European Journal of Obstetrics & Gynecology and Reproductive Biology 219 (2017) 57–65

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

# Spontaneous hemoperitoneum in pregnancy (SHiP) and endometriosis — A systematic review of the recent literature

Marit C.I. Lier[a,*], Romana F. Malik[a], Johannes C.F. Ket[b], Cornelis B. Lambalk[a], Ivo A. Brosens[c], Velja Mijatovic[a]

[a] VU University Medical Center, Endometriosis Center VUmc, Amsterdam, The Netherlands
[b] Vrije Universiteit Amsterdam, Medical Library, Amsterdam, The Netherlands
[c] Leuven Institute for Fertility and Embryology, Leuven, Belgium

ARTICLE INFO

*Article history:*
Received 13 June 2017
Received in revised form 23 September 2017
Accepted 10 October 2017

*Keywords:*
Pregnancy
Hemoperitoneum
Endometriosis

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 1600 mL (IQR 1000mL–2500 mL). From the 45/59 cases (76.3%) in which surgical interventions was carried out during pregnancy, 7/45 cases (15.6%) reported a successful continuation of pregnancy. 5/59 cases reported recurrence of SHiP (recurrence rate 8.5%). The perinatal mortality rate was 26.9% (18/67 fetus), one maternal death was reported (1/59 cases (1,7%)).

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.



**Contents**



* Corresponding author at: VU University Medical Center, Endometriosis Center VUmc De Boelelaan 1118, PK5X194, 1081HZ Amsterdam, The Netherlands.
*E-mail address:* ma.lier@vumc.nl (M.C.I. Lier).

