Severe spontaneous hemoperitoneum in pregnancy may be linked to in vitro fertilization in patients with endometriosis: a systematic review

Ivo A. Brosens, M.D., Ph.D.,[a] Marit C. Lier, M.D.,[b] Velja Mijatovic, M.D., Ph.D.,[b] Marwan Habiba, Ph.D.,[c] and Giuseppe Benagiano, M.D., Ph.D.[d]

[a] Leuven Institute for Fertility and Embryology, Leuven, Belgium; [b] Endometriosis Center VUmc, Department of Reproductive Medicine, VU University Medical Center, Amsterdam, the Netherlands; [c] Department of Obstetrics and Gynecology, Leicester Royal Infirmary, University Hospitals of Leicester, Leicester, United Kingdom; and [d] Department of Gynecology, Obstetrics, and Urology, Sapienza, University of Rome, Rome, Italy

Objective: To evaluate existing evidence of a possible association in women with endometriosis between controlled ovarian hyperstimulation plus embryo transfer (COH-ET) and the occurrence of spontaneous hemoperitoneum in pregnancy (SHiP).
Design: Comprehensive review.
Setting: Not applicable.
Patient(s): None.
Intervention(s): An electronic literature search up to February 2016 was conducted using Scopus and PubMed.
Main Outcome Measure(s): The role of COH-ET in SHiP.
Result(s): Controlled ovarian hyperstimulation plus embryo transfer may increase the severity or incidence of the rare condition known as SHiP. An analysis of published cases shows that bleeding often occurs from multiple or diffuse sites, mainly situated in the posterior pelvic cavity, making it difficult to control without interfering with the pregnancy itself. Spontaneous hemoperitoneum in pregnancy is linked to adverse perinatal outcomes, including stillbirth, neonatal mortality, and very low or low birth weight. In 14 cases a biopsy of the bleeding site was obtained, and in all cases, even in the absence of visible endometriosis, decidualization was documented. At present, the relatively small number of cases published prevents firm conclusions, although they are highly suggestive of a link between COH-ET in women with endometriosis and the occurrence and seriousness of SHiP.
Conclusion(s): Spontaneous hemoperitoneum in pregnancy is a rare but potentially fatal complication for the pregnant woman and her unborn child. In vitro fertilization in women with severe endometriosis may be a risk factor for SHiP. (Fertil Steril® 2016;106: 692–703. ©2016 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)
Key Words: Ectopic deciduosis, endometriosis, IVF, progesterone, spontaneous hemoperitoneum in pregnancy

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It is well recognized that pregnancy can relieve endometriosis-related symptoms and may be curative. Pregnancy is therefore considered within the therapeutic options for endometriosis. Medical literature dating from the middle of the last century also included reference to pregnancy for the *prevention* of endometriosis (1). Joseph Vincent Meigs (2) stated his belief that "avoidance of endometriosis through early

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Reprint requests: Ivo A. Brosens, M.D., Ph.D., Leuven Institute for Fertility and Embryology, Tiensevest 168, B-3000 Leuven, Belgium (E-mail: ivo.brosens@med.kuleuven.be).

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marriage and frequent childbearing is the most important method of prophylaxis." In line with this, the term "pseudopregnancy" was introduced during the 1960s in relation to the therapeutic use of progestin (3).

Endometriosis is a recognized cause of infertility but has only seldom been linked to pregnancy complications. Recent reports highlighted the rare yet life-threatening occurrence of spontaneous hemoperitoneum in pregnancy (SHiP). This dramatic complication has been associated with perinatal mortality and morbidity (4, 5). Doyle and Philips (6) were the first to describe the autopsy of a woman who died from SHiP and linked the bleeding to a small decidual peritoneal lesion on the lateral pelvic wall. O'Leary (7) reviewed pathology reports of cases of SHiP described between 1929 and 2006 and found two maternal deaths, three fetal deaths, and two neonatal deaths in the 10 cases he identified. He described decidualization with no evidence of endometriosis in seven cases and decidualization in an endometriotic lesion in three cases. O'Leary (7) concluded that, although ectopic decidualization is usually no more than a pathologic curiosity, in rare cases it may be linked to feto-maternal mortality and morbidity.

