Obstetrical complications of endometriosis, particularly deep endometriosis

Umberto Leone Roberti Maggiore, Ph.D.,[a] Annalisa Inversetti, M.D.,[b,c] Matteo Schimberni, M.D.,[b,c] Paola Viganò, Ph.D.,[d] Veronica Giorgione, M.D.,[b,c] and Massimo Candiani, M.D.[b,c]

[a] Academic Unit of Obstetrics and Gynaecology, IRCCS Ospedale Policlinico San Martino, Genoa; [b] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, and Maternal and Child Health, University of Genoa, Genoa; [c] Obstetrics and Gynecology Unit, IRCCS San Raffaele Scientific Institute, Milan; and [d] Reproductive Sciences Laboratory, Division of Genetics and Cell Biology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Over the past few years, a new topic in the field of endometriosis has emerged: the potential impact of the disease on pregnancy outcomes. This review aims to summarize in detail the available evidence on the relationship between endometriosis, particularly deep endometriosis (DE), and obstetrical outcomes. Acute complications of DE, such as spontaneous hemoperitoneum, bowel perforation, and uterine rupture, may occur during pregnancy. Although these events represent life-threatening conditions, they are rare and unpredictable. Therefore, the current literature does not support any kind of prophylactic surgery before pregnancy to prevent such complications. Results on the impact of DE on obstetrical outcomes are debatable and characterized by several limitations, including small sample size, lack of adjustment for confounders, lack of adequate control subjects, and other methodologic flaws. For these reasons, it is not possible to draw conclusions on this topic. The strongest evidence shows that DE is associated with higher rates of placenta previa; for other obstetrical outcomes, such as miscarriage, intrauterine growth restriction, preterm birth and hypertensive disorders, results are controversial. Although it is unlikely that surgery of DE may modify the impact of the disease on the course of pregnancy, no study has yet investigated this issue. (Fertil Steril® 2017;108:895–912. ©2017 by American Society for Reproductive Medicine.)

Key Words: Complication, deep endometriosis, placenta previa, pregnancy, surgery

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/21437-24915

Academically, endometriosis is distinguished in three different phenotypes: ovarian endometrioma, superficial peritoneal endometriosis, and deep endometriosis (DE) (1). DE affects ~1% of women of reproductive age and it is considered to be the most severe form of the disease (2). It may involve the rectovaginal septum and/or uterosacral ligaments as well as also other abdominal structures, such as bowel, ureters, and bladder (3).

It is traditionally thought that endometriosis and its related pain symptoms improve during pregnancy not only because of the blockage of ovulation preventing bleeding of endometriotic tissue, but also owing to various metabolic, hormonal, immune, and angiogenesis changes related to pregnancy (4–7). However, in the past few years, several authors have investigated whether endometriosis may affect the regular development of pregnancy and delivery outcomes, showing controversial results (8, 9).

Therefore, the aim of this review is to offer the reader an exhaustive and updated overview on the available evidence on the impact of endometriosis, particularly DE, on obstetrical outcomes.

MATERIALS AND METHODS

We searched Pubmed for articles published in the English language since inception through August 2017 with the use of the following MeSH search terms: "endometriosis" combined with "bladder," "bowel," "deep," "colorectal," "complication," "pregnancy," rectovaginal endometriosis, "urinary tract," "uterosacral," "uterus," "uterine rupture," "abruptio placentae," "adverse pregnancy outcome," "antepartum haemorrhage," "cesarean delivery," "gestational diabetes mellitus," "hypertension," "intrauterine growth restriction," "miscarriage," "placenta previa," "postpartum hemorrhage," "preeclampsia," "preterm labor," "small for gestational age," and "spontaneous hemoperitoneum in pregnancy." Data were extracted independently by three authors (A.I., V.G., and U.L.R.M.), who also performed an initial screening of the title and abstract of all articles to exclude citations deemed by

Received August 28, 2017; revised October 16, 2017; accepted October 20, 2017.
U.L.R.M. has nothing to disclose. A.I. has nothing to disclose. M.S. has nothing to disclose. P.V. has nothing to disclose. V.G. has nothing to disclose. M.C. has nothing to disclose.
Reprint requests: Massimo Candiani, M.D., Obstetrics and Gynecology Unit, IRCCS San Raffaele Scientific Institute, Milano 20132, Italy (E-mail: candiani.massimo@hsr.it).

Fertility and Sterility® Vol. 108, No. 6, December 2017 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2017.10.035

all of the observers to be irrelevant. A manual search of review articles and cross-references completed the search. Data presented exclusively as abstracts in national and international meetings were also excluded. No Institutional Review Board approval was required, because only published deidentified data were analyzed.

ENDOMETRIOSIS-RELATED COMPLICATIONS DURING PREGNANCY

Several authors reported cases of acute endometriosis-related complications occurring during pregnancy. More frequently, this kind of event happens in the second or third trimester of pregnancy and may represent life-threatening conditions for both the mother and the fetus (Table 1; Supplemental Table 1 [available online at www.fertstert.org]) (10–73). The literature search aimed to identify only cases of obstetrical complications reported in women affected by DE.

Intestinal Perforation and Other Bowel Complications

A total of 17 cases of bowel perforation during pregnancy related to the presence of endometriosis have been described among women with a mean (±SD) maternal age of 32.1 ± 4.3 years (Table 1; Supplemental Table 1). Pregnancy was obtained with the use of assisted reproductive technology (ART) procedures in three cases (17.6%). Women did not have an earlier history of endometriosis in 9 out of 14 cases (64.3%) and did not undergo surgery for that indication before pregnancy in 10 out of 14 cases (71.4%; nonsurgical group). In the nonsurgical group, the most frequent location of perforations was the sigmoid colon or rectum (6/10; 60%). Surgery for endometriosis before pregnancy was performed in 4 out of 14 cases (28.6%) including one case of previous colorectal resection for the presence of a rectovaginal nodule (19) (surgical group). Among patients who underwent ovarian cystectomy before pregnancy, one had a diagnosis of a 3-cm rectosigmoid nodule and underwent in vitro fertilization (IVF) treatment; however, her perforation site was at the ileum (21). In the other surgical group cases, perforation occurred in the sigmoid colon (n = 1) or the rectum (n = 2). Among all of the patients, acute abdominal pain was the most common presenting symptom (16/17; 94.1%), with signs of peritonitis in 10 out of 16 patients (62.5%). All women underwent surgical interventions: segmental intestinal resection (11/17; 64.7%), repair of intestinal lesion (2/17; 11.8%), or appendectomy (4/17; 23.5%). In the case described by Setubal et al. (22), the patient underwent only an exploratory abdominal surgery during the 28th week of gestation and was treated with the use of antibiotics. Then, 2 months after a term delivery, total laparoscopic hysterectomy, adnexectomy, partial cystectomy, rectovaginal septum nodule excision, and segmental resection of the rectosigmoid were performed because severe symptoms had renewed. At histologic examination, decidualized endometriosis was demonstrated in all cases (14/14; 100%) for which specimens were obtained during pregnancy. All pregnancies ended in live births, with only 6 out of 16 (37.5%) preterm deliveries (<37 weeks of gestation).

One case of bowel-uterine fistula secondary to endometriosis was described during pregnancy. A 26-year-old women, multigravida, developed acute abdomen, severe sepsis, and disseminated intravascular coagulation at 16 weeks of gestation. Because there was no response to broad-spectrum antibiotics, she underwent explorative abdominal surgery which showed a fistula between the cecum and uterus in a setting of purulent peritonitis. A subtotal hysterectomy with subsequent termination of pregnancy and intestinal resection were performed; the surgical specimen confirmed the presence of a colouterine fistula within extensive adenomyosis of the uterus and endometriosis of the cecum (25).

