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PII: S0301-2115(17)30480-3
DOI: https://doi.org/10.1016/j.ejogrb.2017.10.012
Reference: EURO 10086

To appear in: EURO

Received date: 13-6-2017
Revised date: 23-9-2017
Accepted date: 10-10-2017

Please cite this article as: { https://doi.org/}

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REVISED COPY EJOGRB-17-16261

SPONTANEOUS HEMOPERITONEUM IN PREGNANCY (SHIP) AND ENDOMETRIOSIS –
A SYSTEMATIC REVIEW OF THE RECENT LITERATURE

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TOTAL WORD COUNT: 2361 words (excl. title page, abstract and references)
NO. OF FIGURES: 2
NO. OF TABLES: 2

CONDENSATION

SHIP is a serious complication of pregnancy, associated with adverse pregnancy outcomes. Since preventive measures are lacking, growing awareness and timely recognition is advocated, especially in women diagnosed with endometriosis.
(STANDARD) ABSTRACT

Title: Spontaneous Hemoperitoneum in Pregnancy (SHiP) and Endometriosis – A Systematic Review of the Recent Literature.

Authors: Marit C.I. Lier MD; Romana F. Malik MD; Johannes C.F. Ket; Cornelis B. Lambalk MD, PhD; Ivo A. Brosens MD, PhD; Velja Mijatovic MD, PhD.

Abstract: Spontaneous Hemoperitoneum in Pregnancy (SHiP), an unprovoked (nontraumatic) intraperitoneal bleeding in pregnancy (up to 42 days postpartum), is associated with serious adverse pregnancy outcomes. To evaluate the clinical consequences of SHiP and its association with endometriosis, a systematic review was conducted according to the PRISMA guidelines. PubMed, Embase.com and Thomson Reuters/Web of Science were searched for articles published since the latest review (August 2008) until September 2016.

After assessment for eligibility, forty-four articles were included in this systematic review, describing 59 cases of SHiP. Endometriosis was present in 33/59 cases (55.9%), most often diagnosed prior to pregnancy. An association between the severity of SHiP and the stage of endometriosis could not be found. In the majority of cases, SHiP occurred in the third trimester of pregnancy (30/59 cases (50.8%)); women presented with (sub)acute abdominal pain (56/59 cases (94.9%)), hypovolemic shock (28/59 cases (47.5%)) and/or a decreased level of hemoglobin (37/59 cases (62.7%)). Signs of fetal distress were observed in 24/59 cases (40.7%). Imaging confirmed free peritoneal fluid in (37/59 cases (62.7%)). At time of surgery active bleeding was revealed in 51/56 cases (91.1%), originating from endometriotic implants (11/51 cases (21.6%)), ruptured utero-ovarian vessels (29/51 cases (56.8%)), hemorrhagic nodules of decidualized cells (1/51 cases (2.0%)) or a combination (10/51 cases (19.6%)). Median amount of hemoperitoneum was 1600mL (IQR 1000mL–2500mL). From the 45/59 cases (76.3%) in which surgical interventions was carried out during pregnancy, 7/45 cases
In conclusion, SHiP is a very serious complication of pregnancy, highly associated with adverse pregnancy outcomes and particularly relevant to women with endometriosis. Currently preventive measures are lacking, therefore increasing the awareness and recognition of SHiP is crucial to improve pregnancy outcomes.

KEYWORDS (3-5 key words) Pregnancy, Hemoperitoneum, Endometriosis

INTRODUCTION

Spontaneous Hemoperitoneum in Pregnancy (SHiP), an unprovoked (nontraumatic) intraperitoneal bleeding in pregnancy (up to 42 days postpartum), is associated with serious adverse pregnancy outcomes. (1, 2) SHiP was first described in the late 18th century (3) and since then high maternal mortality rates were reported (Williams 1904 (4), 18/32 cases (56%); Hodgkinson et al. 1950 (5), 37/75 cases (49%)). Rates were even higher in women giving birth. (5) In the last decades of the 20th century, the maternal mortality rate decreased significantly (Ginsburg et al. 1987 (1), 1/28 cases (4%); Brosens et al 2009 (2), 0/25 cases (0%)), however perinatal mortality remained substantially high (10/28 cases (36%)). (2)