https://doi.org/10.1016/j.ejogrb.2017.10.012
0301-2115/

## 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.

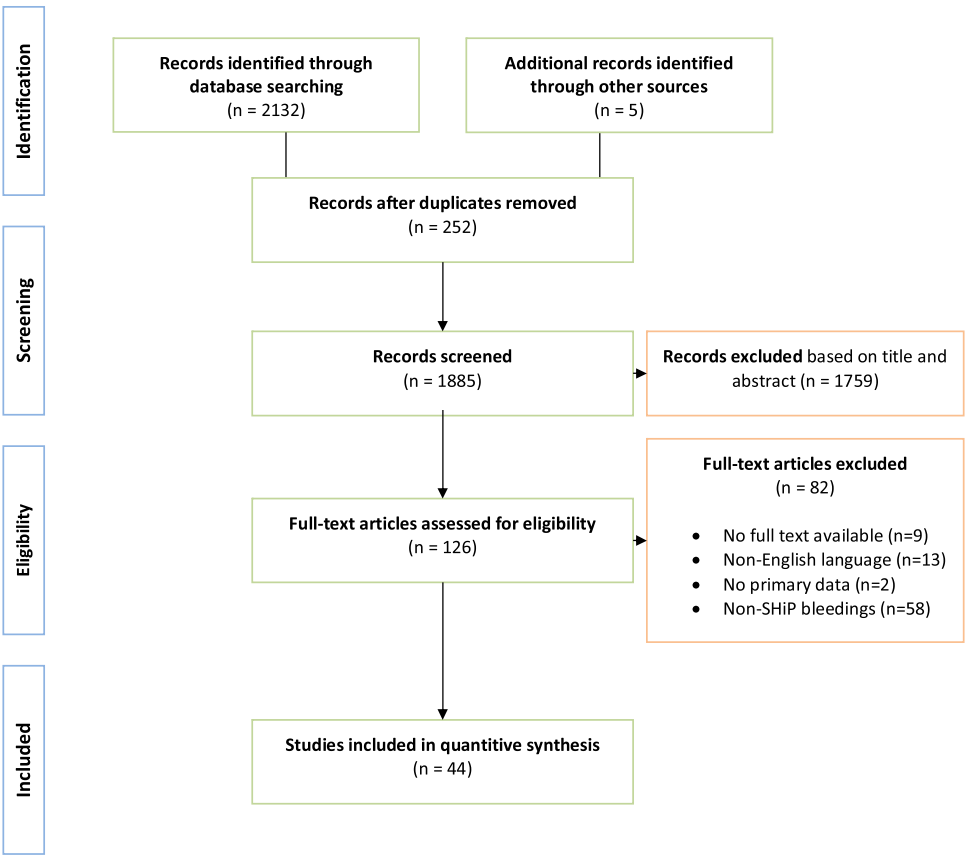


**Fig. 1.** PRISMA flow diagram.
PRISMA flow diagram of the systematic literature search. n = number.

**Table 1**
Summary of cases.

| Case (no.) | Ref. | Episode | Age (y) | Parity | Endometriosis | Stage (rASRM) | ART (+/−) | GA SHiP (wk + d) | Intervention | HP (mL) | Biopsy (+/−) | GA delivery (wk + d) | Mode of delivery | Perinatal mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Roche et al. [9] | * | 43 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 33 + 2 | LT | 3000 | – | 33 + 2 | CS | Yes (2×) |
| 2 | Bouet et al. [10] | | 33 | 0 | No | n.a. | + | 24 | LT | 700 | + | 24 | CS | Yes |
| 3 | Moreira et al. [11] | | 39 | 2 | No | n.a. | – | pp + 0 | LT | 3000 | – | 40 | Vag. | No |
| 4 | Pezzuto et al. [12] | | 40 | 0 | Yes, after pregnancy | Unknown | – | 15 | LS | 3600 | + | 38 | CS | No |
| 5 | Wada et al. [13] | | 31 | 2 | Yes, prior to pregnancy | Severe: III/IV | – | pp + 0 | LT | 2490 | – | 37 | Vag. | No |
| 6 | Zhang et al. [14] | I * | 38 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 29 | LT | 3100 | – | 29 | CS | Yes (2×) |
| 7 | | II | 35 | 0 | Yes, prior to pregnancy | Unknown | + | 35 | LT | 1700 | – | 35 | CS | No |
| 8 | | III | 34 | 1 | No | n.a. | + | 30 | LT | 1500 | – | 30 | CS | No |
| 9 | Bloom et al. [15] | | 28 | 0 | No | n.a. | – | 34 + 4 | LT | 1500 | – | 34 + 5 | Vag. | No |
| 10 | Brouckaert et al. [16] | | 33 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 17 | LT | 3500 | + | 17 | Hysterectomy | Yes |
| 11 | Gao et al. [17] | | 29 | 1 | Yes, during pregnancy | Severe: III/IV | – | pp + 2 | LS | 2000 | + | – | Vag. | No |
| 12 | Giulini et al. [18] | | 31 | 1 | No | n.a. | – | 33 + 2 | LT | 2500 | – | 33 + 2 | CS | No |
| 13 | Grunewald et al. [19] | | 33 | 2 | Yes, during pregnancy | Unknown | – | 27 + 4 | LT | 900 | + | 42 | Vag. | No |
| 14 | Huisman et al. [20] | | 33 | 0 | No | n.a. | – | 36 | LT | 1000 | – | 36 | CS | No |
| 15 | Kim et al. [21] | I * | 33 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 33 | LT | 2000 | – | 33 | CS | No (2×) |
| 16 | | II | 28 | 0 | Yes, during pregnancy | Unknown | – | 25 | LT | 1000 | – | 25 + 6 | CS | No |
| 17 | | III | 37 | 1 | Yes, prior to pregnancy | Severe: III/IV | – | pp + 0 | LT | | – | 40 | Vag. | No |