Appendicitis

Ten cases of acute appendicitis connected to appendiceal endometriosis during pregnancy have been reported (Table 1; Supplemental Table 1). Mean maternal age was 28.5 ± 4.8 years. Surgical history of patients was not reported. Diagnosis was carried out more frequently in the second trimester (mean gestational age 21 ± 8.1 weeks). During pregnancy, open appendectomy (8/10; 80%) or laparoscopic appendectomy (2/20; 20%) was performed in all cases, and on histologic examination, three cases (3/10; 30%) showed inflammation and decidualized endometriosis. One preterm labor with subsequent neonatal death and three live births delivered at term were reported.

Urinary System

Uroperitoneum during pregnancy owing to the presence of endometriosis has been described in two cases (47, 63). In the first case, the patient underwent operative laparoscopy for stage IV endometriosis without removing a deep nodule of the right uterosacral ligament. After 8 months, she conceived, and at 31 weeks of gestation she was hospitalized because of acute abdominal pain. A few hours later, hemorrhagic shock suddenly developed requiring volume resuscitation and abdominal surgery. Urohemoperitoneum detected during surgery was due to injury of both the right uterine artery and right ureter at the level of the homolateral broad ligament. Subsequent ligation of the vessel and ureteroneocystostomy were performed (47). In the second case, the diagnosis of uroperitoneum was performed 6 hours after a preterm delivery at 27+2 gestational weeks (63). One week earlier she had experienced severe abdominal pain and was hospitalized. Her clinical history was remarkable for intestinal and bladder endometriosis: She had undergone transurethral resection of a bladder nodule 2 years before conception. After postpartum bladder resection of endometriotic lesion, clinical resolution was obtained and the follow-up cystography was negative.

In two cases with no history of previous surgery for endometriosis, the disease caused ureteral stenosis with subsequent need of stent placement during pregnancy, without procedure-related complications (59, 62). In one case, pregnancy was uneventful, and in the other case intrauterine fetal death occurred at 16 weeks after

TABLE 1

Acute complications occurring during pregnancy in patients with deep endometriosis.

Complication	Author(s)	No. of cases	Age (y)	History of endometriosis	Surgery before pregnancy (type, time before)	Conception	Presenting symptoms	Site of complication	Onset of complication (GA)	Management	Histologic examination	Pregnancy outcomes, GA at delivery
Bowel												
Intestinal perforation (10–24)	Total	17	Mean 32.1 ± 4.3	No history of endometriosis 9/14 (64.3%)	No surgery before pregnancy: 10/14 (71.4%); surgery before pregnancy: 4/14 (28.6%)	A 3/6 (50%); S 3/6 (50%)	AP 16/17 (94.1%); N or V 3/17 (17.6%); fever 2/17 (11.8%); asymptomatic 1/17 (5.9%)	Ileum 1/17 (5.9%); colon 8/17 (47.1%); rectum 2/17 (11.8%); colon + rectum 2/17 (11.8%); appendix 4/17 (23.5%)	Mean 30.9 ± 6.4 wk; postpartum: 3/17 (17.6%)	Segmental intestinal resection 11/17 (64.7%); repair of intestinal lesion 2/17 (11.8%); appendectomy 4/17 (23.5%)	E: 1/15 (6.7%); E + D: 14/15 (93.3%)	LB 17/17 (100%); preterm deliveries 6/16 (37.5%)
Colouterine fistula	Siriganeshan et al., 2006 (25)	1	26	NR	NR	NR	Fever	Fistula between the cecum and uterus	16	ABD: hysterectomy, fistulectomy, and cecotomy with enteroentero anastomosis were performed.	E + D, adenomyosis	IUD, 16
Appendicitis (26–35)	Total	10	Mean 28.5 ± 4.8	–	–	–	AP 7/9 (77.8%); N or V 5/9 (55.6%); fever 1/9 (11.1%)	Appendix 10/10 (100%)	Mean 21 ± 8.1 wk	ABD appendectomy: 8/10 (80%); LPS appendectomy: 2/10 (20%)	E: 3/10 (30%); E + D: 4/10 (40%); E + D + I: 3/10 (30%)	LB 3/4 (75%); ND 1/4 (25%)
Hemoperitoneum (36–60)	Total	39	Mean 32.8 ± 4.3	No history of endometriosis 10/33 (30.3%); history of endometriosis 23/33 (69.7%)	Surgery before pregnancy 14/21 (66.7%); no surgery before pregnancy 7/21 (33.3%)	A 14/22 (63.6%); S 8/22 (36.4%)	AP 37/39 (94.9%); HS 27/39 (69.3%); N or V 5/39 (12.8%); VB 2/39 (5.1%)	Single site: 30/40 (75%); multiple sites: 10/40 (25%)	Mean 28 ± 7.1; postpartum: 4/39 (10.2%)	ABD 37/40 (92.5%); LPS 1/40 (2.5%); conservative management 1/40 (2.5%); uterine artery embolization 1/40 (2.5%)	E + D: 8/14 (57.1%); E: 6/14 (57.1%)	LB 27/42 (64.3.7%); IUD 13/42 (30.9%); ND 2/42 (4.8%)
Distorsion of renal system anatomy	Yaqub et al., 2008 (61)	1	25	NR	NR	NR	Lower AP	Renal area	34	ABD: removal of cyst by blunt dissection and clamping vascular pedicle	E	LB, 34
	Pezzuto et al., 2009 (62)	1	34	+	–	NR	AP	Broad ligament	35	Ureteral stent	NR	NR, NR
Uroperitoneum	Chiodo et al., 2008 (47)	1	25	+	LOA, OC, DTC, 2 y	NR	AP, hematuria, HS	Sacrouterine ligament with right ureter and uterine artery involvement	31	ABD: ligation of the right uterine artery and ureteroneocystostomy	E + D	IUD, 31
	Leone Roberti Maggiore et al., 2015 (63)	1	30	+	TUNR	A	AP	Bladder	26	ABD: bladder resection	E + D	LB, 26
Uterine rupture (64–73)	Total	63	Mean 32.4 ± 2.7	History of endometriosis 63/63 (100%)	Surgery before pregnancy 10/10 (100%)	A 6/7 (85.7%); S 1/7 (14.3%)	AP 6/8 (75%); AP+HS 4/8 (50%%); HS 1/8 (12.5%); VB 1/8 (12.5%)	Uterus 63/63 (100%)	Mean 28.1 ± 7.8; postpartum: 4/11 (36.4%)	Hysterectomy: 4/9 (44.4%); uterine rupture repair: 5/9 (55.6%)	Adenomyosis 5/6 (83.3%)	LB 8/10 (80%); IUD 2/10 (20%)

Note: A = assisted reproductive technology (ART); ABD = open abdominal surgery; AP = abdominal pain; BS = bilateral salpingectomy; BSO = bilateral salpingo-oophorectomy; CRR = colorectal resection; D = decidual change; DTC = diathermocoagulation of endometriotic lesions; E = endometriosis; GA = gestational age; HS = hemorrhagic shock; I = inflammation; IUD = intrauterine death; LB = live birth; LOA = lysis of adhesions; LPS = laparoscopy; N = nausea; ND = neonatal demise; OC = ovarian cystectomy; RVNE = rectovaginal nodule excision; S = spontaneous; SO = salpingo-oophorectomy; TUNR = transurethral nodule resection; V = vomiting; VB = vaginal bleeding.

Roberti Maggiore. Pregnancy and endometriosis. Fertil Steril 2017.

hemoperitoneum recurrence caused by severe deep endometriosis infiltrating the left parametrium (59, 62). Finally, one case of renal localization of endometriosis discovered during pregnancy has been described (61). The abdominal mass extending form the left iliac region to the left hypochondrium was diagnosed by means of clinical examination and ultrasonography during emergency department admission for labor onset at 34 weeks of gestation. The mass entirely replaced the left kidney, which was not seen with the use of intravenous urography. Because abdominal pain endured after delivery, the patient underwent abdominal surgery to remove the mass.

