4]
– Chronic inflammation due to endometriosis making the utero-ovarian vessels more friable, or the resultant adhesions creating further tension to these vessels as the uterus expands during pregnancy [5, 6]
– Hemodynamic factors, as well as increased hormonal effects caused by pregnancy leading to structural vessel changes able to impair the arterial wall [7]
– Necrosis and shedding of the decidualized endometriotic lesions during the third trimester of pregnancy or following delivery [8]
– Erosion of the uterine artery or its branches by endometriosis [9]
– Possible relation between the site of placental implantation and rupture of uterine vessels [10]
– Potential 2-step process of uterine artery rupture starting with circumscribed hematoma of the broad ligament causing compression of adjacent anatomic structures (ureter, bowel), followed by rupture into the abdominal cavity [11]
– Progesterone resistance in endometriosis could trigger involution of the ectopic decidua surrounding uterine vessels, leading to peritoneal bleeding of unpredictable severity [12]

this complication suggested venous rupture due to a sudden increase in venous pressure associated with muscular activity, defecation, coughing, lifting or coitus [3]. Increased pelvic congestion and blood flow, the tortuous path of the uterine and ovarian veins, their lack of valves and their distension with elevated intraluminal pressure may provide vascular conditions for the dramatic event [4].

For a better understanding of the pathogenesis of SHiP and in the absence of systematic studies of vascular changes occurring at the site of bleeding, we reviewed all case reports in search of information on pathological events at the site of bleeding.

Material and Methods

Search Strategy and Analysis

A Scopus search, undertaken on July 13, 2015, using the term "spontaneous hemoperitoneum in pregnancy," produced a total of 480 publications, starting with the publication by Hodgkinson and Christensen [3] in 1950. The search was extended by probing further into the list of references for additional case reports.

We also undertook a PubMed search using the terms "hemoperitoneum and pregnancy" on February 1, 2016. This yielded 859 articles. We excluded cases related to uterine ruptures, ectopic pregnancies, ruptured cysts and other recognized causes of intra-abdominal bleeding. After reading the abstracts and, if relevant, the full papers, original cases were identified that included a description of the histopathology taken from the bleeding site. This search was limited to articles published in English. Although the purpose of this review is to examine the occurrence of hemoperitoneum during pregnancy, reports of SHiP during the postpartum period (up to 6 weeks after delivery) have been included as well.

Finally, we searched for relevant articles on "deciduosis," defined by the presence of foci of decidualized mesenchymal cells, but the absence of glandular cells, in the sub-peritoneum of pelvic or abdominal structures during pregnancy [13].

Results

The search identified 91 cases of SHiP published between 1950 and 2016. Of these, 24 case reports included a histological description from a biopsy obtained from the bleeding site. In one postpartum case, the site of bleeding was not identified. The series includes 16 cases during pregnancy and 8 cases of SHiP on the day of delivery, or during the postpartum period.

Vascular Pathology at the Site of Bleeding

Histopathology findings of available biopsies are summarized in Table 2. All case reports, except the one obtained in the postpartum period, indicate the presence of decidual cells with or without glandular structures, at the site of bleeding. Seven case reports included a description of blood vessels present in the biopsy.

Three of the 16 biopsies obtained during pregnancy included information about blood vessels at the bleeding site(s). Aziz et al. [24] described a focus of endometriosis and decidualization in a woman who was 30 weeks into her first pregnancy and demonstrated the presence of very thin-walled blood vessels in the decidualized stroma. Mizumoto et al. [6] documented the presence of ruptured vessels on the serosal surface of the uterine fundus at

Table 2. Histopathology of biopsies from the bleeding site in cases of spontaneous hemoperitoneum during pregnancy

