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Running title: The evaluation of the risk of Spontaneous Hemoperitoneum in Pregnancy (SHiP) in women with a history of surgery for endometriosis and those with endometriotic lesions becoming pregnant with IVF

Endometriosis and Spontaneous Hemoperitoneum in Pregnancy (SHiP): evaluation of the magnitude of the risk in women becoming pregnant with IVF

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Capsule: Spontaneous Hemoperitoneum in Pregnancy is uncommon in women with endometriosis achieving pregnancy with In Vitro Fertilization. Further studies are needed to identify risk factors.

ABSTRACT

Objective: To estimate the frequency of Spontaneous Hemoperitoneum in Pregnancy (SHiP) in women with endometriosis achieving pregnancy with IVF.

Design: Retrospective case series of women with endometriosis obtaining pregnancy with IVF

Setting: A referral academic ART center

Patients/Animals: Women with a history of surgery for endometriosis as well as those with ovarian endometriomas or deep endometriotic nodules at the basal transvaginal ultrasound performed prior to initiate the IVF cycle could be included. Women who had a miscarriage before 12 weeks' gestation were excluded.

Interventions: Information regarding basal characteristics, IVF cycle and pregnancy outcome was obtained from patients' charts. A binomial distribution model was used to determine the 95%CI of the proportion of SHiP.

Main Outcome Measure: Rate of SHiP

Results: Overall, 362 pregnancies were included: 238 (66%) had a history of previous surgery for endometriosis and 231 (64%) had endometriosis at ultrasound (107 corresponding to 30% had both). Pregnancies were obtained after fresh and frozen cycles in 244 (67%) and 118 (33%) women, respectively. One case of SHiP was recorded, corresponding to a rate of 0.3% (95%CI: <0.1-1.5%).

Conclusions: SHiP is uncommon in the general population of women with endometriosis undergoing IVF. Future studies should better identify risk factors for SHiP in order to disentangle subgroups of women at higher risk.

KEY WORDS: endometriosis; pregnancy; hemoperitoneum; hemorrhage; IVF

Introduction

It is well recognized that pregnancy can transiently relieve endometriosis-related symptoms (1,2). However, there is growing evidence that women with endometriosis are exposed to the rare yet life-threatening occurrence of spontaneous hemoperitoneum in pregnancy (SHiP) (3,4). This dramatic complication arises abruptly and unexpectedly; it is generally due to the breakage of a pelvic or abdominal vessel causing massive internal hemorrhage. Affected women present with severe pain and signs of hypovolemic shock and commonly require prompt and demanding surgery. SHiP is associated with elevated perinatal mortality and possibly also maternal mortality (3,4). In a recent review including 59 cases reported from 2008 to 2016, Lier *et al*. documented a perinatal and maternal mortality rates of 27% and 2%, respectively (4). Noteworthy, in a preceding systematic review, Brosens *et al*. suggested that the highest risk of SHiP would occur in women with endometriosis achieving pregnancy with IVF (3). Twenty-four out of 64 selected cases took place in IVF pregnancies (38%), of whom 22 had endometriosis (92%). Reasons behind this troublesome association are unknown.

Despite the growing interest on the relation between endometriosis and SHiP, the magnitude of this association remains unclear. Efforts aimed at quantifying this risk are scant and extemporaneous. Katorza *et al*. reported 3 cases of SHiP out of 800 women attending an endometriosis referral center but the precise denominator, i.e. the number of pregnancies was not reported (5). More recent case series of pregnant women with endometriosis suggest that this risk may be very low but the relatively small number of included cases or the study designs hamper a precise estimate of the risk (6-8).

On the other hand, disentangling the rate of SHiP in women with endometriosis is clinically relevant, in particular for those requiring IVF. It would consent to provide a more precise counselling to the women, avoiding excessive alarmism or charitable but unproven reassurance. To

elucidate this aspect, we reviewed outcome of our IVF program over a 9 years period. The main aim of the study was reporting the 95% Confidence Interval (CI) of the rate of SHiP among women with endometriosis who became pregnant with IVF.