Spontaneous Hemoperitoneum in Pregnancy

Thirty-nine cases of endometriosis-related spontaneous hemoperitoneum (SH) in pregnancy were found in the literature (Table 1; Supplemental Table 1). In only one case, SH occurred in two different consecutive pregnancies (60). In all of these cases, the profuse bleeding might have arisen from varicosities on the uterine surface, vessels of the parametrium, or from macroscopic pelvic endometriotic lesions. The mean maternal age was 32.8 ± 4.3 years. Five out of 39 women (12.8%) had twin pregnancies. In 35 out of 39 cases (89.7%), SH occurred during pregnancy at a mean gestational age of 28.0 ± 7.1 weeks, and 4 cases out of 39 (16.0%) occurred within 2 weeks after delivery. In two cases where SH first occurred during the third trimester, the recurrences of SH were reported at 12 and 30 days after delivery. At onset, symptoms and signs of hypovolemic shock were present in 27 out of 39 patients (69.3%). The origin of SH was generally identified at emergency abdominal surgery, except for one hemodynamically stable patient who was treated conservatively (54). Decidualization of endometriosis was diagnosed in eight specimens and only endometriosis in six specimens. During emergency abdominal surgery for SH, cesarean section (CS) was performed in 26 out of 40 (65%); conversely, in nine cases the hemorrhagic complication occurred during postpartum or did not influence the timing of delivery.

Apart from 18 cases in which data on history or earlier surgery for endometriosis were not available, 7 out of 21 patients (33.3%) did not undergo any intervention for endometriosis before pregnancy (nonsurgical group) and 14 out of 21 patients (66.7%) underwent surgery for endometriosis, such as ovarian cystectomy diathermocoagulation of endometriotic lesions or lysis of adhesions (surgical group). At surgery in the nonsurgical group, the sites of bleeding were uterus (3/7; 42.8%), parametrium (3/7; 42.8%), and uterosacral ligament (1/7; 14.3%); in the surgical group the were uterus (8/14; 57.1%), fallopian tube (1/14; 7.1%), parametrium (4/14; 28.6%), and vesicouterine pouch (1/14; 7.1%). There were no differences in pregnancy outcome between the two groups. Live birth rates were 71.4% (10/14) at 32.1 ± 2.7 gestational weeks in the surgical group and 71.4% (5/7) at 30.5 ± 6.8 gestational weeks in the nonsurgical group; no maternal death was reported in both groups.

Twenty-seven live births out of 42 (64.3%) were reported; the miscarriage rate was 11.9% (5/42), and the overall perinatal mortality rate was of 19% (8/42).

Uterine Rupture

Uterine injuries due to endometriosis were confirmed in 63 cases retrieved from the literature (Table 1). Berlac et al. (73) described 52 cases of uterine rupture before and during labor and calculated an odds ratio (OR) of uterine rupture of 2.7 (95% confidence interval [CI] 2.0–3.6) in women with endometriosis. Among those cases, 15 out of 52 (28.8%) occurred in women who had undergone gynecologic surgery.

The mean maternal age was 32.4 ± 2.7 years. It is well known that a uterine rupture is mostly related to a scarred uterus or a minor resistance uterine area caused indirectly by surgical excision of close endometriotic lesions. Indeed, all of the reported cases underwent pelvic surgery: 7 out of 10 (70%) had undergone earlier surgery for endometriosis, and in 3 out of 10 (30%), there was a direct hysterotomy to perform an adenomyomectomy. In most cases (6/7; 85.7%), conception was achieved with the use of ART. In 4 out of 11 cases (36.4%), uterine complications arose postpartum; the mean gestational age at onset was 28.1 ± 7.8 weeks, which was also the mean gestational age at delivery. The most common presenting symptoms were abdominal pain (6/8; 75%) and clinical picture of hemorrhagic shock (5/8; 62.5%). Four out of 9 (44.4%) hysterectomies and 5 out of 9 (55.6%) uterine rupture repairs were performed. Adenomyosis was confirmed histologically in 5 out of 7 cases (71.4%). Eight live births out of 10 (80%) and 2 miscarriages at 16 and 19 weeks (20%) were described. No maternal death was reported.

Endometriosis and Pregnancy Outcomes

A growing number of papers focus on the potential impact of endometriosis on the regular development of pregnancy and on delivery outcomes (Table 2) (57, 73–109). A great heterogeneity among the studies in exposure categorizations, analytic approaches, disease phenotypes, presence/exclusion of adenomyosis, method of conceiving (natural or ART), choice of control subjects, and general methodologic design prevents pooling of the data to perform meta-analyses that would allow drawing more clear conclusions on this issue.

Miscarriage

The rate of miscarriage, defined as the spontaneous interruption of pregnancy before 20 weeks of gestation (106), is often not reported in the studies aiming to investigate outcomes of women affected by DE (47, 49, 66, 73, 76, 85, 93, 96, 100, 103–105, 111).

A recent study by Centini et al. (112) included a cohort of 115 women who underwent laparoscopy for DE and had histologic confirmation of the disease. Concomitant diagnosis of endometriomas was an exclusion criterion to obtain a pure analysis of the association between DE and obstetrical outcomes. Miscarriage rate was not analyzed, but the study demonstrated that laparoscopic excision of DE could enhance both natural and ART pregnancy rates. First surgical treatment of multiple lesions was associated with higher pregnancy rates, whereas isolated lesions influenced the

pregnancy rate regardless of their location and size (112). Vercellini et al. (80) conducted a study including only nulligravid women who achieved natural conception, subdividing them into rectovaginal, ovarian and peritoneal, only ovarian, and only peritoneal endometriosis. All patients included in the study had undergone surgery. This study did not find an association between DE and a higher rate of miscarriage, whereas a trend toward a higher miscarriage frequency in women with ovarian endometriomas was detected (80). In 2014, a study on all natural pregnancies in 49 women with histologically confirmed endometriosis versus 59 without the disease revealed no significant difference in the incidence of miscarriage. However, the proportion of DE among the 49 women affected by endometriosis was not specified (86). A retrospective analysis of prospectively collected data included 80 women who underwent laparoscopic ureterolysis for DE and had complete follow-up. The median follow-up of the 80 women with available long-term outcomes was 52 (range 15–109) months. The whole cohort was analyzed after surgery, and the rate of miscarriage was 15.4% (87). Two years later, the same authors analyzed a cohort of 61 women after laparoscopic ureterolysis for DE and found a similar result (15.6% miscarriage rate) (102). Similarly, Mannini et al. reported a 17.5% miscarriage rate in 40 women affected by DE (104). Mochimaru et al. recruited 36 women with ultrasound or magnetic resonance imaging diagnosis of endometriosis compared with 144 women without uterine abnormalities and found that there were no differences in history of miscarriage (30.6% vs. 34.7%; $P=.84$) (113). Furthermore, a recent study from an Italian group, which analyzed a cohort of women who underwent IVF cycles, reported a lack of association between endometriosis and miscarriage (adjusted OR 0.81, 95% CI 0.53–1.25), and after a secondary analysis excluding women affected by adenomyosis, this finding did not change (adjusted OR 0.86, 95% CI 0.55–1.36) (92). Benaglia et al. conducted a study enrolling 239 women affected by endometriosis (of whom 41% were affected by DE) and compared them with 239 control subjects; they did not find an association between miscarriage rate and endometriosis, although a separate analysis focusing on the DE subgroup was not performed (101).