Author	Site of biopsy	Histopathology
Pregnancy		
Lier et al. [14], 2017 (case II)	Near left ovary, bowel	Endometriotic tissue, decidual changes
Lier et al. [14], 2017 (case IX)	Bladder peritoneum	Endometriotic tissue, decidual changes
Lier et al. [14], 2017 (case XI)	Bladder peritoneum, pouch of Douglas, bowel	Endometriotic tissue, decidual changes
Loh et al. [15], 2015	Left fallopian tube	Endometriosis
Cozzolino et al. [16], 2015	Right adnexa	Endometriotic tissue, decidual changes
Aggarwal et al. [17], 2014	Left fallopian tube	Hemorrhagic foci of endometriosis, decidual changes, atrophic dilated glands
De Vincenzo et al. [12], 2013	Bowel, lymph nodes	Endometriotic tissue, decidual changes
Kondoh et al. [18], 2012	Uterine surface/peritoneum, omentum	Deciduosis
Reif et al. [19], 2011	Left ovary (partial), left fallopian tube, adhesions	Decidualized endometriosis
Brouckaert et al. [20], 2010	Right adnexa, parametrium	Endometriotic tissue, decidual changes
Bouet et al. [21], 2009	Left broad ligament, left adnexa/parametrium	Decidualized endometriosis
Grunewald and Jördens [22], 2009	Right sacro-uterine ligament	Endometriosis
Katorza et al. [23], 2007 (case II)	Right adnexa	Endometriotic tissue, decidual changes
Aziz et al. [24], 2004	Left broad ligament/parametrium	Endometriotic tissue, decidual changes, thin-walled vessels
Mizumoto et al. [6], 1996	Uterine surface	Endometriotic tissue, decidual changes, distended vessel with disintegrated wall
Doyle and Philips [25], 1957	Peritoneal lesion right lateral pelvic wall/pouch of Douglas	Decidual and vascular changes
Intrapartum and postpartum		
Lier et al. [14], 2017 (case IV)	Left uterovesical ligament	Haemorrhagic foci of endometriosis, decidual changes, distended and angiomatous tissue
Zhang and Lou [26], 2015	Right ovary (cyst)	Endometriosis, decidualization
Boztosun et al. [27], 2012	Left ovary	Ectopic decidualization
Gao et al. [28], 2010	Pelvic adhesions	Endometriosis, decidual changes
O'Leary [29], 2005	Adnexa (bilateral)	Decidualization, vascular intrusion
Richter et al. [30], 1983	Uterine surface, adnexa (bilateral), parametrium	Decidual tissue
Sabatelle and Winger [31], 1973	Uterine surface	Decidual changes, distended ruptured vessels
Hulme-Moir and Ross [32], 1969	Omentum	Decidual tissue, vascular changes

20 weeks in a woman during her first pregnancy. Histology demonstrated an intense decidual reaction. The blood vessels were distended and exhibited disintegration of the vessel wall. Doyle and Philip [25] reported the autopsy finding of a very large quantity of blood and blood clots distending the peritoneal cavity of a 37-year-old woman who had SHiP with her first pregnancy. They identified a 2.5 × 2 cm oval-shaped peritoneal lesion with raised edges on the right side of the pouch of Douglas. Microscopically, this exhibited haemorrhagic decidual

tissue without chorionic villi. The blood vessels were distended and had a highly disorganized wall. This area with very vascular decidual reaction was presumed to be the source of the fatal haemorrhage.