Although the exact etiology of SHiP is still unknown, endometriosis and the use of controlled ovarian hyperstimulation for artificial reproductive techniques (ART) seems to be contributive factors in the occurrence and severity of SHiP. (2, 6) This is of importance, as ART is more frequently used in women diagnosed with endometriosis (7). To gain a better insight in this potentially life-threatening complication of pregnancy and evaluate the clinical consequences, a systematic review of the recent literature published since the latest review of Brosens et al. in 2009 (2), was conducted.

MATERIALS AND METHODS
A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement (www.prisma-statement.org). For this paper, no approval of the institutional review board was required, since data were extracted from previously published reports.

SEARCH STRATEGY

PubMed, Embase.com and Thomson Reuters/Web of Science were searched from August 2008 (2) (by MCIL and JCFK). PubMed and Embase.com up to September 15, 2016 and Thomson Reuters/Web of Science up to September 21, 2016. The following terms were used (including synonyms and closely related words) as index terms or free-text words: ‘haemoperitoneum’, ‘rupture’, ‘blood vessels’, ‘spontaneous’, ‘pregnancy’, ‘post-partum’, ‘labor’ and ‘endometriosis’. Duplicate articles were excluded. Reference lists of the retrieved publications were checked for relevant articles. The full search strategies for all databases can be found in the Supplementary Information (appendix I).

ELIGIBILITY CRITERIA

All case reports, case series, cross-sectional studies, prospective and retrospective cohort studies were considered for inclusion when they reported on spontaneous intra-abdominal bleedings in pregnancy, labor or within six weeks of the postpartum period. Only full-text reports were considered for inclusion, congress abstracts and poster-presentations were excluded. The search was limited to articles published in English. Articles reporting on cases of uterine ruptures, ectopic pregnancies, caesarean scar pregnancies, placental abnormalities, uterine abnormalities, artery (pseudo)aneurysm ruptures, trauma, hemolysis elevated liver enzymes and low platelets (HELLP) syndrome, pre-eclampsia, liver- or splenic rupture, malignancies, ruptured ovarian cysts and postpartum hemorrhage (PPH) were excluded (non-SHiP bleedings). Eligibility assessment of the retrieved articles was performed by two authors (MCIL and RFM) independently (not blinded). In case of doubt or disagreement regarding inclusion or exclusion, a third author (VM) was consulted to establish consensus. The flow diagram of the systematic literature search is shown in [figure 1].

DATA EXTRACTION

Data extraction was performed by two authors independently (MCIL and RFM). Items that were included reported about general patient characteristics, clinical presentation, diagnostics, characteristics of the bleeding, treatment, perinatal and maternal outcomes. Authors were contacted in case additional information was required. Since only case reports and case-series were found, the quality of the obtained studies was not assessed.
**STATISTICAL ANALYSIS**

Categorical variables were summarized by frequencies and percentages. Continuous variables were summarized by mean and standard deviation in case of normal distribution and median and inter-quartile range in case of a non-normal distribution. Categorical variables were compared between group with and without endometriosis using chi-square test or Fisher’s exact test in case expected cell count was below 5 for at least one cell. Continuous variables were compared between groups using the independent samples t-test in case of a normal distribution and the Mann-Whitney test in case of non-normal distribution. Two sided p-values < 0.05 were considered to indicate statistical significance. IBM Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp., USA) was used for statistical analyses.

**RESULTS**

**IDENTIFICATION OF THE LITERATURE**

The initial literature search identified 2132 records. Five additional records were identified by checking other sources and references lists. After removal of the duplicates, 1885 records were screened for eligibility; of which 126 records were selected for full-text assessment. From these records 82 articles were excluded for the following reasons; not written in English (n=13), no report of primary data (n=2), no availability of full-text article (in case of congress abstracts or poster-presentations, n=13), reported on other causes of intra-abdominal bleeding (“non-SHiP bleedings” as mentioned in the in- and exclusion criteria, n=58).