Another Italian group conducted a study on the outcomes and complications of pregnancy and delivery among 41 women with a posterior DE nodule persisting after surgery and diagnosed at transvaginal sonography; this group of patients was compared with a control group of 300 women without endometriosis. In this study, an association between DE and miscarriage was not found, whether focusing the analysis on women affected by DE and adenomyosis or on DE without adenomyosis (94). In 2014, a retrospective cohort study was conducted in Canada of both spontaneous and ART pregnancies comparing women with endometriosis (n = 784) versus a nonaffected population (n = 30,284). An increased rate of spontaneous abortion in women with endometriosis (2.8%) versus control subjects (1.5%; OR 1.89, 95% CI 1.23–2.93; $P=.005$) was found, but the proportion of DE among the affected women was not specified (84). In 2016, a nationwide analysis of 5,375 endometriotic women (no details on the proportion of patients with DE) all diagnosed by means of laparoscopy or laparotomy compared with 8,710 pregnant control subjects reported a significant association between endometriosis and miscarriage (adjusted OR 1.76, 95% CI 1.44–2.15) (109). In the same year, Santulli et al. conducted a specific retrospective cohort study on the association of endometriosis and miscarriage, distinguishing the patients in three groups: superficial endometriosis, endometriomas, and DE. They found that the miscarriage rate was significantly higher in women with endometriosis than in women without endometriosis (139/478 [29.1%] vs. 187/964 [19%], respectively; $P<.001$). After a subgroup analysis dividing those who had a history of infertility from those who did not, the miscarriage rates of women with and without endometriosis were 20% versus 12%, respectively ($P=.003$). On the other hand, women with endometriosis and a history of infertility had a 53% rate of miscarriage versus 30% of non-endometriosis women with a history of infertility ($P<.001$). More interestingly, the positive association was maintained in the subgroup of DE compared with women without endometriosis after adjustment for age, body mass index, previous ART treatment, smoking habits, and fertility status (adjusted incidence rate ratio 1.55, 95% CI 1.16–2.06; $P=.003$) (97).

In conclusion, it is difficult to debate on the association of endometriosis and the rate of miscarriage owing to the inclusion of different types of endometriosis in the same cohort in most of the studies. Only one of the above-described studies (97) found an increased rate of miscarriage in all three types of endometriosis (superficial, endometriomas, and DE). Future studies must stratify the different cohorts of patients according to the type of endometriosis and the presence of adenomyosis to understand better the pathogenetic mechanisms.

HYPERTENSIVE DISORDERS

In studies by Berlac et al., Stephansson et al., and Glavind et al., an increased risk for preeclampsia among women with endometriosis (adjusted OR 1.13, 95% CI 1.02–1.26 [$P=.05$]; adjusted OR 1.7, 95% CI 1.5–2.0 [$P<.05$]; and OR 1.37, 95% CI 1.06–1.77 [$P<.05$], respectively) was observed (73, 77, 105). However, a lack of distinction between women with DE and with other forms was lacking: These nationwide studies reported only the presence or absence of endometriosis, without subdividing different types, probably because the clinical data were extracted from large national databases. Another recent nationwide study in Taiwan confirmed the results of the previous three studies (adjusted OR 2.27; 95% CI 1.76–2.93; $P<.05$) and presented the same limitations (107). In 2007, a Belgian retrospective case-control study compared the incidence of preeclampsia and pregnancy-induced hypertension between 245 pregnancies of women with endometriosis and 274 pregnancies following treatment for male-factor infertility. Interestingly, the incidence of preeclampsia was significantly lower in the endometriosis group (0.8%) compared with the control group (5.8%; OR 7.5, 95% CI 1.7–33.3; $P=.002$). Furthermore, pregnancy-induced hypertension occurred in 3.5% and 8.7% of case and control pregnancies, respectively (OR 2.6, 95% CI 1.2–6.0; $P=.018$) (75). In 2012, Vercellini et al. performed a study on nulligravid women with natural

TABLE 2

Association between first, second, and third trimester complications and deep endometriosis (DE): studies from the literature.

Author, year (ref.)	Population (case vs. control)	Type of study	Spontaneous/ART	Type of DE	% DE/total	Pre- or postsurgical	Miscarriage	PPROM
Kortelahti et al., 2003 (74)	137 vs. 137	Case-control	ART	NR	NR	NR	–	NR
Brosens et al., 2007 (75)	245 vs. 274	Retrospective case-control	ART and non-ART	NR	NR	NR	NR	NR
Hadfield et al., 2009 (76)	3,239 vs. 205,640	Retrospective population-based	841/3,239 vs. 4,935/205,640	2,386 peritoneal, 514 multiple sites affected	NR	Post	NR	NR
Stephansson et al., 2009 (77)	13,090 vs. 1,429,585	Retrospective	(Stratification only for preterm birth) 1,207 ART endometriosis, 14,688 ART nonendometriosis, 8,938 non-ART endometriosis, 1,071,607 non-ART nonendometriosis	NR	NR	NR	NR	NR
Fernando et al., 2009 (78)	535 ART endometriosis, 95 ART endometrioma, 1,201 ART infertile, 156 subfertile women, 1,260 fertile non-ART controls for all forms of endometriosis, 1,140 fertile non-ART controls for ovarian endometriomata.	Retrospective cohort	535 ART endometriosis, 95 ART endometrioma, 1,201 ART infertile, 156 subfertile women, 1,260 fertile non-ART controls for all forms of endometriosis, 1,140 fertile non-ART controls for ovarian endometriomata	NR	NR	NR	NR	NR
Healy et al., 2010 (79)	1,265 vs. 5,465	Retrospective cohort	1,265 ART endometriosis, 5,465 ART nonendometriosis	NR	NR	NR	NR	NR
Vercellini et al., 2012 (80)	419 cases	Retrospective cohort	Spontaneous	150/419 rectovaginal lesions	35.8%	Post	– (30/150 in RV endometriosis [20%])	NR
Kuivasaari-Pirinen et al., 2012 (81)	49 vs. 26,870	Retrospective cohort	49 ART endometriosis, 26,870 non-ART nonendometriosis	NR	NR	NR	NR	NR
Tobias et al., 2013 (82)	388 vs. 26,451	Prospective cohort	388 non-ART endometriosis women, 26,451 non-ART nonendometriosis	NR	NR	Post	NR	NR
Takemura et al., 2013 (83)	44 vs. 305	Retrospective cohort	44 ART endometriosis women, 305 ART nonendometriosis	NR	NR	Pre, post	NR	NR
Aris et al., 2014 (84)	784 vs. 30,284	Retrospective cohort	784 women with endometriosis, 30,284 without endometriosis (not specified if natural or ART)	NR	NR	Post	+	NR
Conti et al., 2014 (85)	219 vs. 1,331/97 vs. 592	Retrospective cohort	35% (ART in DE) vs. 5.8% (ART in controls)/15% vs. 4.1%	NR	19% DE, 21% mixed ovarian and DE	Post	NR	+
Mekaru et al., 2014 (86)	49 vs. 59	Retrospective cohort	49 non-ART endometriosis, 59 non-ART nonendometriosis	NR	NR	Post	–	NR
Uccella et al., 2014 (87)	80	Retrospective cohort	NR	Ureteral endometriosis	100%	Post	15.6%	NR
Carassou-Maillan et al., 2014 (88)	258	Retrospective cohort	ART	NR	NR	NR	+	NR
Stern et al., 2015 (89)	406 and 590 vs. 297,987	Retrospective	406 endometriosis ART and 590 endometriosis non-ART vs. 297,987 fertile non-ART	NR	NR	NR	NR	NR

Preterm labor	SGA/FGR	Antepartum hemorrhage	Postpartum hemorrhage	Abruptio placentae	Placenta previa/accreta	Preeclampsia/ hypertension	Gestational diabetes	Operative delivery	Cesarean section
–	–	–	NR	–	–	–	–	–	–
NR	NR	NR	NR	NR	NR	–	NR	NR	NR
NR	NR	NR	NR	NR	NR	–	NR	NR	NR
+	–	+	NR	NR	+ (expressed as placental complications)	+	NR	NR	+
+	+ (in the endometrioma group)	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	–	+	–	+	NR	NR	NR	NR
15.1%	SGA 11.8%	NR	NR	1.7%	7.6%	–	NR	NR	+ (42.9%)
+	–	NR	NR	–	+	–	–	NR	NR
NR	NR	NR	NR	NR	NR	NR	–	NR	NR
NR	NR	NR	NR	NR	+	NR	NR	NR	NR
–	–	NR	NR	NR	NR	–	–	NR	NR
+	+ (NR if only in DE)	NR	–	NR	NR.	–	+ (NR if only in DE)	–	–
–	–	–	NR	–	NR	–	NR	NR	–
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
+	NR	NR	NR	NR	+	–	–	NR	–
–	–	+	NR	NR	NR	–	–	NR	+

TABLE 2

Continued.