A series of recent reports drew attention to a possible link between IVF carried out in women with endometriosis and SHiP. In one retrospective report, Katorza et al. (8) reviewed the clinical notes of 800 women attending an endometriosis center and identified three women who had intra-abdominal bleeding between 26 and 29 weeks' gestation. All three women had IVF. Other case series of SHiP after IVF, mostly in women with endometriosis, have since been published (8–12). In a series of 11 cases of SHiP in women with endometriosis, Lier et al. (9) documented six cases following IVF treatment. Two maternal deaths have recently been reported due to a delay in the diagnosis of SHiP (13, 14). Ueda et al. (15) reported abscess formation and rupture in 2 of 25 cases with endometriomas who underwent IVF. On the other hand, assisted reproductive technology was not linked to adverse pregnancy outcomes. This reflects the fact that SHiP is very rare. It has also been reported in singleton and twin pregnancies (16, 17), although it may be more common in women with endometriosis who conceive after IVF. To test for a possible association, we undertook a literature review of reported cases of SHiP in women with and without endometriosis related to the use of IVF.

MATERIALS AND METHODS

Search Strategy

A Scopus search, undertaken using the term "spontaneous hemoperitoneum in pregnancy," produced a total of 474 publications, starting with the publication by Reid in 1945 (18). The search was extended by mining the references for case reports, case series, and reviews. After reading the abstracts and, if relevant, the full articles, a total of 57 case reports were identified. All cases with an established known cause explaining the hemoperitoneum were then excluded. This search was limited to articles published in English, French, or Spanish. For completion, a PubMed search was also carried out using the terms "hemoperitoneum" and "pregnancy," yielding 859 articles. When the search was limited to the period 2007–2016, it yielded 318 articles. A manual search of these articles was undertaken to exclude those dealing with ectopic pregnancy, pregnancy in a bicornuate horn, placenta accreta or percreta, uterine rupture, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, pre-eclampsia, ovarian hyperstimulation, and hepatic or splenic rupture. This left 80 references; 55 of them contained the word "spontaneous" and 25 did not. Finally, all articles concerning endometriosis and/or IVF were selected. Because the purpose of this review is to examine occurrence of hemoperitoneum during pregnancy, reports of SHiP during labor or the postpartum period were excluded.

RESULTS

The aggregated search identified 45 articles, encompassing 64 case reports. These were divided into three groups on the basis of whether patients received assisted conception and the presence or absence of endometriosis. Group 1 included 24 cases of SHiP in women who underwent IVF. This group includes 22 cases in women who were diagnosed with endometriosis. Group 2 included 20 cases in women who conceived spontaneously and who had endometriosis. This group included all cases published since the first reported case of endometriosis and SHiP in 1992. Group 3 included 20 cases in women who had natural conception and who did not have endometriosis. In this group, in the absence of biopsies, the presence of ectopic deciduosis cannot be excluded. Because the first case of SHiP after IVF was published in 2007, we used the same year for including publications in group 3.

Clinical Features

Group 1 (Table 1) included 24 pregnancies following controlled ovarian hyperstimulation and embryo transfer (COH+ET). Women's age ranged between 25 and 43 years. Nineteen women (79%) were nulliparous. Twenty-two women (92%) had severe, stage III or IV endometriosis. Group 2 (Table 2) included 16 cases with surgical diagnosis of endometriosis and 4 cases with no prior diagnosis of endometriosis, where the biopsy showed the presence of decidua, allowing a diagnosis of ectopic deciduosis, as described by Kondoh et al. (36). The age range of the group was between 25 and 37 years. Thirteen women (65%) were nulliparous. The stage of endometriosis varied from minimal to severe. Four women had ectopic deciduosis. Group 3 (Table 3) included 20 cases of SHiP with an age range of 21–40 years; eleven women (55%) were nulliparous. Women in this group did not have endometriosis at the time of laparotomy, although no biopsies were taken from the site of bleeding. It should be noted that in one case, deep endometriosis was diagnosed 4 years later by magnetic resonance imaging.

Localization and Number of Bleeding Sites

In group 1 SHiP occurred in 21 women (88%) during the second half of pregnancy and at 6, 17, and 19 weeks in the other 3 cases. In group 2, bleeding occurred between 21 and 37 weeks in all cases. In group 3, the bleeding occurred after

TABLE 1

Details of subjects with a diagnosis of endometriosis who conceived through COH-ET.