| 18 | | IV | 29 | 0 | Yes, prior to pregnancy | Unknown | + | 40 + 6 (L) | LT | | – | 40 + 6 | CS | No |
| 19 | Shahnewaj et al. [22] | | 26 | 0 | No | n.a. | – | >30 | LT | 2000 | – | >30 | CS | Yes |
| 20 | Kapila [23] | | 21 | 0 | No | n.a. | – | 29 | Autopsy | | – | 29 | n.a. | Yes |
| 21 | Nakaya et al. [24] | | 25 | 0 | No | n.a. | – | 28 + 5 | LT | 850 | – | 28 + 5 | CS | No |
| 22 | Williamson et al. [25] | | 37 | 0 | Yes, after pregnancy | Severe: III/IV | – | 37 | EM | | – | 37 | Vag. | Yes |
| 23 | Al Qahtani [26] | | 37 | 4 | No | n.a. | – | 38 | LT | 2500 | – | 38 | CS | No |
| 24 | Boztosun et al. [27] | | 25 | 0 | Yes, during pregnancy | Mild: I/II | – | pp + 0 | LT | 1500 | + | 38 | Vag. | No |
| 25 | Kondoh et al. [28] | | 31 | 0 | No | n.a. | – | 29 | LT | 2000 | + | 29 | CS | No |
| 26 | Maya et al. [29] | | 30 | 1 | No | n.a. | – | 29 | LT | 3500 | – | 37 | CS | No |
| 27 | Munir et al. [30] | | 32 | 2 | No | n.a. | – | 38 | LT | 3000 | – | 38 | CS | No |
| 28 | De Vincenzo et al. [31] | | 33 | 0 | Yes, during pregnancy | Severe: III/IV | – | 24 | LT | 2500 | + | 24 | CS | Yes |
| 29 | Doger et al. [32] | * | 26 | 0 | No | n.a. | + | 32 | LT | 400 | – | 32 | CS | No (2×) |
| 30 | Duhan et al. [33] | | 24 | 0 | No | n.a. | – | pp + 0 | LT | 1500 | – | 40 | Vag. | No |
| 31 | Fan et al. [34] | | 30 | 0 | No | n.a. | – | 28 | LT | 1000 | + | 28 | CS | Yes |
| 32 | Nguessan et al. [35] | * | 33 | 0 | No | n.a. | – | 35 | LT | 1100 | – | 35 | CS | No (2×) |
| 33 | Aggarwal et al. [36] | * | 31 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 21 + 6 | LT | 2200 | + | 22 + 2 | CS | Yes (2×) |
| 34 | Black et al. [37] | | 37 | 1 | No | n.a. | – | pp + 7 | LS | 2500 | – | 38 + 6 | Vag. | No |
| 35 | Diaz-Murillo et al. [38] | | 35 | 0 | No | n.a. | – | 37 | LT | | – | 37 | CS | No |
| 36 | Lim et al. [39] | | 24 | 0 | No | n.a. | – | 37 (L) | LT | 1500 | – | 37 | CS | No |
| 37 | Shi et al. [40] | | 33 | 1 | No | n.a. | – | 32 | LT | 1500 | – | 33 | CS | No |
| 38 | Sreedhar et al. [41] | | 24 | 1 | Unknown | n.a. | – | 32 | LT | 200 | – | 32 | CS | No |
| 39 | Cozzolino et al. [42] | | 33 | 1 | Yes, prior to pregnancy | Mild: I/II | – | 29 | LT | 1500 | – | 29 | CS | No |
| 40 | Farahbakhsh et al. [43] | | 32 | 0 | Unknown | n.a. | – | 30 | LT | 2000 | – | 30 | CS | No |
| 41 | | | 35 | 2 | Unknown | n.a. | – | 32 | LT | 1300 | – | 32 | CS | No |