Author, year (ref.)	Population (case vs. control)	Type of study	Spontaneous/ART	Type of DE	% DE/total	Pre- or postsurgical	Miscarriage	PPROM
Lin et al., 2015 (90)	249 vs. 249	Retrospective cohort	249 non-ART endometriosis, 249 non-ART nonendometriosis	NR	NR	Post	NR	NR
Kmietowicz et al., 2015 (91)	5,375 vs. 8,280	Cohort study	NR	NR	NR	NR	+	NR
Leonardi et al., 2016 (92)	313 vs. 313	Case-control study	ART	DE, adenomyosis	100%	Pre, post	–	NR
Allerstorfer, et al., 2016 (93)	51 cases	Retrospective cohort	NR	51/51 (100)	100%	Post	NR	1 (2%)
Exacoustos et al., 2016 (94)	101 (52 obtained a pregnancy)	Multicenter, observational, and cohort study	27 (51.9%) spontaneous/25 (48.1%) ART	60.4% posterior DE + adenomyosis, 32.7% posterior DE + endometrioma, 4% posterior DE + bladder association, 1% umbilical localization + posterior DE	100%	Post	21.2%	NR
Petresin et al., 2016 (57)	1	Case report	NR	DE (rectovaginal endometriosis)	NR	Post	NR	NR
Saavalainen et al., 2016 (95)	53	Retrospective cohort study	22.6% ART, 11% spontaneous	Urinary tract endometriosis	100%	Post	NR	NR
Jaques et al., 2016 (96)	113/113	Retrospective single-center case-control study	100% ART	43.4% DE, 9.3% adenomyosis	43.4%	Pre, post	NR	–
Santulli et al., 2016 (97)	870	Retrospective cohort study	NR	52 (18.3%) SUP, 64 (22.5%) OMA, 168 (59.2%) DE (34 [20.2%] uterosacral ligament, 14 [8.3%] vagina, 19 [11.3%] bladder, 85 [50.6%] intestine, 16 [9.5%] ureter)	59.2%	Post	+	NR
Kim et al., 2016 (98)	1	Case report	NR	Adenomyosis	NR	NR	NR	NR
Harada et al., 2016 (99)	330	Cohort study in Japan	80.6% spontaneous, 80.6% ART	NR	NR	NR	–	+
Fujii et al., 2016 (100)	92	Retrospective cohort study	ART	NR	NR	Post	NR	NR
Benaglia et al., 2016 (101)	239/239	Retrospective matched case-control study	ART	NR	41%	Pre, post	NR	–
Uccella et al., 2016 (102)	61	Retrospective study	9 ART, 11 spontaneous	Ureteral endometriosis	100%	Post	– (15.4%)	1 (3.6%)
Thomin et al., 2016 (103)	72 pregnancies from 67 women	Retrospective cohort study.	40% ART	18 (27%) anterior DE, 41 (61%) previous colorectal surgery, 28 (41%) colpectomy, 7 (41%) surgery for anterior DE	100%	Pre, post	NR	NR
Mannini et al., 2017 (104)	262/524	Retrospective cohort study	194 spontaneous, 68 ART	NR	40 (15.3%)	Post	NR	NR
Berlac et al., 2017 (73)	11,739	Retrospective cohort	19% ART, 81% spontaneous	NR	NR	Pre, post	NR	+

Preterm labor	SGA/FGR	Antepartum hemorrhage	Postpartum hemorrhage	Abruptio placentae	Placenta previa/accreta	Preeclampsia/ hypertension	Gestational diabetes	Operative delivery	Cesarean section
+	–	NR	NR	–	+	-	NR	NR	+
+	NR	+	+	NR	+	NR	NR	NR	+
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
4 (7.8%)	NR	NR	NR	NR	0/0	0	NR	NR	+ 20 (39.2%)
+	–	NR	–	+	+	+	–	–	+
+	NR	+	NR	NR	NR	NR	NR	NR	+
NR	NR	NR	NR	NR	NR	NR	NR	NR	75% (83%) intraoperative difficulties: severe adhesions, 4 cases of difficulties with extraction of the neonate, 2 cases of bladder laceration, 1 case of uterine atony, and 1 case of difficult placental retrieval
+	–	+	–	NR	–	+ OR 8.53 but not significant when comparing DE vs. endometrioma	–	NR	+
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
+	NR	NR	NR	NR	NR	NR	NR	NR	NR
+	–	NR	NR	+	+	–	NR	NR	25.8%
+	–	NR	NR	NR	+	NR	NR	NR	NR
–	–	NR	NR	–	+	–	–	–	–
3 (11.5%)	2 (8.3%)	1 (3.8%)	– (3.8%)	NR	NR	NR	NR	– (15.4%)	+ 9 (40.9%)
NR	NR	NR	6% in the cesarean section group, 2% globally	NR	1 case (low numbers for statistical analysis)	– (1.38%)	NR	28%	+ (50%)
+	NR	NR	–	NR	+	–	–	NR	–
+	+	+	– in the whole group, + in the cesarean section group	+	+	+	NR	NR	+

TABLE 2

Continued.

Author, year (ref.)	Population (case vs. control)	Type of study	Spontaneous/ART	Type of DE	% DE/total	Pre- or postsurgical	Miscarriage	PPROM
Glavind al., 2017 (105)	1,213 women with diagnosis of endometriosis, affecting 1,719 pregnancies	Danish cohort study	86.5% spontaneous, 13.5% ART	NR	NR	Pre, post	NR	NR
Pallaks et al., 2017 (106)	150/588	Retrospective cohort study	ART	NR	NR	NR	+	NR
Pan et al., 2017 (107)	2,578 vs. 10,312	Population-based longitudinal study	Spontaneous	NR	NR	Post	NR	NR
Li et al., 2017 (108)	98	Retrospective cohort study	74 spontaneous, 24 ART	NR	NR	NR	NR	NR
Saraswat et al., 2017 (109)	8,710	National population-based cohort study via record linkage	NR	NR	NR	Post	+	NR

Note: + present; − absent; ART, assisted reproductive technology; FGR = fetal growth restriction; NR = not reported; PPROM = preterm premature rupture of membranes; SGA = small for gestational age.

Roberti Maggiore. Pregnancy and endometriosis. Fertil Steril 2017.

conception who had previously undergone surgery for endometriosis and subdivided them into rectovaginal, ovarian and peritoneal, only ovarian, and only peritoneal endometriosis. In the subgroup with DE (rectovaginal group; n = 150), they did not find an association between the disease and a higher rate of hypertensive disorders in pregnancy (80).

Another study evaluating only women affected by DE reported that the risk of gestational hypertensive disorders (3.8%; 10 out of 26 patients) did not seem to be increased in women with previous laparoscopic ureterolysis, compared with the risk in the general population of pregnant women (reported as 5%–10% for gestational hypertensive disorders globally and 3.9% for preeclampsia) (102). Thomin et al. conducted a retrospective cohort study enrolling 72 pregnancies from 67 women affected by colorectal endometriosis, both in situ and resected, with the aim of evaluating delivery and neonatal outcomes in this specific population, describing only one case of preeclampsia (1.38%) (103). Similarly, an Italian group performed a retrospective cohort study on 40 women with DE versus 222 women without DE. The primary aim was evaluating the incidence of intrahepatic cholestasis in pregnant women with endometriosis compared with women without endometriosis. The secondary aims were evaluating the incidence of other obstetrical complications in the same population and in the subgroups of DE versus non-DE. In this study, significant differences in hypertensive disorders in pregnancy for both outcomes were not found (104). In contrast, an interesting study by a French group on only ART pregnancies (cases matched with ART for male infertility) highlighted a positive correlation between endometriosis and preeclampsia (OR 8.53, 95% CI 1.05–69.40; $P=.04$), but the association was no longer significant when comparing women with deep locations (n = 49) versus the endometrioma group (n = 39). However, the authors suggested that this observation had to be considered with caution owing to the small size of the population and the presence of only one case of preeclampsia among the control subjects (the expected prevalence was 3%–4% in the global population) (96). Exacoustos et al. analyzed 52 women with a posterior DE nodule ≥2 cm centimeters in size who desired a pregnancy and a control group of women (n = 300) with no previous recorded diagnosis of endometriosis, reporting a higher rate of gestational hypertension in the DE group (OR 4.114, 95% CI 1.45–11.65; $P=.01$). The authors declared that the two groups differed for age, parity, and body mass index. However, these data were not adjusted for these possible confounders or for ART procedures, which are recognized as possible causes of an increase of hypertensive disorders in pregnancy (94).