Materials and methods

All women with endometriosis who underwent IVF and became pregnant at the Infertility Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy between January 2010 and December 2018 were retrospectively reviewed. Both women with a history of surgery for endometriosis and those with endometriotic lesions as ovarian endometriomas or deep endometriotic nodules at the basal transvaginal ultrasound performed prior to initiate the IVF cycle could be included. Both pregnancies obtained with fresh and frozen cycles could be included. Women who had a miscarriage before 12 weeks' gestation were excluded. Women lost to follow-up were also excluded. Women could be included more than once if they had more than one pregnancy. Information was obtained from patients' charts. The study was approved by the local Institutional review board (Comitato Etico Milano Area 2). An informed consent was not required since this is a retrospective study. However, all women referring to our unit signed an informed consent for their data to be used for scientific purposes.

In our department women with endometriosis routinely undergo an in-depth diagnostic work-up and are then informed regarding the possible options for treatment, including surgery, hormonal treatment and IVF (9). A multi-disciplinary approach is used. The main aim is taking a shared and well-informed decision with the woman. A long-term plan for management is generally elaborated, a plan that takes into consideration also present or future desire for childbearing. Considering in particular women who are facing infertility at the time of consultation, the counselling generally focusses on two main options, i.e. surgery versus IVF (even if, in rare cases, hormonal therapy to

manage pain and then straight IVF could also be decided). Arguments in favor of surgery include the enhanced chance of natural fertility, the beneficial effect on pain symptoms if present, the presence of endometriomas larger than 4 cm, the presence of deep peritoneal lesions causing intestinal or urinary symptoms, non-reassuring imaging findings, younger age, preserved ovarian reserve and normal semen analyses. Arguments favoring IVF include a history of previous surgery and the presence of bilateral endometriomas (because of the risk of severe post-surgical damage to ovarian reserve). Women are also systematically informed about the additional endometriosis-specific risks of surgery, IVF and pregnancy (9). Considering this latter point and the risk of SHiP in particular, women are not proposed surgery with the exclusive purpose of preventing this complication. Surgery to improve IVF results was suggested only in the presence of hydrosalpinx (9).

All women scheduled for IVF in our unit underwent a transvaginal ultrasound in our center. The assessment was repeated at least once prior to initiate the cycle. The diagnoses of endometriomas and deep peritoneal lesions were done according to established criteria (10,11) and had to be documented on at least two occasions and at least two menstrual cycles apart. Softs signs of endometriosis (11) were systematically recorded but were not deemed sufficient for diagnosing endometriosis in the absence of endometriomas or deep peritoneal lesions. A history of surgery for endometriosis was based on the outpatient charts. In our Center, women with a history of gynecological surgery were routinely requested to provide the documentation of the intervention to obtain the surgical description and histological confirmation. This documentation was systematically filed in the outpatient chart.

Women undergoing IVF followed standardized protocols that are reported in detail elsewhere (12-14). According to the policy of our Center and in line with local legislation, all women obtaining a pregnancy with IVF were actively followed up 9-12 months after the successful cycle. They were contacted by phone and interviewed using a standardized questionnaire. For those delivering in our

hospital, provided information were linked to electronic charts of the obstetrics unit and verified. In case of failed contact (impossibility to have a phone contact after several attempts), the male partner could be contacted. With this policy that was not modified over the years, the annual rate of pregnancies lost to follow-up was always below 1%.

The sample size was calculated based on the main outcome of the study, i.e. 95%CI of the rate of SHiP. We aimed at providing estimates shrinking the amplitude of this interval below 1.5%. Hypothesizing that the rate of SHIP would be below 0.5% (5,6,8), we calculated that the number of pregnancies needed to be included in the study was about 340 (http://www.openepi.com/SampleSize/SSPropor.htm). Since women could be included more than once, the denominator used to describe our population is the number of pregnancies, not the number of patients. Data was analyzed using the SPSS software 18.0 (Chicago, IL). A binomial distribution model was used to determine the 95%CI of the frequency of SHiP.