## 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). [8] 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 in- or exclusion, a third author (VM) was consulted to establish consensus. The flow diagram of the systematic literature search is shown in (Fig. 1).

**Table 1** (*Continued*)

| Case (no.) | Ref. | Episode | Age (y) | Parity | Endometriosis | Stage (rASRM) | ART (+/−) | GA SHiP (wk + d) | Intervention | HP (mL) | Biopsy (+/−) | GA delivery (wk + d) | Mode of delivery | Perinatal mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Fatnassi et al. [44] | | | | | | | | | | | | | |
| 42 | Kekhashan et al. [45] | | 30 | 2 | Unknown | n.a. | – | 34 | LT | 1500 | – | 34 | CS | No |
| 43 | Loh et al. [46] | * | 31 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 21 + 6 | LT | 3000 | + | 22 | CS | Yes (2×) |
| 44 | Mandal et al. [47] | | 22 | 0 | Unknown | n.a. | – | 38 | LT | 850 | – | 38 | CS | No |
| 45 | Zhang et al. [48] | | 25 | 0 | Yes, prior to pregnancy | Severe: III/IV | – | 41 (L) | LT | 1000 | – | 41 | CS | No |
| 46 | Stochino Loi et al. [49] | 1st/2nd | 26 | 0 | Yes, during pregnancy | Severe: III/IV | – | 16/16 + 5 | LS –> LT/LT | 3000/? | – | 16 + 5 | D&C | Yes |
| 47 | Petresin et al. [50] | II | 25 | 0 | Yes, prior to pregnancy | Severe: III/IV | – | 28 + 2 | LT | | – | 28 + 3 | CS | No |
| 48 | Ploteau et al. [51] | | 27 | 0 | Yes, prior to pregnancy | Severe: III/IV | – | 29 | LT | 1500 | – | 29 | CS | Yes |
| 49 | Lier et al. [52] | I | 38 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 19 + 3 | LS –> LT | 3000 | – | 39 | CS | No |
| 50 | Lier et al. [52] | II | 35 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 28 | LT | 600 | + | 28 + 5 | CS | No |
| 51 | Lier et al. [52] | III 1st/2nd | 34 | 2 | Yes, prior to pregnancy | Severe: III/IV | – | 23 + 2/24 + 3 | LT/EM | 1000/n.a. | – | 35 + 5 | CS | No |
| 52 | Lier et al. [52] | IV 1st/2nd | 33 | 0 | Yes, during pregnancy | Severe: III/IV | – | 34 + 2/pp + 12 | LT/LS –> LT | 600/2000 | + | 34 + 2 | CS | No |
| 53 | Lier et al. [52] | V 1st/2nd | 37 | 1 | Yes, prior to pregnancy | Severe: III/IV | – | 40 + 5 (L)/pp + 30 | EM/LS –> LT | n.a./3000 | – | 40 + 5 | Vag. | No |
| 54 | Lier et al. [52] | VI 1st/2nd | 33/36 | 0/1 | Yes, prior to pregnancy | Severe: III/IV | +/+ | 32 + 2/6 + 0 | LT/LS –> LT | 3500/2000 | – | 32 + 2/6 + 0 | CS/D&C | No/Yes |
| 55 | Lier et al. [52] | VII | 28 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 37 + 6 (L) | LT | 100 | – | 37 + 6 | CS | No |
| 56 | Lier et al. [52] | VIII | 37 | 2 | Yes, prior to pregnancy | Unknown | – | 21 | LS –> LT | 2000 | – | 37 | CS | No |
| 57 | Lier et al. [52] | IX | 31 | 0 | Yes, during pregnancy | Severe: III/IV | – | 33 + 5 | LT | 3000 | + | 33 + 5 | CS | No |
| 58 | Lier et al. [52] | X | 27 | 0 | Yes, after pregnancy | Severe: III/IV | – | 37 + 4 (L) | LT | 2500 | – | 37 + 4 | CS | No |
| 59 | Lier et al. [52] | XI | 37 | 0 | Yes, prior to pregnancy | Severe: III/IV | + | 30 + 1 | LT | 1250 | + | 30 + 1 | CS | No |

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.

*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%)). Placental abruption or uterine rupture were often mentioned as differential diagnosis prior to intervention.

*Intervention*

Surgical intervention was performed in 56/59 cases (94.9%); carried out for maternal reasons (39/56 cases (69.6%)), fetal