In conclusion, it is hard to derive conclusions on this matter because the reported studies are still characterized by several limitations, including small sample size, lack of adjustment for confounders, and lack of adequate control. Nationwide studies, on the other hand, tend to suggest that endometriosis can result in adverse pregnancy outcomes and that this occurs even in the absence of ART treatment.

FETAL GROWTH RESTRICTION

Analyzing the possible correlation between surgically treated DE and fetal growth restriction (FGR) during fetal life, only one study out of four could detect a positive association (94, 96, 102, 104). Allerstorfer et al., who analyzed pregnancy outcomes from surgical treated DE women, did not report data on fetal growth (93).

Jacques et al. found that during fetal life there was a significant increase in FGR in a DE group versus an ovarian location group (12% vs. 0%; $P=.03$) (96). The baby birth weight in the endometriosis group was significantly lower than in the DE group (2,939 g vs. 3,239 g; $P<.0004$). Moreover, these newborns were smaller adjusting for gestational age, with weight at the 44th percentile, compared with control newborns, who were at the 53rd percentile ($P=.02$). However,

Preterm labor	SGA/FGR	Antepartum hemorrhage	Postpartum hemorrhage	Abruptio placentae	Placenta previa/accreta	Preeclampsia/ hypertension	Gestational diabetes	Operative delivery	Cesarean section
+	–	NR	–	NR	NR	+	NR	NR	+
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	+	NR	NR	NR
+ (in ART group)	NR	NR	+	–	–	–	-	NR	–
+	NR	NR	+	–	+	–	+	+	+

other authors did not find an increased rate of FGR in the DE groups after surgery: Uccella et al. evaluated 26 women who underwent laparoscopic ureterolysis for endometriosis, Exacoustos et al. focused on 52 women with a posterior DE nodule who desired a pregnancy and a control group of women (n = 300) with no previous recorded diagnosis of endometriosis, and Mannini et al. compared 40 women with DE versus 222 women without DE but affected by ovarian and/or peritoneal endometriosis (94, 102, 104).

Among the four studies that analyzed specifically women with endometrioma, only Fernando et al. reported an increased risk for small for gestational age (SGA) in the ovarian endometrioma ART group compared with women who underwent ART for infertility other than endometriosis (adjusted OR 1.95, 95% CI 1.06–3.60; $P=.05$). However, in the ovarian endometrioma group, the potential association of DE was not specified (78, 80, 101, 114).

Highlighting the results of the large nationwide studies, analyzing together all types of endometriosis, two out of five reported a higher risk of FGR in women with endometriosis (73, 77, 89, 105, 109). Stern et al. reported an association between endometriosis and low birth weight (<2,500 g) in the group of endometriosis without ART treatment (adjusted OR 1.46, 95% CI 1.07–1.99; $P<.05$) but not in the group of endometriosis who underwent ART treatments (adjusted OR 0.97, 95% CI 0.70–1.33) (89). Berlac et al., in a large nationwide Danish study, analyzed 19,331 deliveries and reported a higher risk of SGA babies in the endometriosis cohort (OR 1.5, 95% CI 1.4–1.6; $P<.05$) (73). In that study, the definition of SGA corresponded to a birth weight less than two standard deviations below the sex and gestational age–specific average, but the authors did not adjust for ART procedures.

In conclusion, on the basis of available evidence, an association between endometriosis and FGR is not present. Future studies are required to explore the hypothesis that adenomyosis might be related to FGR.

PRETERM BIRTH

As stated by Leone Roberti Maggiore et al., although there is some evidence suggesting an association between endometriosis and preterm birth, especially in large nationwide studies based on records, it should be considered that the majority of studies is characterized by marked differences in population and design (63, 73, 77, 91, 105, 109). This makes it difficult to draw definitive conclusions. Fernando et al. first delineated the importance of distinguishing between different types of endometriosis in evaluating the risk of preterm birth. They conducted a large retrospective cohort study with the primary outcome of reporting preterm birth and SGA rates from ART patients with ovarian endometrioma (n = 95) compared with a control group of non-ART fertile women randomly selected from the general population (n = 1,140). That study found that preterm birth was increased in the ovarian endometrioma group (adjusted OR 1.98, 95% CI 1.09–3.62; $P<.05$). More interestingly, another subgroup including ART women with endometriosis but without ovarian endometriomas (n = 535) was analyzed and no increased risk for preterm birth was detected. As previously mentioned, whether women with ovarian endometriomas were affected by DE was not specified (78). Vercellini et al. showed that the presence of ovarian endometriosis was associated with a lower rate of preterm birth compared with other types of endometriosis (rectovaginal and peritoneal), with incidences of 1.4% compared with 14.7% (OR 0.08; 95% CI 0.01–0.60) (80). Allerstorfer et al. did not find an increased rate of premature birth in a group of 51 women who delivered after surgery for DE: 60.8% delivered spontaneously, and 39.2% underwent CS (93).

In contrast, four studies on DE after surgery found an association between DE and preterm deliveries before 37 weeks (94, 96, 102, 104). Respectively, an evaluation of 26 women undergoing laparoscopic ureterolysis for DE showed an increased risk of preterm birth compared with control

subjects (9% before 34 weeks and 13.6% before 37 weeks), but after excluding the two twin pregnancies from the analysis, the risks of preterm birth at 34 weeks and 37 weeks were 5% and 10%, respectively (102). Further studies on deep locations by Jacques et al. highlighted an increased rate of premature deliveries among patients with operated endometriosis undergoing ART (OR 2.05, 95% CI 1.01–4.16; $P=.04$), even evaluating separately women with deep locations (25% rate of prematurity) versus women with ovarian locations (4.5%) (96). Similarly, two other studies described only cases of DE after surgery, finding an increased rate of preterm deliveries (OR 6.867, 95% CI 3.069–15.36 [$P<.05$]; and OR 0.14, 95% CI 0.05–0.37 [$P<.001$]) (94, 104).

In conclusion, although there are contradictory results on the association between endometriomas and premature delivery, a trend toward a correlation between DE and premature delivery can be stated. Furthermore, we found an increased rate of preterm delivery in four studies that analyzed DE after surgery (94, 96, 102, 104), whereas in only one study (93) was surgery for DE not associated with increased rate of preterm deliveries; however, before arguing a causative role of surgery, it will be necessary to distinguish between cases with only DE, only adenomyosis, and DE plus adenomyosis.