Results

Three hundred forty-eight women were selected, none was lost to follow-up. Overall, 362 pregnancies were included (13 patients had more than one pregnancy). One hundred seventy-six of these pregnancies were included in a previous multicenter study (6). Basal characteristics of the population are summarized in Table 1. Endometriotic lesions were documented at ultrasound in 231 cases (64%) before starting IVF cycles. Two hundred thirty-eight (66%) patients presented a history of surgery for endometriosis. Specifically, 202 women underwent surgery once, 35 women were operated twice, and one patient underwent three interventions. In 121 of the 238 operated women (51%), the intervention was performed to enhance natural fertility. One hundred-seven previously operated women had also detectable lesions at basal evaluation. Details on the US findings and the interventions done are shown in Table 2. In addition, 72 women (21%) were previously operated on

for other gynecological indications: operative hysteroscopy for polyps (n=20), myomectomy (n=20), cystectomy of non-endometriotic cysts (n= 19) and unilateral or bilateral salpingectomy (n=14). Considering the basal characteristics of the patients before starting IVF cycles, a concomitant male indication to IVF was present in 98 cases (27%). Studied pregnancy were obtained after fresh and frozen cycles in 244 (67%) and 118 (33%) women, respectively. The main characteristics of correspondent fresh and frozen cycles are shown in Supplemental Table 1 and Supplemental Table 2, respectively.

We recorded one case of SHiP in a 36 years old woman with a twin pregnancy at 22 weeks' gestation. She did not undergo previous surgery for endometriosis and she was diagnosed at cycle entry with a right endometrioma and a deep recto-vaginal nodule. She retrieved seven oocytes and obtained the pregnancy with a fresh transfer of two embryos. At 21 weeks' gestation, she underwent a therapeutic abortion for a chromosomic anomaly of one of the two fetuses. Four days later, she was admitted in the hospital for sudden onset of abdominal pain and signs of hypovolemic shock. She underwent exploratory laparotomy revealing extensive hemoperitoneum. Due to the impossibility to localize the site of hemorrhage, cesarean delivery of the fetuses was performed: one was already death, the second one did not survive. Thereafter, two active sites of hemorrhage were identified, one in the left hypogastric artery and one at the left uterine veins. A causal relation with the previous selective pregnancy termination was excluded because of the location of the bleeding sites. Management of the bleeding was demanding but could be achieved without performing hysterectomy. Three years later, the woman underwent three additional IVF cycles. She ultimately became pregnant with a single frozen embryo transfer on a natural cycle. She had an unremarkable pregnancy and gave birth to a healthy child.

Overall, one case of SHiP was recorded out of 362 pregnancies, corresponding to a rate of 0.3% (95%CI: <0.1-1.5%). The precise 95%CIs in the different subgroups of women are detailed in Table 3.

Albeit it has not to be classified as SHiP, it is interesting to report that another woman carrying a vaginal nodule of 2 cm was hospitalized from 23 weeks' gestation till the delivery for a modest but persistent vaginal bleeding from the nodule. Expectant management was decided and, finally, a caesarian section was performed ad 37 weeks' gestation with the birth of a healthy child.

Discussion

In our study we found that the frequency of SHiP in women with endometriosis achieving pregnancy with IVF was 0.3% with a 95%CI ranging between <0.1 and 1.5%. Currently, this is the first study specifically designed to assess the magnitude of this risk.

SHiP happened mostly in the second half of pregnancy, in particular in the third trimester (3,4). The most common presentations are sudden onset of severe abdominal pain (95%) and systemic evidence of hypovolemia and collapse in the absence of vaginal bleeding (47%) (4). The diagnosis is difficult, and it is rarely done before exploratory laparotomy. Surgery is also demanding. Bleeding mostly originates from the reproductive tract vasculature of the posterior trait of the uterus or the broad ligament, which are difficult if not impossible to access without prior cesarean delivery. Lier *et al* reported that the active bleeding was mostly often from ruptured utero-ovarian vessels (57%) followed by endometriotic implants (23%), haemorragic nodules (2%) and combination of these events (20%) (4). Brosens et al. suggested a critical role of decidualization in the pathogenesis of SHiP (3). They also claim that ovarian hyperstimulation may boost the process of decidualization, thus explaining the enhanced risk in women who underwent IVF. Jarvela *et al*. speculated that the pharmacological high levels of progesterone may be crucial since they can accelerate and/or intensify the decidualization process (15). In this regard, the additional case reported in our study of a long-lasting and persistent bleeding from a rectovaginal nodule is interesting. In fact, ectopic sites of decidualization is presumably common in women with

endometriosis. However, massive hemorrhage as a consequence of this phenomenon is conversely and fortunately very rare. Finally, it has to be mentioned that pelvic adhesions that are typically associated to endometriosis may also play a role in the pathogenesis of massive bleeding. Indeed, one may hypothesize that, due to the progressive enlargement of the uterus with pregnancy, some SHiPs could be caused to the tear of vascularized and poorly extensible adhesions.