Eventually forty-four articles were included in the analysis (9-52). All articles that were eligible for inclusion were either case reports or case-series and described a total of 59 cases of SHiP. A summary of the cases is given in [table 1].

**PATIENT CHARACTERISTICS**

Nulliparous women represented 40/59 cases (67.8%), 7/59 (11.9%) being twin pregnancies. 16/59 pregnancies (27.1%) were conceived after ART. Mean age was 31.5 (SD ±4.7). Endometriosis was present in 33/59 cases (55.9%; 6.1% rASRM stage I-II; 75.7% rASRM stage III-IV; 18.2% rASRM stage unknown); the majority of these women 22/33 cases (66.7%) were known to have surgically confirmed endometriosis, prior to pregnancy.

**CLINICAL PRESENTATION & DIAGNOSTICS**
The onset of SHiP varied from 6 weeks of gestation up to 30 days postpartum, in the majority of cases SHiP occurred in the third trimester of pregnancy (30/59 cases (50.8%)). Women presented with (sub)acute abdominal or flank pain (56/59 cases (94.9%)) in combination with signs of hypovolemic shock (28/59 cases (47.5%)) and/or a decreased level of hemoglobin (37/59 cases (62.7%)). Signs of fetal distress (abnormal or absent fetal cardiac activity) were observed in 24/59 cases (40.7%). Free peritoneal fluid was confirmed by imaging modalities in 37/59 cases (62.7%); most frequently visualized by ultrasound sonography (US; 33/37 cases (89.2%)).

**INTERVENTION**

Surgical intervention was performed in 56/59 cases (94.9%); carried out for maternal reasons (39/56 cases (69.6%)), fetal distress (2/56 cases (3.6%)) or a combination of both (15/56 cases (26.8%)). In one case a hemoperitoneum was confirmed on autopsy (1/59 cases (1.7%)). In two cases expectant management was chosen (2/59 cases (3.4%)). At the time of surgery active bleeding was revealed in 51/56 cases (91.1%); originating from endometriotic implants (11/51 cases (21.6%)), ruptured utero-ovarian vessels (29/51 cases (56.8%)), hemorrhagic nodules of decidualized cells (1/51 cases (2.0%)) or a combination of these (10/51 cases (19.6%)). Bleeding sites were most often situated on the posterior surface of the uterus or the utero-ovarian vessels located in the parametrium [figure 2]. In 15/56 cases (26.8%) a biopsy was taken during the surgical intervention; histological reports described signs of decidualized endometriosis (10/15 biopsies (66.7%)), deciduosis (2/15 biopsies (13.3%)); endometriosis (2/15 biopsies (13.3%)) or hemorrhagic infiltration (1/15 biopsies (6.7%)) in the specimens. The median amount of hemoperitoneum was 1600mL (IQR 1000mL–2500mL). A laparotomy was the initial intervention in 50/59 cases (84.7%). In 6/59 cases (10.2%) a laparoscopy was performed, although in half of these cases conversion to a laparotomy was needed due to blurred vision or the inability to reach the bleeding site. Of the cases in which a laparoscopic intervention was successful, one was carried out in the early stage of pregnancy (15 weeks of gestation), the other two in the postpartum period. Suture ligation was most frequently applied to achieve hemostasis, a hysterectomy had to be performed in 4/59 cases (6.8%). An association between the severity of the bleeding and the stage of endometriosis could not be found (p=0.43).