PLACENTA PREVIA

A higher incidence of placenta previa in women affected by endometriosis has been reported by several studies, although most of the available evidence is in ART populations, which are per se associated with a higher rate of placental abnormalities (73, 77, 79, 81, 83, 90, 91, 100, 109). Of note, in the retrospective study performed by Lin et al., who compared 249 women with endometriosis versus 249 control subjects, ART pregnancies were excluded and a positive association between endometriosis and a higher risk of placenta previa was detected (adjusted OR 4.51, 95% CI 1.23–16.50) (90). Furthermore, in a prospective cohort study examining the effects of endometriosis on pregnancy outcome in 330 pregnant Japanese women previously diagnosed for endometriosis versus 8,856 control subjects, a positive association between a higher rate of placenta previa and endometriosis among women without infertility treatment was reported, after adjustment for age, alcohol drinking, smoking, and passive smoking (adjusted OR 3.31, 95% CI 1.16–9.41; $P<.05$). In the same study, the ORs of placenta previa were significantly higher than in women never diagnosed with endometriosis who conceived naturally or conceived after infertility treatment, except for ART therapy (99). In 2012, Vercellini et al. retrospectively assessed pregnancy outcomes in 419 women who achieved a first spontaneous singleton pregnancy after surgery for endometriosis and stratified the results obtained by endometriosis localization. It was interesting to observe a higher incidence of placenta previa in the DE population. No cases of placenta previa were observed in patients with ovarian endometriomas only, but a sixfold increase of placenta previa rate was reported in rectovaginal patients compared with only ovarian and peritoneal cases (OR 5.81, 95% CI 1.53–22.03; $P=.03$) (80).

A French study found similar results with an increase of antenatal bleeding that the authors linked to a higher rate of placenta previa (88). Also an Italian group, who analyzed 52 women affected by posterior DE versus 300 control subjects, found an association but did not adjust for ART procedures (OR 61.56, 95% CI 7.351–515.5; $P<.001$) (94). Similarly, another Italian group supported this positive correlation (OR 0.29, 95% CI 0.10–0.81; $P=.03$) without adjusting for ART treatments (104). In contrast, Jacques et al. did not find an increased rate of placenta previa among ART patients with operated endometriosis, even evaluating separately women with deep locations ($n = 39$) versus ovarian locations ($n = 49$) (96). A number of studies did not report any association, owing to the low incidence of the disease (93).

In conclusion, there is a strong need for adjustment for ART procedures to understand the real contribution of endometriosis as a possible causal factor for placenta previa.

OBSTETRICAL HEMORRHAGES (ABRUPTIO PLACENTAE AND ANTEPARTUM AND POSTPARTUM BLEEDING)

Considering all the different types of endometriosis as a unique group (DE, adenomyosis, superficial peritoneal endometriosis, and endometriomas), a number of studies excluded a higher incidence of placental abruption among women affected by the disease (74, 79, 81, 90). Vercellini et al. reported a similar incidence of placental abruption in rectovaginal cases compared with ovarian and peritoneal endometriosis, but the numbers were considered by the authors to be too small to evaluate statistical significance (80). Analyzing the large nationwide studies made on records as a group apart, Stephansson et al. and Stern et al. reported a higher incidence of bleeding without distinguishing antepartum and postpartum hemorrhage (77, 89). Only Healy et al. described a higher incidence of postpartum bleeding in women affected by endometriosis and undergoing ART (adjusted OR 1.28, 95% CI 1.06–1.56; $P<.05$) (79). In line with those large studies, a recent Scottish nationwide study reported a higher incidence of unexplained antepartum hemorrhage (OR 1.67, 95% CI 1.39, 2.00; $P<.05$) and postpartum hemorrhage (OR 1.30, 95% CI 1.61, 1.46; $P<.05$) in women with endometriosis, without specifying the type of the disease or the severity (109). In 2015, Kmietowicz et al., after adjusting the data for age and previous pregnancy, found that among women who carried the pregnancy past 24 weeks, those with endometriosis (type of endometriosis not specified) were also more likely to have unexplained antepartum hemorrhage (OR 1.67, 95% CI 1.39–2.00; $P<.05$) and postpartum bleeding (OR 1.30, 95% CI 1.61–1.46; $P<.05$) than women without endometriosis (91).

In contrast, in a large Danish cohort study, Glavind et al. did not find differences between an endometriosis group and control subjects regarding postpartum hemorrhage, even after adjusting for ART procedures (105). In another large Danish study, the OR for antepartum hemorrhage was increased in

the endometriosis group (adjusted OR 2.3, 95% CI 2.0–2.5; $P<.05$) after adjusting for age and calendar year. Postpartum hemorrhage was surprisingly slightly lower in women with endometriosis than in unexposed women. When stratified by mode of delivery, women with endometriosis who delivered by means of CS had an adjusted OR of bleeding of 1.1 (95% CI 1.0–1.2; $P<.05$) (73). Focusing on DE, a study by Uccella et al., conducted with 26 women who underwent laparoscopic ureterolysis for endometriosis, reported only one case (3.8%) of hemorrhage during pregnancy and no cases of postpartum hemorrhage (102). Jacques et al. also did not find an increased rate of postpartum hemorrhage among patients with endometriosis compared with control subjects, even evaluating separately women with deep locations (n = 39; 8.2%) versus women with ovarian locations (n = 49; 7.7%), all analyzed after surgery (96). Thomin et al., considering 72 pregnancies of women affected by colorectal endometriosis and comparing those who delivered by means of CS (n = 36) versus those who delivered vaginally (n = 36), did not find differences between the two groups and reported only two cases of postpartum bleeding (2% globally) in the CS group (103). Petresin et al. described a case of rectovaginal endometriosis left in situ during laparoscopic intervention (consent to treat it surgically was lacking) and causing, years later, recurrent heavy vaginal bleeding during the 27th and 28th weeks of gestation. Owing to the impossibility of individuating the cause of bleeding, obstetricians decided to perform a CS despite the early gestational age. Numerous actively bleeding serosal defects were found on the posterior uterine wall and anterior surface of the rectum, and a torn adhesion was found between the bowel (sigmoid colon/rectum) and the uterus. Attempted hemostasis with the use of sutures was unsuccessful owing to tissue vulnerability. The posterior uterine wall was therefore covered with hemostatic fibrin glue and compression applied. A Robinson drain was inserted also, and there were no postoperative complications (57).

Exacoustos et al. reported a case of postpartum hemorrhage due to an extensive vaginal laceration, requiring blood transfusion, in the group of posterior DE, but when compared with control subjects statistical significance was not reached (94). Similarly, an Italian group compared 40 women with DE versus 222 women without DE and again did not find significant differences in postpartum hemorrhage (104).

In conclusion, considering all types of endometriosis we can debate an eventual association with postpartum hemorrhage, considering that adjustment for ART is rarely performed. On the other hand, a clear association between DE and postpartum bleeding can not be stated. Therefore, knowing the risks associated with endometriosis in general and with increased risk of bleeding could be helpful in planning the delivery of women affected by endometriosis in the appropriate setting, i.e., where specialist care is available.

CESAREAN SECTION

There are no guidelines concerning the mode of delivery in pregnant women after surgery for DE. The "Guideline for Diagnosis and Therapy of Endometriosis" only suggests that the mode of delivery should be discussed with each patient individually (115). In 2016 an interesting study by a French group evaluated a group of women affected by colorectal endometriosis, subdividing those after surgery and those with colorectal endometriosis left in situ. Presence of or earlier surgery for DE with colorectal endometriosis was not considered to be an indication for systematic CS. However, a high incidence of CS was reported in both groups, regardless of the earlier intervention (56% in the surgery group and 41% in women with in situ colorectal endometriosis); 39% of the CSs were planned, and 61% were performed during labor. Thus, previous surgery is not a determining parameter in the decision of the route of delivery. The high incidence of planned CS was explained by the authors by a high incidence of breech presentations and 40% of pregnancies from IVF treatments, although they did not specify how IVF treatments were considered to be indications for CS. Furthermore, the authors reported three important and innovative considerations of their data First, a high incidence of difficulty at extraction during CS was observed particularly in women with anterior DE, but not in women with previous colorectal surgery. Second, both CS and vaginal delivery were associated with a high risk of postpartum complications, but the lower incidence after vaginal delivery compared with CS (14% vs. 39%; $P=.03$) should promote vaginal delivery in case of DE. Third, vaginal delivery in women with colorectal endometriosis was associated with a high rate of operative procedures (28%), particularly in the group who had not previously undergone surgery (41% vs. 16%) (103).