					Maternal outcome			Perinatal outcome		
Group 1, author, year (reference)	**Age (y)**	**Para**	**Endometriosis stage**	**Site of bleeding**	**No. of bleeding sites**	**Blood loss (mL)**	**Surgical intervention**	**Gestation age (wk)**	**Birth weight (g)**	**Outcome**
Singleton pregnancies										
Lier et al., 2016 (9)	38	0	Stage IV	Posterior uterine varicosities	M	3,000	Laparotomy 19 wk Cesarean section 39 wk	19	2,984	Live birth
	35	0	Stage IV	Left ovary, bowel	M	1,100	Cesarean section	28	1,245	Live birth
	33	0	Stage IV	Right broad ligament varicosities	M	3,500	Cesarean section	32	2,265	Live birth
	36	1	Stage IV	Right broad ligament Right uterine artery	1	2,000	Laparoscopy, laparotomy, surgical evacuation	6	—	Miscarriage
	28	0	Stage IV	Back of uterus, left and right broad ligament, bilateral hematoma	M	100	Cesarean section	37	3,145	Live birth
	37	0	Stage IV	Right broad ligament, right round ligament Left uterosacral ligament, bladder	M	1,750	Cesarean section	30	1,620	Live birth
Brouckaert et al., 2010 (19)	33	0	Stage IV endometrioma	Right ovary (1st episode) Broad ligament (2nd episode)	D	14,600	1st Ovariectomy 2nd Hysterectomy fetus in situ	17	—	Fetal loss
Kim et al., 2010 (10)	29	0	Severe endometriosis	Pouch of Douglas adhesions	M	Large clots	Cesarean section	40	3,200	Live birth
Zhang et al., 2009 (11)	35	0	Stage II	Right broad ligament varicosities	1	1,700	Cesarean section	35	2,580	Life birth
	38	1	Surgically confirmed	Posterior wall of uterus varicosities	M	1,500	Cesarean section	30	1,070	Live birth
Passos et al., 2008 (12)	32	0	Stage III	Right and left broad ligament varicosities	2	Large clots	Cesarean section	31	1,570	Live birth
Katorza et al., 2007 (8)	31	1	Severe endometriosis Endometrioma	Right broad ligament and adnexa	M	3,000	Termination of pregnancy Adnexectomy	26	Not available	Fetal Loss
	32	0	Severe endometriosis Endometrioma	Anterior and posterior wall of uterus	M	Small amount	Cesarean section	29	1,425	Live birth
Twin pregnancies										
Loh et al., 2015 (16)	31	0	Stage IV endometrioma	Posterior wall of uterus, left fallopian tube	M	3,500	Hysterotomy Left adnexectomy	21	—	Stillbirth, neonatal death

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TABLE 1

Continued.

					Maternal outcome				Perinatal outcome	
Group 1, author, year (reference)	**Age (y)**	**Para**	**Endometriosis stage**	**Site of bleeding**	**No. of bleeding sites**	**Blood loss (mL)**	**Surgical intervention**	**Gestation age (wk)**	**Birth weight (g)**	**Outcome**
Aggarwal et al., 2014 (17)	31	0	Severe endometriosis	Left fallopian tube	M	2,200	Cesarean section	22	—	Stillbirth, neonatal death
Doger et al., 2013 (20)	26	0	No endometriosis	Posterior wall of uterus, Utero-ovarian vein	1	400	Cesarean section	32	1,760 1,730	Live birth
Reif et al., 2011 (21)	25	0	Stage III endometrioma	Left ovary	D	1,500	Cystectomy	27	1,190 890	Live birth
Andrés-Orós et al., 2010 (22)	32	0	No endometriosis	Posterior wall of uterus varicosities	1	1,000	Cesarean section	37	2,715 2,340	Live birth
Kim et al., 2010 (10)	33	0	Stage IV	Posterior wall of uterus varicosities	M	2,000	Cesarean section	33	2,190 2,300	Live birth
Zhang et al., 2009 (11)	38	0	Stage III	Posterior wall of uterus varicosities	1	3,100	Cesarean section	29	—	Stillbirth
Passos et al., 2008 (12)	30	0	Stage III endometrioma	Posterior wall of uterus, left broad ligament hematoma	D	Large clots	Vaginal delivery and cesarean section	32	1,830 1,740	Live birth
Roche et al., 2008 (23)	43	1	Stage IV	Posterior wall of uterus, right uterine artery	M	3,000	Cesarean section	33	—	Stillbirth
Katorza et al., 2007 (8)	29	0	Severe endometriosis	Posterior wall of uterus varicosities, ovarian fossa	M	2,000	Cesarean section	28	1,075 1,210	Live birth
Wu et al., 2007 (24)	31	1	Severe endometriosis Endometrioma	Posterior wall of uterus	1	4,000	Cesarean section	33	Not available	Live birth

Note: D = diffuse; M = multiple.