Our unique case displayed several classical features of SHiP; the presence of endometriotic lesions at baseline, the recent ovarian hyperstimulation, the sudden onset, the necessity for prompt surgery, the need for cesarean section to manage the hemorrhage and the origin from ripped pelvic vessels. However, it also showed some peculiarities. Firstly, the event occurred at the beginning of the second half of pregnancy, thus earlier compared to the vast majority of previously reported cases (3,4). The larger dimension and the more rapid enlargement of the gravid uterus due to the twin gestation may explain this anticipation. However, this plausible explanation contrasts with the low frequency of twin pregnancies in previously reported cases (two out of 64 cases) (3). Secondly, the event occurred soon after a selective abortion of one fetus. The anatomical findings at surgery tend to rule out a causal link with the procedure but this conclusion cannot be considered unquestionable because of the very short interval of time between the two events (4 days). To note, if the selective abortion ever played a role, the frequency of SHiP would be over-estimated in our study. However, the conclusion that this event is exceedingly rare would remain unchanged. Thirdly, bleeding was found to originate from two distinct sites. This is surprising. Presumably, one of the bleeding points may have been caused by the trauma of the first part of the intervention when the surgeons performed the cesarean delivery of the fetuses and exteriorized the uterus to properly inspect the pelvis.

At prima faces, a risk below 1.5% seems too low to justify any prophylactic measure. Regardless of the possible interventions that could reduce this risk, the number of women needed to be treated would be 362 (95%CI: 65-2000). On the other hand, it has to be emphasized that the risk may differ

according to baseline characteristics of the affected women. One may speculate that SHiP could be more frequent in women carrying endometriotic lesions that could be identified by ultrasound before initiating IVF, in particular deep peritoneal lesions. To note, when exclusively focusing on women carrying these lesions in our series, the risk was substantially higher (Table 3). Unfortunately, the sample size of this subgroup of women is insufficient for precise estimates (the 95%CI ranged from 0.4% to 11.8%). Larger series exclusively focusing on women with deep lesions are necessary to disentangle the magnitude of the risk of SHiP in these women. In this regard, it has also to be underlined that, in general, risk factors for SHiP are yet unclear. Multicenter efforts aimed at recruiting a high number of SHiP cases are required to address this point. Identify a population of established elevated risk of SHiP would consent a more precise counseling and could delineate the characteristics of women who may benefit from prophylactic interventions. To note, at present, only surgery may be foreseen to be of potential benefit. On the other hand, indication to surgery with the exclusive aim of preventing SHiP cannot currently be given. We lack scientific data to support this view and systematically exposing women to risks in the absence of robust evidence of benefits is questionable. Indeed, the risk of both major and minor surgical complications is not negligible in women with endometriosis, in particular for those carrying deep peritoneal lesions or those with a history of repeated surgery (9,16). The most troublesome complications include fistula, infections, bladder dysfunction and rectal incontinence (9,17). Robust evidence to guide the indication to surgery to prevent SHiP will take time prior to become available. In the meantime, we advocate a wise and shared approach with the women that starts with an in-depth and comprehensive evaluation. The pros and cons of approaches like IVF straight, surgery and then IVF if natural pregnancy does not occur and surgery then immediate IVF without attempting to become pregnant naturally have to be carefully balanced. In our opinion, the risk of SHiP and the possible preventive role of surgery also merits consideration in this multifaceted evaluation.

Some limitations of our study deserve to be commented. Firstly, our study is retrospective. This study design inevitably exposes our findings to some inaccuracies. On the other hand, a prospective recruitment was not feasible given the necessity to select a very high number of cases. Despite being a referral center, we had to review patients over a 9 years period to achieve an informative number of subjects. Secondly, the study is monocentric. Even if we were able to achieve the scheduled sample size alone, it has to be recognized that inferences of findings obtained in a single center could be exposed to criticisms. Local policies of endometriosis management vary significantly among centers and countries. In particular, the role of surgery remains highly debated because of the paucity of clinical trials (18). To note, most of the patients included in our series were previously treated in other centers and the general characteristics of our population do not even reflect our policies. As a consequence, characteristics of women scheduled for IVF may markedly differ among centers in terms of presence and characteristics of endometriotic lesions and history and type of previous surgery. Multicenter international surveys are required to overcome this limitation. Thirdly, the histological confirmation of the diagnosis of endometriosis is lacking in one third of cases. However, even if we cannot totally exclude some misdiagnoses, we believe that this may be an exceptional event. The accuracy of the sonographic diagnosis of endometriosis is well established. According to a recent Cochrane meta-analysis, transvaginal ultrasound for ovarian endometriomas has a sensitivity of 93% (95%CI: 87-99%) and a specificity of 96% (95%CI: 92-99%) (19). Moreover, another recent meta-analysis about deep endometriosis compared the performance of TVS and MRI for the detection of DIE involving the rectosigmoid. They found that the accuracy of the two techniques were similar, with 85% sensitivity for both MRI and TVS and specificity of 95% and 96%, respectively (20).