Four of the 8 case reports with biopsies obtained postpartum included description of vasculature. Lier et al. [14] described a case of late postpartum SHiP in a patient with ovarian endometriosis. Histologically, there was a vascular lesion with multiple distended vessels and haemorrhagic deposits. O'Leary [29] published one case of massive postpartum SHiP in which, following supracervical hysterectomy, it was possible to identify the origin of brisk bleeding as a tumour-like mass. Bleeding was controlled by clamping and ligation of the left uterine artery at its origin from the hypogastric artery. Bilateral salpingo-oophorectomy was performed because of a presumptive diagnosis of a malignant lesion with multiple tumour-like masses located on both ovaries and on the left pelvic sidewall. Histopathology confirmed bilateral ovarian endometriosis with extensive decidualization but no malignant degeneration. A section of the hypogastric artery was examined: this exhibited decidualized stroma protruding into the large distended arterial lumen. Sabatelle and Winger [31] reported a case of severe intrapartum SHiP arising from a focus of ectopic deciduosis. The serosal surface over the posterior lower uterine segment was roughened and exhibited marked decidual reaction with large blood-filled sinuses communicating with the surface. Multiple sections through the uterine wall revealed no evidence of laceration or haemorrhage within the myometrium. Hulme-Moir and Ross [32] reported a case of postpartum SHiP presenting with abdominal pain 1 week after delivery. The woman had haemorrhagic appendices epiploicae in the transverse colon. Omental biopsy showed multiple small, well-defined foci of decidual cells in the fat immediately below the serosa. The small vessels were dilated and there was interstitial haemorrhage and early necrosis of some of the decidual cells. There were no glandular structures suggestive of endometriosis.

Clinical Features of SHiP

As mentioned, the search identified 16 women with SHiP during pregnancy and 8 women with SHiP on the day of delivery, or during the postpartum period (Table 3), from whom histological reports were available. Age in the first group ranged between 25 and 38 years and in the second group between 25 and 41 years.

Among women with SHiP during pregnancy, 13 (81%) were primigravida, whereas in the second group, 3 (38%) had delivered for the first time. In the pregnant group, all had the diagnosis of endometriosis (75%) or deciduosis (25%), while in the intrapartum or postpartum group, 5 (63%) had the diagnosis of deciduosis and 2 (25%) of endometriosis. No information was available on the eighth case.

SHiP occurred in the pregnancy group between weeks 17 and 33 with a median of week 26 and was associated with a stillbirth or neonatal death rate of 56%.

Discussion

Endometriosis and Deciduosis Are Associated with Decidual Bleeding

Histopathology of the 24 biopsies obtained from the bleeding site in women with SHiP documented in all cases the presence of decidualized stromal cells. Decidual vessels were described in 7 cases and invariably these exhibited vascular changes, including distension of the lumen, medial disorganization, or loss of vascular integrity. Craven et al. [33] documented that decidual arteries were significantly different from arteries seen in the secretory endometrium, leading to the conclusion that structural modifications take place during the initial stage of physiological remodelling of the placental bed spiral arteries, before the vessel is affected by intravascular and interstitial trophoblast invasion. The early arterial changes are characterized by more endothelial basophilia, vacuolization, loss of elasticity and dilatation. In addition, some vessels show disorganized or hypertrophied smooth muscle layers. Similar structural alterations occur in endometrial arterioles in the decidua parietalis of intrauterine pregnancies and in cases with ectopic pregnancy.

This clearly shows that in the placental bed, decidual spiral artery remodelling starts before the beginning of cellular interaction between the vessel and the intravascular or interstitial trophoblast. These physiological changes transform the decidual and myometrial segments of some 50 spiral arteries in the placental bed and allow an appropriate blood flow into the placenta during the progression of pregnancy [34].

SHiP in patients with endometriosis raises the possibility of multiple bleeding sites in the pelvis. All of these need to be identified in order to achieve haemostasis. This can be very challenging, as the large uterus obstructs access to the posterior pelvic cavity during pregnancy. The posterior pouch of Douglas can also be obstructed by the presence of endometriosis-related adhesions and multiple endometriotic implants.