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TABLE 2

Details of subjects with a diagnosis of endometriosis (or deciduosis during pregnancy) who conceived naturally.

					Maternal outcome			Perinatal outcome		
Group 1, author, year (reference)	Age (y)	Para	Endometriosis stage	Site of bleeding	No. of bleeding sites	Blood loss (mL)	Surgical intervention	Gestation age (wk)	Birth weight (g)	Outcome
Endometriosis										
Lier et al., 2016 (9)	34	2	Stage IV	Left uterosacral ligament	1	1,100	Laparotomy at 23 wk Cesarean section at 35 wk	35	2,965	Live birth
	33	0	Yes	Uterovesical fold, left uterosacral ligament	2	600	Cesarean section Laparotomy 2 wk postpartum	34	2,290	Live birth
	37	2	Yes	Posterior uterine wall adhesions	1	2,000	Laparotomy at 21 wk Cesarean section at 37 wk	37	2,940	Live birth
Stochino et al., 2016 (25)	26	0	Deep infiltrating nodule	Left broad ligament Left uterine artery	1	3,000	Laparotomy Termination of pregnancy	16	—	Stillbirth
Cozzolino et al., 2015 (26)	33	1	Stage II	Right ovary, Posterior uterine surface	2	1,500	Cesarean section Adnexectomy	29	1,390	Live birth
De Vincenzo et al., 2013 (27)	33	0	Surgical confirmed	Posterior uterine surface, bowel, left uterine artery	1	2,500	Cesarean section Bowel resection	24	—	Stillbirth
Girard et al., 2012 (28)	31	0	Severe	Left broad ligament Uterine artery	1	Massive	Forceps delivery Laparoscopy, laparotomy	41	3,700	Neonatal death
Williamson et al., 2011 (29)	37	0	Endometrioma	Left broad ligament hematoma	1	Hematoma	Vaginal delivery	37	2,700	Stillbirth
Tourette et al., 2011 (30)	28	1	Sigmoid endometriosis	Posterior uterine wall, left uterine artery	1	Massive	Cesarean section Tumor excision	28	1,200	Live birth
Grunewald et al., 2010 (31)	33	2	Stage I	Right uterosacral ligament at 27 wk	1	900	Laparotomy	42	4,665	Live birth
Kim et al., 2010 (10)	28	0	Surgical confirmed	Posterior uterine wall varicosities	M	1,000	Cesarean section	25	720	Live birth
	37	1	Stage II	Subserosal vessel Pouch of Douglas adhesions	2	Clots	Vaginal delivery Hysterectomy	40	Not available	Live birth
Wada et al., 2009 (32)	31	2	Stage IV	Posterior uterine wall varicosities	1	2,490	Laparotomy	37	2,354	Live birth
Chiodo et al., 2008 (33)	25	0	Stage IV	Right broad ligament Right uterine artery	1	2,000	Ureter implantation	31	—	Stillbirth
Aziz et al., 2004 (34)	30	0	Surgical confirmed	Left broad ligament Anterior uterine wall	1	4,000	Adnexectomy	20	—	Stillbirth
Inoue et al., 1992 (35)	37	0	Severe	Anterior uterine all Varicose veins	1	3,000	Cesarean section	29	1,416	Live birth
Deciduosis										
Lier et al., 2016 (9)	31	0	No	Right broad ligament Uterine vein	1	3,000	Cesarean section	33	2,400	Live birth

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TABLE 2

Continued.