On the other hand, our study has some relevant strengths. Firstly, in contrast to previous evidence, the study was designed a priori. We selected the cohort of women to be studied and then identified the possible cases of SHiP. From a methodological perspective, this approach is less biased and

should be considered more reliable to estimate the incidence this complication. Studies describing case reports and subsequently estimating the frequency of the event inevitably overestimate the frequency of SHiP. Secondly, the follow-up was extremely complete. None of the selected women was lost to follow-up. This achievement was favoured by the local Italian legislation. Systematic follow-up of IVF pregnancies up to delivery is indeed mandatory in our country since 2004 and it is actively performed (including the possibility to contact the partner). This is particularly important for a rare and life-threatening condition like SHiP. Thirdly, the sample size was large and allowed us to shrink the 95%CI to less than 1.5% for the whole cohort. Subgroup analyses, however, were inevitably less precise.

In conclusion, in the general population of women with endometriosis achieving pregnancy with IVF, the risk of developing SHiP is very low. However, this risk may markedly differ according to baseline characteristics of the affected subjects. The presence of deep peritoneal lesions in particular represents a source of concern. Future studies should precisely determine risk factors for SHiP in order to identify a subgroup of women at highest risk, a subgroup for whom considering prophylactic surgery.

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Table 1. Baseline characteristics of the study group (n=362).

Characteristics	Number (%) Mean ± SD
Age (years)	35.3 ± 3.7
BMI (Kg/m^2)	21.5 ± 3.2
Smoking	77 (22%)
Previous deliveries	40 (11%)
Previous miscarriages	46 (13%)
Previous ectopic pregnancies	12 (3%)
Duration of infertility (years)	3 ± 2
Day 3 serum FSH (IU/ml)	7.8 ± 3.1
AMH (ng/ml)	2.6 ± 2.6
AFC	11.0 ± 6.6

Table 2. Characteristics of previous or present endometriosis at the time of the IVF cycles (n=362)

Characteristics	Number (%)
Previous surgery for endometriosis in general	238 (66%)
Previous excision of endometriomas	187 (50%)
Unilateral adnexectomy	5 (1%)
Previous removal of deep peritoneal nodules	66 (18%)
Endometriosis at ultrasound prior to IVF	231 (64%)
Unilateral endometrioma	163 (45%)
Bilateral endometriomas	41 (11%)
Endometriomas' diameter (mm)	22 ± 10
Endometriomas ≥ 40 mm	14 (7%)
Deep peritoneal nodules	44 (12%)
Nodules' diameter (mm)	16 ± 6
Deep peritoneal nodules ≥ 20 mm	13 (29%)
Adenomyosis at ultrasound prior to IVF	62 (17%)

The sum of percentages could exceed 100% because women could belong to more than one group.

Some forms of endometriosis could be detected at the time of IVF in 107 previously operated women (30% of the total).

Table 3. Frequencies and 95%CIs of SHiP in different subgroups of patients.

Subgroup	n / N	Rate	95%CI
History of surgery	0 / 238	0.0%	0.0-1.6%
Endometriosis at ultrasound	1 / 231	0.4%	<0.1-2.4%
Endometriomas at ultrasound	1 / 204	0.5%	<0.1-2.7%
Deep peritoneal lesions at ultrasound	1 / 44	2.3%	0.4-11.8%
Fresh cycle	1 / 244	0.4%	<0.1-2.3%
Frozen cycle	0 / 118	0.0%	0.0-3.2%
Whole cohort	1 / 362	0.3%	<0.1-1.5%