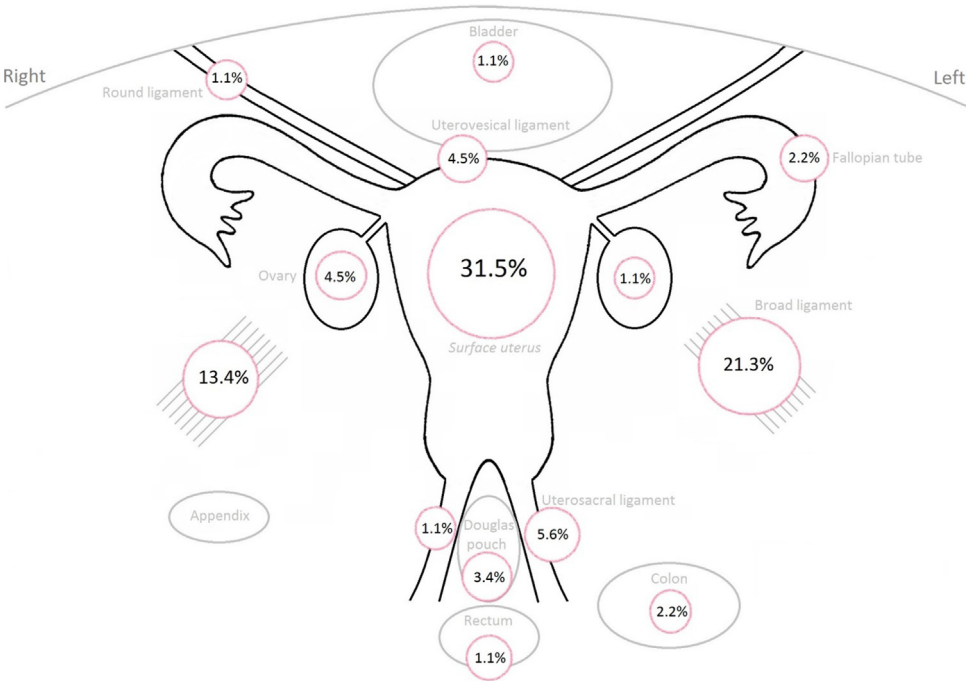


**Fig. 2.** Map bleeding sites.
Map of the bleeding sites.
In five cases no bleeding points could be identified.

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 Fig. 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 1600 mL (IQR 1000mL–2500 mL). 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 and 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

**Table 2**
SHiP characteristics endometriosis vs. no endometriosis.

| | Endometriosis (n = 33) | No endometriosis (n = 26) | p-value |
|---|---|---|---|
| Age (years)<br>*mean (standard deviation)* | 32.5 (± 4.6) | 30.2 (±4.9) | 0.09 |
| Conceived after ART<br>*number of cases (%)* | 13 (39.4%) | 3 (11.5%) | 0.017** |
| Singleton pregnancy<br>Twin pregnancy<br>*number of cases (%)* | 28 (84.8%)<br>5 (15.2%) | 24 (92.3%)<br>2 (7.7%) | 0.38 |
| Gestational age SHiP (weeks)<br>*median (25th- 75th percentile)* | 28.0 (21.0–33.0) | 32.0 (29.0–35.5) | 0.008** |
| Gestational age delivery (weeks)<br>*(median with 25th- 75th percentile)* | 33.5 (28.3–37.8) | 34.0 (30.0–37.5) | 0.77 |
| Preterm birth <37 weeks<br>*number of cases (%)* | 19 (57.6%) | 16 (61.5%) | 0.72 |
| Amount hemoperitoneum (mL)<br>*median (25th- 75th percentile)* | 2000 (1062.5–3000) | 1500 (1000–2375) | 0.15 |
| Maternal mortality<br>*number of cases (%)* | 0 (0%) | 1 (3.8%) | 0.44 |
| Perinatal mortality<br>*number of cases (%)* | 10 (29.4%) (n = 34)* | 4 (15.4%) | 0.20 |
| Severe perinatal morbidity<br>*number of cases (%)* | 1 (2.9%) (n = 34)* | 2 (3.8%) | 0.22 |
| Recurrence SHiP<br>*number of cases (%)* | 5 (15.2%) | 0 (0%) | 0.06 |

ART = assisted reproductive techniques; mL = milliliters; n = number. * including second episode of SHiP (recurrence) in consecutive pregnancy (Lier et al. [52] Case VI).
** p-value = < 0.05.

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.

## 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.

## Conflict of interest statement

The authors reports no conflicts of interest.

## 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.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ejogrb.2017.10.012.