Group 1, author, year (reference)	Age (y)	Para	Endometriosis stage	Maternal outcome				Perinatal outcome			
				Site of bleeding	No. of bleeding sites	Blood loss (mL)	Surgical intervention	Gestation age (wk)	Birth weight (g)	Outcome
Kondoh et al., 2012 (36)	31	0	No	Posterior wall of uterus, omentum	M	Large amount	Cesarean section	29	1,318	Live birth
Bouet et al., 2009 (37)	33	0	No	Left broad ligament rent; uterine artery	1	700	Cesarean section	24	—	Stillbirth
Muzimoto et al., 1996 (38)	28	0	No	Posterior wall of uterus veins	M	4,000	Cesarean section	28	1,250	Neonatal death

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27 weeks in all cases. The mean duration of gestation at the time of bleeding was 28.6 weeks for group 1, 30.9 weeks for group 2, and 32.3 weeks for group 3. The difference between group 1 and 3 was statistically significant ($P=.004$). There were no statistically significant differences in the duration of gestation between group 2 and either group 1 ($P=.29$) or group 3 ($P=.079$) (unpaired t test). In the majority of cases bleeding was from the serosa of the posterior wall of the uterus, the broad ligaments, or the utero-sacral ligaments, and bleeding was recorded as venous at the site of varicosities. In some cases bleeding occurred at the site of a peritoneal tear, suggesting a two-step process whereby a hematoma forms in the loose areolar tissue of the parametrium before rupturing into the peritoneum. The bleeding site could not be identified in two cases in group 3.

Multiple (more than two) or diffuse bleeding points were observed in 16 cases (67%) in group 1, in 3 cases (15%) in group 2, and 3 cases in group 3. The difference between group 1 and the two other groups was statistically significant ($P=.0005$). Among cases in which total blood loss was reported, the average amount of blood loss was higher in group 1 (2,720 mL) compared with group 2 (2,152 mL) and group 3 (1,805 mL), but the difference between the groups was not statistically significant. When the report included histopathology of bleeding sites (n=14), decidualization was confirmed in all cases.

Perinatal and Maternal Outcomes

Adverse perinatal outcome included stillbirth, neonatal death, cerebral palsy, miscarriage, and prematurity. Delayed transportation was considered a contributory factor in the one maternal death that occurred in group 3 (14). In most cases delivery was by cesarean section. This was linked to extended laparotomy to allow access to the posterior aspect of the uterus and to the adnexa. Adverse maternal morbidities included the need for hysterectomy and adnexectomy. In most cases there was considerable blood loss requiring extensive transfusion of blood and blood products. The surgical challenge posed by this presentation is considerable, as demonstrated by detailed literature accounts (20, 23).

DISCUSSION

Pathophysiology of SHiP

There are a number of well-known causes of intraperitoneal bleeding during pregnancy. The most common during early pregnancy is a ruptured ectopic pregnancy or a ruptured hemorrhagic ovarian cyst.

Intraperitoneal bleeding is less common in late pregnancy, but obstetricians are well familiar with possible causes, namely uterine rupture, an abnormally invasive placentation, and *abruptio placenta*e leading to uteroplacental apoplexy (also known as *Couvelaire uterus*), a situation in which the retro placental blood infiltrates the uterine wall ending in the peritoneal cavity. HELP syndrome complicating pregnancy has also been linked to bleeding from liver rupture. The literature also contains case reports of less frequently encountered causes of nontraumatic spontaneous

TABLE 3

Details of subjects with no prior diagnosis of endometriosis who conceived naturally.