Table 3. Clinical data

Author	Age, years	Para	Endometriosis/ deciduosis, ART	Site of bleeding	Blood loss, mL	Gestational age, weeks	Type of surgical intervention	Birth weight, g	Outcome
Pregnancy									
Lier et al. [14], 2017 (case II)	35	0	E IVF	Descending colon, rectosigmoid, near left ovary	1,100	28	Caesarean section, resection, compression	1,245	Live birth
Lier et al. [14], 2017 (case IX)	31	0	E –	Posterior right broad ligament/right uterine vein	3,000	33	Caesarean section, suture-ligation	2,400	Live birth
Lier et al. [14], 2017 (case XI)	37	0	E IVF	Right broad ligament, right round ligament, left uterosacral ligament, bladder	1,750	30	Caesarean section, suture-ligation	1,620	Live birth
Loh et al. [15], 2015	31	0	E IVF	Left fallopian tube	3,500	21	Hysterotomy, salpingectomy	NA	1 × stillbirth, 1 × neonatal death
Cozzolino et al. [16], 2015	33	1	E –	Right ovary and right posterior side uterus	1,500	29	Caesarean section, adnexectomy, coagulation, suture-ligation	1,390	Live birth
Aggarwal et al. [17], 2014	31	0	E IVF	Left fallopian tube, adhesions, surface uterus	2,200	22	Caesarean section, salpingectomy	NA	2 × stillbirth
De Vincenzo et al. [12], 2013	33	0	E –	Posterior side uterus, left uterine artery, bowel, lymph nodes	2,500	24	Caesarean section, bowel resection, suture-ligation	NA	Stillbirth
Kondoh et al. [18], 2012	31	0	D –	Posterior side uterus, peritoneal and omental surface	Large (TBL: 2,475)	29	Caesarean section	1,318	Live birth
Reif et al. [19], 2011	25	0	E IVF	Left ovary (partial), left fallopian tube, adhesions	1,500	27	Caesarean section, cystectomy, tubectomy	1,190, 890	2 × live birth
Brouckaert et al. [20], 2010	33	0	E IVF	Right ovary (1st episode); right ovary, right broad ligament (2nd episode)	2,600 (1st); 3,500 (2nd)	17	Adnexectomy, hysterectomy with fetus in situ, coagulation, suture-ligation	NA	Stillbirth
Bouet et al. [21], 2009	33	0	D –	Left broad ligament/ parametrium	700	24	Adnexectomy, caeserean section	NA	Stillbirth
Grunewald et al. [22], 2009	33	2	E –	Right sacro-uterine ligament	900	27	Coagulation, hemostasic agents	4,665	Live birth (42 weeks)
Katorza et al. [23], 2007 (case II)	31	1	E IVF	Right adnexa, parametrium	3,000	26	Adnexectomy	NA	Pregnancy termination (parental request)
Aziz et al. [24], 2004	30	0	E –	Left broad ligament/ parametrium, left ovary	3,000	20	Adnexectomy, caeserean section	NA	Stillbirth
Mizumoto et al. [6], 1996	28	0	E, D –	Enlarged, dilated veins/ serosa uterine fundus	4,000	28	Suture ligation, caesarean section	1,250	Neonatal death
Doyle and Phillips [25], 1957	37	0	D –	Right lateral pelvic wall/pouch of Douglas	Large	33	Maternal death (autopsy)	NA	Fetal death (autopsy)
Intrapartum and postpartum									
Lier et al. [14], 2017 (case IV)	33	1	D –	Left uterovesical ligament	2,000	PP Day 12	Suture-ligation, haemostatic agents	NA	NA

Table 3. (continued)

Author	Age, years	Para	Endometriosis/ deciduosis, ART	Site of bleeding	Blood loss, mL	Gestational age, weeks	Type of surgical intervention	Birth weight, g	Outcome
Zhang and Lou [26], 2015	25	0	E –	Ovarian cyst, posterior uterine wall vessels	2,500	Intrapartum	Caesarean section, adhesiolysis, cystectomy, suture-ligation	Unknown	Livebirth
Boztosun et al. [27], 2012	25	0	E –	No active bleeding	1,500	PP Day 0	Explorative laparotomy: no interventions	NA	NA
Gao et al. [28], 2010	29	1	Unknown	Bilateral pelvic and ovarian adhesions, left uterine artery	2,000	PP Day 3	Ligation left internal iliac artery	NA	NA
O'Leary [29], 2005	41	1	D –	Left pelvic sidewall (diffuse)	2,000	PP Day 11	Hysterectomy, ligation left uterine artery, bilateral adnexectomy	NA	NA
Richter et al. [30], 1983	36	3	D –	Posterior left broad ligament/parametrium	800	PP Day 0	Hysterectomy, bilateral salpingo-oophorectomy	NA	NA
Sabatelle and Winger [31], 1973	23	0	D –	(Bloodvessels) posterior uterine wall	3,000	PP Day 0	Hysterectomy	NA	Stillbirth
Hulme-Moir and Ross [32], 1969	25	1	D –	Omentum	Unknown	PP Day 9	Explorative laparotomy	NA	NA