## References

[1] Ginsburg KA, Valdes C, Schnider G. Spontaneous utero-ovarian vessel rupture during pregnancy: three case reports and a review of the literature. Obstet Gynecol 1987;69(3 Pt 2):474–6.
[2] Brosens IA, Fusi L, Brosens JJ. Endometriosis is a risk factor for spontaneous hemoperitoneum during pregnancy. Fertil Steril 2009;92(4):1243–5.
[3] Casaubon. Sur des tumeurs sanguines à la vulve. Recuel périodique de la Societé de Santé a Paris 1797;I(An V):455–74.
[4] Williams JW. Intrapelvic hematoma following labor not associated with lesions of the uterus. Am J Obstet 1904;50:442–55.
[5] Hodgkinson CP, Christensen RC. Hemorrhage from ruptured utero-ovarian veins during pregnancy; report of 3 cases and review of the literature. Am J Obstet Gynecol 1950;59(5):1112–7.
[6] Brosens IA, Lier MC, Mijatovic V, Habiba M, Benagiano G. Severe spontaneous hemoperitoneum in pregnancy may be linked to in vitro fertilization in patients with endometriosis: a systematic review. Fertil Steril 2016;106(3):692–703.
[7] Glavind MT, Forman A, Arendt LH, Nielsen K, Henriksen TB. Endometriosis and pregnancy complications: a Danish cohort study. Fertil Steril 2017;107(1):160–6.
[8] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339(Jul):b2535.
[9] Roche M, Ibarrola M, Lamberto N, Larrañaga C, García MA. Spontaneous hemoperitoneum in a twin pregnancy complicated by endometriosis. J Matern Fetal Neonatal Med 2008;21(12):924–6.
[10] Bouet PE, Sentilhes L, Lefebvre-Lacoeuille C, Catala L, Gillard P, Descamps P. Endometriosis and spontaneous rupture of uterine vessels with hemothorax during pregnancy. Eur J Obstet Gynecol Reprod Biol 2009;144(1):95–6.
[11] Moreira A, Reynolds A, Baptista P, Costa AR, Bernardes J. Case report: intrapartum utero-ovarian vessels rupture. Arch Gynecol Obstet 2009;279(4):583–5.
[12] Pezzuto A, Pomini P, Steinkasserer M, Nardelli GB, Minelli L. Successful laparoscopic management of spontaneous hemoperitoneum at 15 weeks of pregnancy: case report and review of literature. J Minim Invasive Gynecol 2009;16(6):792–4.
[13] Wada S, Yoshiyuki F, Fujino T, Sato C. Uterine vein rupture at delivery as a delayed consequence of laparoscopic surgery for endometriosis: a case report. J Minim Invasive Gynecol 2009;16(4):510–2.
[14] Zhang Y, Zhao Y, Wei Y, Li R, Qiao J. Spontaneous rupture of subserous uterine veins during late pregnancy after in vitro fertilization. Fertil Steril 2009;92(1):395.e13-6.
[15] Bloom SL, Uppot R, Roberts DJ. Case records of the Massachusetts general hospital. case 32–2010: a pregnant woman with abdominal pain and fluid in the peritoneal cavity. N Engl J Med 2010;363(17):1657–65.
[16] Brouckaert OM, Oostenveld E, Quartero H. Spontaneous hemoperitoneum and fetal demise in a nulliparous woman requiring hysterectomy with fetus in situ. Int J Gynaecol Obstet 2010;110(3):273.
[17] Gao JL, Lortie K, Singh SS. Laparoscopic internal iliac artery ligation for postpartum spontaneous hemoperitoneum. J Obstet Gynaecol Can 2010;32(12):1172–5.
[18] Giulini S, Zanin R, Volpe A. Hemoperitoneum in pregnancy from a ruptured varix of broad ligament. Arch of Gynecol Obstet 2010;282(4):459–61.
[19] Grunewald C, Jördens A. Intra-abdominal hemorrhage due to previously unknown endometriosis in the third trimester of pregnancy with uneventful neonatal outcome: a case report. Eur J Obstet Gynecol Reprod Biol 2010;148(2):204–5.
[20] Huisman CM, Boers KE. Spontaneous rupture of broad ligament and uterine vessels during pregnancy. Acta Obstet Gynecol Scand 2010;89(10):1368–9.
[21] Kim TH, Lee HH. Hemoperitoneum during pregnancy with endometriosis; report of four cases. Iran J Reprod Med 2010;8(2):90–3.
[22] Shahnewaj K, Al Sayed M, Jabin K. Spontaneous rupture of uterine veins in pregnancy. Bangladesh J Obstet Gynecol 2010;25(2):85–6.
[23] Kapila P. Fatal non-traumatic spontaneous hemoperitoneum in second trimester of pregnancy?autopsy findings. J Forensic Leg Med 2011;18(3):139–40.
[24] Nakaya Y, Itoh H, Muramatsu K, et al. A case of spontaneous rupture of a uterine superficial varicose vein in midgestation. J Obstet Gynaecol Res 2011;37(8):1149–53.