					Maternal outcome			Perinatal outcome		
Group 3, author, year (reference)	Age (y)	Para	Endometriosis stage	Site of bleeding	No. of bleeding sites	Blood loss (mL)	Surgical intervention	Gestation age (wk)	Birth weight (g)	Outcome
Lier et al., 2016 (9)	27	20	Yes (no biopsy)	Adhesion posterior wall uterus	1	2,500	Cesarean section	37	3,045	Live birth
Fatnassi et al., 2015 (39)	35	2	No	Left broad ligament varicosities		1,300	Cesarean section	32	3,100	Live birth
Diaz-Murillo et al., 2014 (40)	35	0	No	Posterior wall of uterus, left broad ligament varicosities	M	Moderate	Embolization Cesarean section	37	Not available	Live birth
Lim et al., 2014 (41)	24	1	No	Posterior uterine varicosities	M	1,500	Cesarean section	37	1,730	Live birth
Shi et al., 2014 (42)	33	1	No	No bleeding lesion	0	1,500	Laparotomy	32	2,390	Live birth
Munir et al., 2012 (43)	32	2	No	Left utero-ovarian ligament	1	3,000	Cesarean section	38	3,300	Live birth
Al Quahtani et al., 2012 (44)	37	4	No	Posterior uterine varicosities	1	2,500	Cesarean section	38	Not available	Live birth
Detriche et al., 2012 (45)	27	0	No	Posterior uterine varicosities	1	400	Cesarean section	32	1,700	Live birth
Girard et al., 2012 (28)	36	1	No	Right broad ligament tear	1	1,500	Cesarean section	29	1,410	Live birth
Nguessan et al., 2013 (46)	33	0	No	Right broad ligament varicosities	M	1,100	Cesarean section	35	Not available	Twin live birth
Kapila et al., 2011 (14)	21	0	No	Left broad ligament tear	1	Large amount	Maternal death	29	1,700	Still birth
Nakaya et al., 2011 (47)	25	0	No	Right broad ligament: superficial vein	1	850	Cesarean section	28	1,150	Live birth
Andrés-Orós et al., 2010 (22)	36	0	No	Posterior uterine varicosities		2,000	Cesarean section	33	—	Twin still birth
Bloom et al., 2010 (48)	28	0	No	Right and left broad ligament Uterine artery	1	1,500	Vaginal delivery Postpartum laparotomy	34	2,570	Live birth
Giulini et al., 2010 (49)	31	1	No	Left broad ligament varicosities	1	2,500–3,000	Cesarean section	33	2,110	Live birth
Pezzuto et al., 2009 (50)	40	0	No	Left broad ligament tear Uterine artery	1	3,600	15 wk: Laparoscopy 38 wk: Cesarean section	38	3,600	Live birth
Moreira et al., 2009 (51)	39	2	No	Left broad ligament, bladder varicosities	1	3,000	Vaginal birth, exploratory laparotomy	40	3,680	Live birth
Rosales et al., 2008 (52)	23	2	No	Right broad ligament, Uterine artery	1	2,500	Hemostatic suture at 22 wk	38	3,000	Live birth

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TABLE 3

Continued.

Group 3, author, year (reference)	Age (y)	Para	Endometriosis stage	Site of bleeding	Maternal outcome: No. of bleeding sites	Maternal outcome: Blood loss (mL)	Surgical intervention	Perinatal outcome: Gestation age (wk)	Perinatal outcome: Birth weight (g)	Perinatal outcome: Outcome
Koifman et al., 2007 (53)	24	0	No	No bleeding site	0	700	Cesarean section	37	2,650	Live birth
Fiori et al., 2007 (54)	28	0	No	Posterior wall of uterus Uterine artery		800	Cesarean section	27	1,000	Live birth

Note: M = multiple.

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intraperitoneal bleeding in pregnancy. Some of these relate to bleeding from nonreproductive organs, such as the splenic vein (55, 56), splenic artery (57), visceral branches of abdominal aorta (58), or the suprarenal glands (57). Bleeding has been also reported from hepatic rupture (59, 60), liver hemangioma (61), or a ruptured gall bladder (62). Of particular interest are reported cases in which there are features of decidualization in the bleeding lesions.

Rare cases have also been reported of bleeding during the postpartum from the ovarian (63) or uterine arteries (13) and uterine veins (57, 64, 65).

Typically, women presenting with SHiP are mostly in the second half of pregnancy. More rarely, they may present during the first half of pregnancy or early in the postpartum period. They present with severe sudden onset of abdominal pain, systemic evidence of hypovolemia, and collapse with no vaginal bleeding. The diagnosis is rarely made before exploratory laparotomy. Identifying and addressing the source of the severe bleeding is very challenging and often requires input from other surgical specialties. Bleeding from the reproductive tract vasculature often originated from the posterior aspect of the uterus or the broad ligament, which are difficult if not impossible to access without prior cesarean delivery. Bleeding can also be retroperitoneal. For the offspring the condition has been associated with a high rate of stillbirth and prematurity, and for the mother with the need for hysterectomy, adnexectomy, and repeat laparotomy and has rarely proved fatal owing to the difficulty in ensuring timely response to bleeding and in view of the significant surgical challenge.

Main Findings

In this article we adopted the term COH+ET as proposed by Järvelä et al. (66) to refer to traditional ovarian stimulation IVF. To the best of our knowledge this is the first review that specifically examined the possible link between COH+ET and the occurrence of SHiP in women with endometriosis. Although this conclusion seems warranted by the evidence collected, caution is required because the rarity of the condition forced us to rely on case reports with different degrees of accuracy. An important observation is the larger number of bleeding points observed in women with endometriosis undergoing COH+ET using traditional ovarian stimulation cycles. This is a point that warrants consideration.