ART, assisted reproductive techniques; D, deciduosis; E, endometriosis; IVF, in vitro fertilization; NA, not applicable; PP, postpartum; TBL, total blood loss.

The phenomenon of "deciduosis," defined as extra-uterine decidualization of stromal cells, has been well described in the peritoneum, cervix and ovary. Although its formation under hormonal stimulation suggests a relationship with endometriosis, the clinico-pathological process is distinct and deciduosis does not always indicate underlying endometriosis [35]. Büttner et al. [36] investigated biopsies of tissues taken from the omentum (n = 60) and various abdominal organs (n = 48) at the time of caesarean section or ectopic pregnancy at different gestational ages. Focal or diffuse deciduosis was observed in all cases. Vacuolar degeneration and fragmentation, which are manifestations of regressive changes of the decidual cells, were noted in cases of advanced pregnancy. In more than 80% of cases, blood vessels or the area with ectopic decidua showed proliferation and enlargement when compared to areas of normal fat tissue. Immunohistochemistry demonstrated hormone-induced metaplasia of the sub-mesothelial mesenchyme. The exact onset and involution of extra-uterine decidua are not known, but available observations suggest that it starts during the second or third month of pregnancy and its involution seems complete between 4 and 6 weeks postpartum. As a rule, deciduosis does not give rise to clinical symptoms. Abdominal pain similar to appendicitis, intra-abdominal haemorrhages and haematuria has only very rarely been observed. Markou et al. [37] examined 307 consecutive women at the time of Caesarean section and obtained biopsies from all (n = 31) subjects who were noted to have a macroscopic peritoneal lesion. All biopsies showed histological evidence of decidualization. Women with visible deciduosis were more likely to report abdominal pain during pregnancy, but the finding of deciduosis was not linked to preeclampsia, preterm labour or fetal growth restriction. In this study, deciduosis was not related to endometriosis. In this group, the occurrence of pain may be secondary to subclinical hemoperitoneum or to degenerative changes during the regression phase of these lesions.

Mechanisms of Ectopic Decidual Bleeding

We have previously reported that IVF in women with endometriosis increases the risk of SHiP [2]. Emerging evidence suggests that endometriosis is associated with progesterone resistance characterized by the suboptimal expression of target genes [38]. Therefore, it is tempting

to speculate that "functional" progesterone withdrawal triggers the involution of the decidual phenotype of the ectopic endometrium surrounding distended parametrial arterioles, leading to peritoneal bleeding of unpredictable severity [39].