[25] Williamson H, Indusekhar R, Clark A, Hassan IM. Spontaneous severe haemoperitoneum in the third trimester leading to intrauterine death: case report. Case Rep Obstet Gynecol 2011;(2011):173097.
[26] Al Qahtani NH. Spontaneous intraperitoneal haemorrhage during pregnancy. BMJ Case Rep 2012;11:2012.
[27] Boztosun A, Sümer D, Cetin M, Cetin A. Idiopathic spontaneous hemoperitoneum during early postpartum period: case report. Turk Klinikleri J Med Sci 2012;32(6):1718–20.
[28] Kondoh E, Shimizu M, Kakui K, Mikami Y, Tatsumi K, Konishi I. Deciduosis can cause remarkable leukocytosis and obscure abdominal pain. J Obstet Gynaecol Res 2012;38(12):1376–8.
[29] Maya ET, Srofenyoh EK, Buntugu KA, Lamptey M. Idiopathic spontaneous haemoperitoneum in the third trimester of pregnancy. Ghana Med J 2012;46(4):258–60.
[30] Munir SI, Lo T, Seaton J. Spontaneous rupture of utero-ovarian vessels in pregnancy. BMJ Case Rep 2012(30).
[31] De Vincenzo R, Zannoni GF, Ricci C, Conte C, Masciullo V. Bowel endometriosis with hemoperitoneum complicating pregnancy. J Endometr Pelvic Pain Disord 2013;5(4):166–9.
[32] Doger E, Cakiroglu Y, Yildirim Kopuk S, Akar B, Caliskan E, Yucesoy G. Spontaneous rupture of uterine vein in twin pregnancy. Case Rep Obstet Gynecol 2013;(2013):596707.
[33] Duhan N, Sangwan N, Rajotia N, Kadian YS, Singla SL. Spontaneous uterine artery rupture at delivery. J Obstet Gynecol India 2013;63(1):72–3.
[34] Fan Y, Inocencio G, Azevedo S, Carinhas MJ, Rodrigues O. Spontaneous rupture of utero-ovarian vessels in pregnancy. Acta Obstet Ginecol Port 2013;7(3):215–8.
[35] Nguessan KL, Mian DB, Aissi GA, Oussou C, Boni S. Spontaneous rupture of uterine varices in third trimester pregnancy: an unexpected cause of hemoperitoneum: a case report and literature review. Clin Exp Obstet Gynecol 2013;40(1):175–7.
[36] Aggarwal I, Tan P, Mathur M. Decidualised fallopian tube endometriotic implant causing spontaneous haemoperitoneum in a twin pregnancy. BMJ Case Rep 201417(July).
[37] Black JD, Yuhasz M, Lee AY. Uterine artery rupture during the second stage of labor. Int J Gynaecol Obstet 2014;124(2):176.
[38] Diaz-Murillo R, Tobias-Gonzalez P, Lopez-Magallon S, Magdaleno-Dans F, Bartha JL. Spontaneous hemoperitoneum due to rupture of uterine varicose veins during labor successfully treated by percutaneous embolization. Case Rep Obstet Gynecol 2014;(2014):580384.
[39] Lim PS, Ng SP, Shafiee MN, Kampan N, Jamil MA. Spontaneous rupture of uterine varicose veins: a rare cause for obstetric shock. J Obstet Gynaecol Res 2014;40(6):1791–4.
[40] Shi Q, Zhou HG, Liu XR, Li JP. Spontaneous hemoperitoneum with intrahepatic cholestasis during the third trimester of pregnancy. Int J Gynecol Obstet 2014;127(3):297–8.
[41] Sreedhar S, Rajeswari KS, Sivasundari M. Surprise in pandora box: spontaneous intra-abdominal hematoma in pregnancy. J SAFOG 2014;6(3):171–2.
[42] Cozzolino M, Corioni S, Maggio L, Sorbi F, Guaschino S, Fambrini M. Endometriosis-related hemoperitoneum in pregnancy: a diagnosis to keep in mind. Ochsner J 2015;15(3):262–4.
[43] Farahbakhsh F, Barati M, Moramezi B, Zamanpoor Z. Spontaneous uterine vessels rupture in a pregnant woman: a case report. Jentashapir J Health Res 2015;6(4):e28705.
[44] Fatnassi R, Mkhinini I, Torki E, et al. Hemoperitoneum caused by spontaneous uterine varicose vein rupture in the third trimester of pregnancy-A case report. Gynecol Obstet (Sunnyvale) 2015;5:291.
[45] Kekhashan A, Sree S, Hassan KA. Spontaneous rupture of right uterine artery in a pregnant women: a rare entity. JEMDS 2015;4(44):7684–8.
[46] Loh MJ, Wee JY, Teo SB. Endometriosis in a twin pregnancy leading to massive hemoperitoneum and intrauterine death: a case report. J Endometr Pelvic Pain Disord 2015;7(2):86–8.
[47] Mandal D, Ray A, Goswami AK, Mandal A. Spontaneous rupture of uterine varicose vein at 38 weeks of pregnancy: a rare case report. JEMDS 2015;4(14):2403–7.
[48] Zhang Z, Lou J. Acute hemoperitoneum after administration of prostaglandin E2 for induction of labour. Case Rep Obstet Gynecol 2015;(2015):659274.
[49] Stochino Loi E, Darwish B, Abo C, Millischer-Bellaiche AE, Angioni S, Roman H. Recurrent hemoperitoneum during pregnancy in large deep endometriosis infiltrating the parametrium. J Min Invasive Gynecol 2016;23(4):643–6.