**MATERNAL AND PERINATAL OUTCOMES**

From the 45/59 cases (76.3%) in which surgical interventions was carried out during pregnancy, seven cases reported a successful continuation of pregnancy (7/45 cases (15.6%); SHiP first presented between 15 – 32 weeks of gestation). In five of these cases (5/45 cases (11.1%)) pregnancy could continue beyond 37 weeks. Recurrence of SHiP was described in five cases (5/59 cases (8.5%).
recurrence rate); all recurrences, except for one, were reported during the same pregnancy or postpartum period. Maternal death was reported once (1/59 cases (1.7%)): a 21 year old primigravida presented at 29 weeks of gestation with an acute pain in the abdomen and signs of hypovolemic shock; she was dead on arrival at the hospital (23). 14/59 cases reported on fetal or neonatal death (including four twin pregnancies), resulting in a perinatal mortality rate of 26.9% (18/67 fetus). Severe neonatal morbidity was reported in 3/67 infants (4.5%); two infants were admitted to the neonatal intensive care unit (NICU) due to asphyxia and cerebral ischemia. One newborn showed signs of severe respiratory distress. Perinatal mortality and morbidity rates were similar between women with and without endometriosis, as shown in [table 2].

COMMENTS

In this systematic review we evaluated the clinical course and pregnancy outcomes of SHiP. This overview can be used as a guidance for medical decision making and preconception counseling of women with endometriosis and a future child wish. It should however be noticed that endometriosis-associated acute hemoperitoneum outside pregnancy has also been described in a few cases and presents with similar clinical signs. (53)

SHIP AND ENDOMETRIOSIS

Although it is believed that pregnancy has a favorable influence on endometriosis, women should also be informed about the possible obstetric and postpartum complications that can occur. In general, the negative influence of endometriosis on pregnancy outcomes is currently a growing area of concern. A recent literature review discussed the wide spectrum of negative obstetrical events possibly related to endometriosis and adenomyosis. (54) The left lateral predisposition that endometriotic implants show (55, 56) and the fact that bleeding sites of SHiP are more frequently found in the left lateral hemipelvis, is of supportive evidence for the association between SHiP and endometriosis. Despite the growing evidence that endometriosis is a causative factor in the development of SHiP, it is still not possible to determine which patients are at risk for developing SHiP and no evidence exists whether treatment of endometriosis or surgery prior to pregnancy may be a preventive measure to lower the risk of SHiP bleedings. Moreover extensive surgery can also have negative consequences by further weakening of fragile intra-abdominal structures and adhesions formation; one case described a ruptured utero-ovarian vein probably as a late complication of laparoscopic resection of deep endometriosis prior to pregnancy. (13)

CLINICAL PRESENTATION & DIAGNOSTICS
Pregnant women presenting with (sub)acute abdominal or flank pain should be suspected of SHiP, which remains the major presenting symptom for women with and without endometriosis. Depending on the severity of the intraperitoneal bleeding, the abdominal pain can be accompanied by signs of hypovolemic shock, decreased level of hemoglobin or signs of fetal distress. In both groups, imaging modalities seems to be of added value for the detection of hemorrhagic peritoneal fluid. Better equipment, training and experience of radiologists may have contributed to this improved detection. Especially ultrasound sonography is an easy first-line examination tool which can be helpful to quantify the amount and occasionally the origin of the bleeding, by which misdiagnosis can be avoided.

**INTERVENTION**

Management of SHiP depends on the clinical presentation as a result of the extent of the intra-abdominal hemorrhage and the gestational age. A surgical approach is often unavoidable, but expectant management can be considered when signs of hypovolemic shock or fetal distress are absent, especially in the postpartum period. However, since spontaneous intra-abdominal hemorrhages in pregnancy are most frequently of venous origin (2) and therefore of substantial quantity, a laparotomy is commonly the first-choice treatment. Additionally, surgery gives the opportunity to establish the presence of endometriosis, in approximately 33% of the SHiP cases endometriosis was not diagnosed until pregnancy complications occurred. It is recommended to have a histological confirmation of endometriosis and take a biopsy from the bleeding lesions, since decidual changes of endometriotic tissue may impede the diagnosis. (2, 57, 58)

Successful treatment with uterine artery embolization (UAE) has only been described in cases of uterine artery aneurysms (59), but could theoretically also be applied (with caution) in cases of SHiP with an arterial origin. Expectant management, combined with fluid resuscitation, can be considered when women are hemodynamic stable without signs of fetal distress. However, recurrence of SHiP is noted and close monitoring is advised.