Approximately one-third of all cases identified in the present search refer to women who underwent IVF. Only two (8%) of the cases with SHiP in the IVF group did not have endometriosis, with the majority having moderate or severe disease. The profile of reported cases suggests that COH+ET in women with endometriosis may increase the incidence or severity of SHiP. Several observed features seem to support the existence of an association: first, the presence of multiple or diffuse bleeding sites; second, the occurrence of decidualization in all cases that had a biopsy of the bleeding site; and third, the site of decidualization, which largely involved the parametrium and ovarian endometriomas. The common site of bleeding was in the posterior pelvic cavity, which is

difficult to reach in the presence of advanced pregnancy without interfering with the pregnancy itself.

On the basis of pelvic inspection and biopsy, three clinical subgroups of SHiP can be distinguished: [1] *ectopic deciduosis* in women without endometriosis; [2] *decidualized foci of endometriosis*; and [3] *diffuse decidualization* in patients with SHiP linked to COH+ET. The severity of the presentation is reflected by adverse perinatal outcome, including stillbirth, neonatal mortality, very low birth weight, or low birth weight.

Although the paucity of reported cases in the group of women with IVF who did not have a diagnosis of endometriosis suggests that COH+ET is a risk factor for SHiP in the subgroup of women with moderate or severe endometriosis, their very limited absolute numbers necessitate a word of caution.

Thirty-eight of the cases identified in this review (59%) had endometriosis, which again suggests that endometriosis may to be linked to an increased incidence of SHiP. The group who underwent COH+ET and subsequently developed SHiP had a high incidence of advanced endometriosis, including a high incidence of endometrioma-related surgery. However, although endometriosis is well recognized as a cause of pelvic adhesions, which can cause severe limitation of uterine mobility as detected clinically or at the time of surgery, little is understood about how these adapt to pregnancy to allow uterine enlargement. The process can be envisaged to be associated with considerable stretch or breakdown, perhaps facilitated by softening in response to higher than usual circulating levels of P during early pregnancy in women who underwent COH+ET (66). It is also possible that a breakdown of adhesions and associated vasculature can occur within this process. The surgical difficulty in controlling the bleeding is further evidence of increased tissue susceptibility and the need for a judicious surgical approach. This must also be understood with reference to the hyperdynamic circulatory state and the extensive pelvic varicosities of pregnancy. One important argument against the role of stretch in the pathogenesis of SHiP is that it that there does not seem to be a higher number of reported cases in twin pregnancy.

The cases presented here illustrate the surgical challenge when attempting to control bleeding from multiple decidualized lesions. Decidualization has long been a recognized feature of the peritoneum during pregnancy and does not in itself indicate underlying endometriosis (67, 68). Yet the tissue can be friable to handle, and attempts to control bleeding with suture material or diathermy may be futile, culminating in the need for excisional surgery and removal of the uterus or adnexa. The impact on affected women is considerable. Surgical access can also be difficult because bleeding is often from the posterior uterine wall or the posterior aspect of the broad ligament, which are difficult to access in a pregnant woman. It seems that most attempts to control bleeding while maintaining the pregnancy have been unsuccessful, and cases have been reported with recurrent bleeding necessitating hysterotomy and supracervical hysterectomy (16, 19). Therefore, in the presence of SHiP during the third trimester, consideration should be given to delivery by cesarean section at an early stage. One further difficulty is that the diagnosis of SHiP has been rarely made preoperatively, because imaging for intraperitoneal bleeding is very difficult in advanced pregnancy owing to the position of the uterus. It is unclear whether heightened attention to the existence of SHiP may enable a provisional diagnosis before surgery or the identification of less severe cases that do not undergo surgery.

Risk of Ovarian Endometrioma in SHiP

Group 1 included 17 cases (89%) with stage III or IV endometriosis. Ovarian endometrioma was reported in seven cases, but extrapolation from literature reports suggests that it is likely that these were under-reported (69). Pateman et al. (70) reported that the majority of endometriomas were observed to regress during pregnancy when followed up by serial ultrasound and that 12% of cases showed evidence suggestive of decidualization, such as a thick and irregular inner wall, papillary projections, and high vascularity on Doppler examination. These features can pose diagnostic challenges because they may mimic ovarian malignancy. Pregnancy-dependent changes in an ovarian endometrioma include rapid development of abundantly vascularized intracystic excrescences that regress at the end of pregnancy (71). Although a recent literature review lends support to conservative management of endometrioma during pregnancy (72), COH-ET may constitute an additional risk factor for SHiP that should be taken into consideration.