[50] Petresin J, Wolf J, Emir S, Müller A, Boosz AS. Endometriosis-associated maternal pregnancy complications – case report and literature review. Geburtshilfe Frauenheilkd 2016;76(8):902–5.
[51] Ploteau S, Lopes P. Regarding recurrent hemoperitoneum during pregnancy in large deep endometriosis infiltrating the parametrium. J Minim Invasive Gynecol 2016;23(7):1200–1.
[52] Lier MCI, Malik RF, van Waesberghe JHTM, et al. Spontaneous haemoperitoneum in pregnancy and endometriosis: a case series. BJOG 2017;124(2):306–12.
[53] Buggio L, Aimi G, Vercellini P. Hemoperitoneum following sexual intercourse in a woman with deep infiltrating endometriosis. Gynecol Obstet Invest 2016;81(6):559–62.
[54] Vigano P, Corti L, Berlanda N. Beyond infertility: obstetrical and postpartum complications associated with endometriosis and adenomyosis. Fertil Steril 2015;104(4):802–12.
[55] Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. Obstet Gynecol 1986;67(3):335–8.
[56] Al-Fozan H, Tulandi T. Left lateral predisposition of endometriosis and endometrioma. Obstet Gynecol 2003;101(1):164–6.
[57] Aziz U, Kulkarni A, Lazic D, Cullimore JE. Spontaneous rupture of the uterine vessels in pregnancy. Obstet Gynecol 2004;103(5 Pt 2):1089–91.
[58] Lier MCI, Brosens IA, Mijatovic V, Habiba M, Benagiano G. Decidual bleeding as a cause of spontaneous hemoperitoneum in pregnancy and risk of preterm birth. Gynecol Obstet Invest 2017;82(4):313–21.
[59] Konishi T, Mori K, Uchikawa Y, et al. Spontaneous hemoperitoneum in pregnancy treated with transarterial embolization of the uterine artery. Cardiovasc Intervent Radiol 2016;39(1):132–6.
[60] INOSS. Internet]. Oxford: International Network of Obstetric Survey Systems. 2017 [updated 2015 Jan 05; cited 2016 Jun 14]. Available from: https://www.npeu.ox.ac.uk/inoss.