**MATERNAL AND PERINATAL OUTCOMES**

Although in women with endometriosis, SHiP presented earlier in pregnancy, no significant differences in perinatal or maternal outcomes were observed between both groups. However, perinatal mortality and morbidity remains a major problem of SHiP and does not seem to improve over the last decades. (1, 2) To improve the outcome it seems necessary to create further awareness, in order to facilitate timely recognition and diagnosis of SHiP. Recently several countries took the initiative to register the occurrence of SHiP in a prospective way, gathered in a multinational
collaboration (INOSS) (60), with the aim to further understand this rare complication of pregnancy and get insight in the exact prevalence and recurrence rate of SHiP.

**STRENGTH AND LIMITATIONS**

This review was systematically conducted according to the PRISMA guidelines (8), ensuring methodological quality. Since this systematic review consists of case reports mainly, publication bias can be involved. Especially a potential bias regarding cases of SHiP in pregnancies conceived after ART or in women diagnosed with endometriosis. Since no other studies were available, the use of case reports was inevitable. Despite the use of all available cases, the sample size remained insufficient to detect small differences between groups. However, with 59 unique cases of SHiP, this systematic review is the largest inventory of these cases in the literature.

**CONCLUSIONS**

SHiP is a very serious complication of pregnancy and highly associated with adverse pregnancy outcomes. In particularly perinatal mortality and morbidity remains a major problem of SHiP and has not improved over the last decades. Endometriosis is the major risk factor for the occurrence of SHiP. Since the number of pregnant women with endometriosis is increasing, it is important to acknowledge the link between SHiP and endometriosis. An association between the severity of SHiP and the stage of endometriosis could not be established. As preventive measures and evidence-based interventions are currently not available, increasing the awareness and recognition of SHiP is crucial to further improve pregnancy outcomes.

**ACKNOWLEDGMENTS**

We gratefully acknowledge P.M. van de Ven PhD (Department of Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam) for his excellent assistance with the statistical data analysis.

**CONFLICT OF INTEREST STATEMENT**

The authors reports no conflicts of interest.

**FINANCIAL SUPPORT**

No financial support was provided.

**CONTRIBUTION TO AUTHORSHIP**
MCIL – Contributed to conception and design of the study. Contributed to the acquisition, analysis and interpretation of data. Drafted the manuscript.

RFM - Contributed to conception and design of the study. Contributed to the acquisition of data. Critically revised the manuscript.

JCFK – Contributed to design of the study and developed the search strategy. Critically revised the manuscript.

CBL – Contributed to conception and design of the study and interpretation of data. Critically revised the manuscript.

IAB - Contributed to conception and design of the study and interpretation of data. Critically revised the manuscript.

VM - Contributed to conception and design of the study. Contributed to the acquisition and interpretation of data. Critically revised the manuscript.

All authors agree about the content of the paper and approved the final version of the manuscript.

REFERENCES


FIGURE LEGENDS

Figures may be reproduced in color on the Web. Black-and-white versions are attached to this manuscript for printing purposes.

Title [Figure 1]

Figure 1. PRISMA flow diagram

Legend

PRISMA flow diagram of the systematic literature search. n = number.

Title [Figure 2]

Figure 2. Map bleeding sites

Legend

Map of the bleeding sites.