In recent years, molecular mechanisms of decidual uterine spiral arteries remodelling in early pregnancy have been investigated. These involve a coordinated series of events, including the creation of a decidual immune cell environment, vascular cell disruption and loss. This is followed by extra villous trophoblast colonization and completion by mid-pregnancy. Smith et al. [40] performed a detailed analysis of the spatial and temporal loss of vascular extracellular matrix in the walls of remodelling decidual spiral artery in early pregnancy. They immuno-stained serial sections of these vessels for a panel of extracellular matrix markers and showed that the initial stages of spiral artery remodelling are characterized by the loss of laminin, elastin, fibrillin, collagen types III, IV, and VI from the basement membrane, vascular media and/or adventitia, and surrounding decidual stromal cells. Loss of extracellular matrix correlated with disruption and disorganization of vascular smooth muscle cells. The majority of changes occurred prior to extensive colonization of the vessel wall by extravillous trophoblast. Given the co-distribution of uterine natural killer (uNK) cells and decidualized stromal cells, a mutual interaction might provide the correct regulatory environment in case of placentation [41]. The uNK cells and macrophages within remodelling vessels seem to prime decidual vessels for extravillous trophoblast invasion and to play a role in recruiting extravillous trophoblasts to line the vessel wall [42, 43]. However, no information is available on the presence or potential role of uNK cells in ectopic decidualization. While plasma progesterone levels remain elevated throughout human pregnancy, as mentioned decidual bleeding in pregnancy may be elicited by a functional progesterone withdrawal, as indicated by significantly reduced decidual cell nuclear expression of progesterone receptor-A and -B. Functional withdrawal of progesterone results in increased phospho-ERK1/2 pathway initiating decidual bleeding and causing obstetrical complications such as abruption-induced preterm delivery [44]. Mechanical as well as cellular changes can contribute to the occurrence of SHiP. Changes in vessel wall can lead to weakening and increased predisposition to bleeding in response to trauma or increased pressure and can also render the vessels more friable resulting in difficulty in obtaining haemostasis. On the other hand, regression of deciduosis can itself lead to increased susceptibility and possibly vascular breakdown.

Subclinical Decidual Bleeding as a Potential Risk Factor for Preterm Birth

A subset of patients with preterm labour has vascular lesions of the placental bed, including failure of physiological remodelling of the myometrial spiral arteries [34, 45], a lesion that is common in preeclampsia. Understanding why some women with these vascular lesion and abnormal angiogenic profile develop preeclampsia and others preterm labour can provide insight into the pathophysiology of both conditions [46]. Pathogenetic mechanisms implicated in these disorders include defective deep placentation, oxidative and endoplasmic reticulum stress, autoantibodies to type-1 angiotensin-II receptor, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction and the presence of an antiangiogenic state, among which an imbalance of angiogenesis has emerged as one of the most important factors [47]. Premature decidual senescence without progesterone withdrawal has been implicated in placentation disorders including preterm birth. The localization, severity and timing of the angiogenic imbalance, together with maternal susceptibility such as in the presence of endometriosis, may determine the clinical presentation. Recently, Marcellin et al. [48] demonstrated that decidua in women with endometriosis is able to generate endometriotic-like lesions in contact with the fetal membranes and found significant deregulation for genes know to be enriched in processes involved among others in neoangiogenesis.

In a retrospective case study of preterm placentas, Salafia et al. [49] suggested a relation between decidual hemosiderin deposition in the placenta or membranes and preterm delivery. A total of 196 of 462 (43%) preterm placentas or membranes had any decidual hemosiderin compared with one of 108 (0.8%) at term ($p < 0.00001$). Sakata et al. [50] reviewed recent advances in hemo/iron-mediated signalling. Decidual haemorrhage may result in high levels of free heme and iron. Several important preterm birth-specific genes and proteins overlap with those known to be regulated by iron. Free iron oxidatively modifies lipid and protein, leading to DNA and cell damage. Collectively, decidual haemorrhage and inflammation are considered to be major contributors to the pathogenesis of preterm birth. Although the majority of patients with hemosiderin deposition had no history of gestational bleeding, this is an area where more research is needed.

The phenomenon of ectopic decidualization has traditionally been regarded as benign, but accumulating evidence suggests the need for systematic studies to further our understanding of the condition and its significance.

Conclusion

Available evidence suggests that during pregnancy a link exists between ectopic decidualization, particularly that occurring in endometriotic foci, and the occurrence of SHiP. Alterations in vessels' walls have been demonstrated in the few cases where relevant biopsies were obtained and examined. Indeed, it seems that arterioles can become modified in the absence of trophoblast. There is a need to carefully examine vascular alterations at the site of bleeding leading to SHiP to gain information on the pathophysiology of this serious complication. Finally, whereas there are indications that subclinical decidual bleeding may be a potential risk factor for preterm labour, further clinical, pathological and molecular investigations are required.

Disclosure Statement

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