A retrospective study of the outcome of ovarian endometriosis during pregnancy included two cases with pregnancy after IVF. Among 24 ovarian endometriomas observed during pregnancy, the size of the cyst increased significantly during the second trimester in the two IVF cases. One of these subsequently ruptured, and one developed an abscess (15). Nevertheless, there remains a lack of consensus about the optimal management of endometrioma in women undergoing IVF (73).

Although 17β-E_2 and P concentration in peritoneal fluid and serum are comparable during the normal menstrual cycle (74), local P concentrations are significantly higher in the peritoneum close to the corpus luteum compared with other peritoneal samples and systemic blood (75). This suggests that endometriotic implants near the ovaries are more likely to undergo decidual changes in the first trimester of pregnancy as observed in typical peritoneal implants (76).

The Pathology of SHiP in Women with Deciduosis or Endometriosis

Pathologic evaluation of bleeding sites reveals decidualized stromal cells, including in patients without visible endometriosis. Glandular cells were seen in few cases and were reported as atrophic. The histopathology of groups 1 and 2 was characterized by the presence of decidual cells. There are no case reports with histopathology from group 3; but the high prevalence of decidualization during pregnancy suggests that similar findings may be possible.

A second significant finding is the occurrence of bleeding from submesothelial ectopic decidua. This is a phenomenon noted during pregnancy where multiple, irregularly

distributed submesothelial deposits of decidual cells can be noted in the serosa of abdominal and pelvic organs (77 ,78, 79).

In the case described by Doyle and Phillips (6) the autopsy found the presence of a small peritoneal lesion on the lateral side of the pelvis as cause of the fatal hemoperitoneum. At microscopy the lesion showed hemorrhagic decidual tissue without chorionic villi. The very vascular decidual reaction was apparently the source of the fatal bleeding.

In a series of 10 cases, Zaytsev and Taxy (67) observed two cases of submesothelial ectopic decidua that had small amounts of free blood in the peritoneal cavity. A third finding is that reported by O'Leary et al. (7) of a case with vascular intrusion by decidual cells, suggesting a mechanism of damage and bleeding in the thin-walled vessels of the decidual nodule.

It can be speculated that the high, nonphysiologic P levels observed early in pregnancies achieved after COH+ET (66) can accelerate or exacerbate the decidualization process. As shown in the endometriosis control group, the presence of any stage of endometriosis can be a risk factor, although the link with severe endometriosis may be indirect through the indication for COH+ET.

Implications for Clinical Practice and Research

Our study raises important issues for clinical practice and research. First, awareness of the condition may enable earlier diagnosis. Second, the recognition that COH+ET in women with severe endometriosis may represent a significant risk factor for SHiP can affect the choice of treatment. It is possible but uncertain that embryo freezing with replacement in unstimulated cycles will be advantageous. In some women endometriosis may not have been diagnosed before pregnancy, which lends support to the recognition of risk factors such as the presence of neonatal uterine bleeding (80).

Research is needed to enhance the role of imaging in the early diagnosis and monitoring of women at high risk of SHiP. It remains possible that subclinical hemoperitoneum may play a role in major obstetric presentations, such as preterm labor or unexplained abdominal pain (81). Further research is urgently indicated to examine the role of decidualization and the vascular changes at the site of bleeding in biopsies or resection specimen, such as adnexectomy or hysterectomy specimens.

Strengths and Limitations

The study highlights an important clinical problem and suggests a possible preventative measure, but it is important to emphasize that because of the rarity of SHiP it was necessary to design this study as a retrospective literature review. Thus, conclusions are dependent on available publications and their details and quality. A possible bias inherent in this approach may lie in a greater likelihood of cases of SHiP identified after IVF to be submitted for publication. However, SHiP rather than IVF was the main focus in most reported cases, whereas the role of IVF attracted little or no attention.

Although it is recognized that decidualization is a very common feature of the subserosal tissue during pregnancy, the exact incidence and natural history of this finding remain little understood. Decidualization is associated with atrophy of the glandular component, which can render confident diagnosis of endometriosis difficult.

In conclusion, SHiP is a rare but potentially fatal complication for both the pregnant woman and her unborn child. In vitro fertilization in women with severe endometriosis may be a significant risk factor for SHiP.

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