Footnote

In five cases no bleeding points could be identified.
[FIGURE 1] PRISMA flow diagram

Records identified through database searching  
\( n = 21231 \)

Additional records identified through other sources  
\( n = 51 \)

Records after duplicates removed  
\( n = 252 \)

Records screened  
\( n = 1885 \)

Records excluded based on title and abstract  
\( n = 1759 \)

Full-text articles assessed for eligibility  
\( n = 126 \)

Full-text articles excluded  
\( n = 82 \)
- No full text available  
  \( n = 9 \)
- Non-English language  
  \( n = 13 \)

Studies included in quantitative synthesis  
\( n = 44 \)
Figure 2
TABLE LEGENDS

**Title [Table 1]**

**Table 1. Summary of cases**

<table>
<thead>
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<th>Case (no.)</th>
<th>Ref.</th>
<th>Episode</th>
<th>Age (y)</th>
<th>Parity</th>
<th>Endometriosis</th>
<th>Stage (ASRM)</th>
<th>ART (+/-)</th>
<th>GA SHIP (wk+d)</th>
<th>Intervention</th>
<th>HP (mL)</th>
<th>Biopsy (+/-)</th>
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<th>Mode of delivery</th>
<th>Perinatal mortality</th>
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<td>+</td>
<td>33+2</td>
<td>LT</td>
<td>3000</td>
<td>-</td>
<td>33+2</td>
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<td>24</td>
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<td>+</td>
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<td>LT</td>
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<td>29</td>
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**Legend**

- CS: Cesarean section
- LS: Lower segment
- EM: External version
- LT: Lower uterine segment
- D&C: Dilatation and curettage
- pp: Premature placenta
- Vag.: Vaginal delivery
- n.a.: Not available
- +/-: Unknown
ART = assisted reproductive techniques; rASRM = revised American Society for Reproductive Medicine; CS = caesarean section; d = day; D&C = dilation and curettage; EM = expectant management; HP = hemoperitoneum; (L) = labor; LS = laparoscopy; LT = laparotomy; mL = milliliters; mort. = mortality; no. = number; n.a. = not applicable; pp = postpartum; ref. = reference; vag. = vaginal delivery; wk = week; y = years. * = twin pregnancy.
### Table 2. SHiP characteristics endometriosis vs. no endometriosis

<table>
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<th></th>
<th>Endometriosis (n=33)</th>
<th>No endometriosis (n=26)</th>
<th>p-value</th>
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<td><strong>Age (years) mean (standard deviation)</strong></td>
<td>32.5 (± 4.6)</td>
<td>30.2 (±4.9)</td>
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<td><strong>Conceived after ART number of cases (%)</strong></td>
<td>13 (39.4%)</td>
<td>3 (11.5%)</td>
<td>0.017**</td>
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<td><strong>Singleton pregnancy number of cases (%)</strong></td>
<td>28 (84.8%)</td>
<td>24 (92.3%)</td>
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<td><strong>Gestational age SHiP (weeks median (25th- 75th percentile))</strong></td>
<td>28.0 (21.0–33.0)</td>
<td>32.0 (29.0 – 35.5)</td>
<td>0.008**</td>
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<td><strong>Gestational age delivery (weeks median with 25th– 75th percentile)</strong></td>
<td>33.5 (28.3 – 37.8)</td>
<td>34.0 (30.0 – 37.5)</td>
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<td><strong>Preterm birth &lt; 37 weeks number of cases (%)</strong></td>
<td>19 (57.6%)</td>
<td>16 (61.5%)</td>
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<td><strong>Amount hemoperitoneum (mL median (25th– 75th percentile))</strong></td>
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<tr>
<td><strong>Maternal mortality number of cases (%)</strong></td>
<td>0 (0%)</td>
<td>1 (3.8%)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Perinatal mortality number of cases (%)</strong></td>
<td>10 (29.4%) (n=34)*</td>
<td>4 (15.4%)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Severe perinatal morbidity number of cases (%)</strong></td>
<td>1 (2.9%) (n=34)*</td>
<td>2 (3.8%)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Recurrence SHiP number of cases (%)</strong></td>
<td>5 (15.2%)</td>
<td>0 (0%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Legend

ART = assisted reproductive techniques; mL = milliliters; n = number. * including second episode of SHiP (recurrence) in consecutive pregnancy (Lier et al. [2017] Case VI). ** p-value = < 0.05