Analyzing five studies in which only women affected by DE after surgery were enrolled, four of them reported a higher incidence of CS compared with non-DE patients (93, 94, 96, 102, 104). In the study by Allerstorfer et al., the Enzian classification for DE was used, defining compartment A as the rectovaginal septum and vagina, B the sacrouterine ligament and pelvic wall, and C the bowel. The author reported that women with endometriosis of Enzian compartment A or C had a statistically higher risk of delivery via CS than women without endometriosis in those compartments ($P=.020$ and $P=.031$). There was also a statistically significant elevated CS rate when a rectal resection had been performed ($P=.029$) (93). All of the large studies evaluating nationwide databases on all types of endometriosis reported a higher rate of CS compared with control subjects (73, 77, 89–91, 105, 109). In contrast, evaluating only endometrioma groups, Benaglia et al. did not find a higher rate of CS (101, 114).

In conclusion, a higher incidence of CS among women with DE has been reported, with several reasons suggested (association with IVF procedures, different approach to "precious pregnancies" [pregnancies achieved via ART], anxiety of the gynecologists). The most innovative findings regarding DE and CS are two: first, a higher incidence of difficulty at extraction during CS in women with anterior DE, but not in women with prior colorectal surgery; and second, the lower incidence of postpartum complications after vaginal delivery compared with CS, suggesting a promotion of vaginal delivery in case of DE.

DISCUSSION

Over the past few years, the potential impact of endometriosis on pregnancy and delivery outcomes has become a hot topic among clinicians and researchers. The issue is particularly relevant because it may influence the management of pregnancy and delivery of the population of patients affected by endometriosis, and it may allow the offering to these women of more exhaustive counseling to be informed about potential higher risks compared with the general population. Overall, almost all published studies are significantly biased by several confounding factors (disease phenotypes, presence/exclusion of adenomyosis, method of conceiving [natural or ART], choice of control, and general methodologic design) that prevent drawing reliable conclusions on the impact of endometriosis on the normal course of pregnancy and delivery. The present review aimed to summarize the available evidence on the impact of DE on obstetrical outcomes. However, very few studies focused specifically on patients with DE or stratified their analyses considering this population of patients; therefore, it was complex to extrapolate information from the available evidence and to elucidate if the three different phenotypes (ovarian endometrioma, superficial peritoneal endometriosis, and DE) may differently interfere with the pregnancy and delivery.

In addition, we consider that one main criticism of the current literature is the poor evaluation on the coexistence of adenomyosis in patients with DE. In fact, it is well established that adenomyosis may be associated with endometriosis, with a prevalence 22%–91% (116–118). In particular, adenomyosis may play an important role in the onset of obstetrical complications (e.g., uterine rupture) and alterations of the physiologic development of the pregnancy. Correlations of adenomyosis with miscarriage, preterm premature rupture of membranes, and preterm birth have been reported (111, 119–121). This can be explained by the fact that alterations in the inner myometrium occurring in women with adenomyosis may be at the root of a defective remodeling of the myometrial spiral arteries from the onset of decidualization and result in vascular resistance and increased risk of defective deep placentation. The association of major obstetrical syndromes and different types of defective remodeling of the myometrial spiral arteries has been well documented (120). Therefore, future studies should carefully consider the presence of adenomyosis in patients with endometriosis to overcome this limitation, and, ideally, case-control studies should be designed to assess the impact of adenomyosis itself on pregnancy.

The present literature review has shown that several types of acute complications may occur during pregnancy among women with DE. A total of 120 cases of DE-related complications during pregnancy have been reported; SH (n = 25), bowel perforation (n = 17), and uterine rupture (n = 63) are the most common events. However, it is likely that the frequency of these events is underestimated owing to unreported cases, suggesting the need to design epidemiologic studies aiming to estimate the incidence of these complications in the population of pregnant women with endometriosis. In particular, such research should also be finalized to distinguish the occurrence of obstetrical complications according to the subtype of endometriosis and to the stage of the disease to identify high-risk patients. On the basis of available evidence, obstetrical complications in pregnant women with endometriosis are rare and unpredictable. Currently, there is no study that aimed to elucidate whether the surgical treatment of endometriosis before the onset of pregnancy may reduce the risk of these acute complications. Theoretically, surgery for endometriosis consisting of lysis of adhesions and excision of endometriotic lesions may reduce the risk of spontaneous rupture of viscera and of SH. On the other hand, the treatment of endometriosis located at the level of the uterine isthmus or the surgical excision of rectovaginal nodules may weaken the posterior uterine wall, putting the uterus at risk of rupture during pregnancy or delivery. However, the absence of evidence on this issue does not support any form of prophylactic surgery before pregnancy to prevent such complications.

Results on pregnancy and delivery outcomes are extremely controversial. As previously stated, the studies investigating this topic are characterized by several limitations, including small sample size, lack of adjustment for confounders, and lack of adequate control.

It is difficult to debate on the association between DE and miscarriage owing to the inclusion of different subtypes of endometriosis without clear distinction and stratification of the findings. Most of the studies investigating this issue did not find any association (80, 86, 92, 94, 101, 113). However, two large cohort studies reported an increased risk among women affected by endometriosis (84, 109). Furthermore, one of the analyzed studies found an increased rate of miscarriage among women affected by all of the three types of endometriosis (superficial endometriosis, endometriomas, and DE) (97).

The majority of the studies trying to unravel the possible association between endometriosis and hypertensive disorders in pregnancy did not find an association between the two conditions (75, 76, 81, 84–86, 89, 90, 109). On the other hand, nationwide studies tend to suggest that endometriosis can result in higher rates of hypertensive disorders, including preeclampsia, and these events would occur even in the absence of ART treatment. However, it is important to emphasize that none of these studies stratified the results to consider only women affected by DE.

Although an association between endometriosis in general and surgically treated DE with FGR has not been observed, interesting findings derived from studies investigating the relationship between DE and preterm delivery suggest a higher risk in this population of patients. An intriguing challenge of future studies will be to distinguish between spontaneous and iatrogenic preterm birth, answering the question of whether endometriosis per se may cause uterine contractions and preterm labor or may create clinical or behavioral conditions (bleeding, abdominal pain, anxiety in the operators) that can result in a CS in early gestational ages.

Considering all types of endometriosis, some evidence suggests a potential association with antepartum and

postpartum hemorrhages (considering that adjustment for ART is rarely performed), whereas a clear association between DE and obstetrical hemorrhages can not be stated.

Overall, a higher incidence of CS among women with DE has been reported. However, future studies should clarify the main indication of CS, because it is rarely reported in currently available studies. In fact, it can be hypothesized that previous surgery for endometriosis may influence the choice for elective CS. Moreover, the high number of patients with endometriosis conceiving by ART procedures should be considered. These pregnancies may be seen to be more valuable than others and, despite absence of any clinical indication, compared with the general population, such babies are more frequently delivered by means of CS in common clinical practice (122).

A higher incidence of placenta previa in women affected by endometriosis has been reported in several studies (73, 77, 79, 81, 83, 90, 91, 100, 109), also considering patients with only DE (80, 88, 94, 104). The presence of ART populations should be considered as a potential confounding factor because ART is associated per se with a higher rate of placental abnormalities, and future studies should carefully distinguish the modality of conceiving to draw clearer conclusions on this topic. The higher rates of placenta previa in patients with endometriosis may be explained by the abnormal frequency and amplitude of uterine contractions demonstrated in women with endometriosis causing anomalous blastocyst implantation (123).

The current literature prevents elucidating the role of surgical treatment of endometriosis on pregnancy and delivery outcomes. Surgery may be indicated to increase the chances of getting pregnant (124), but in our opinion, it is unlikely that surgery may represent the cure for the molecular and functional abnormalities of the eutopic endometrium (125), the local and systemic higher levels of inflammation (126–128), the alteration in the uterine JZ (127, 129), and the inadequate uterine contractility (130) reported in women with endometriosis. However, no study has investigated whether prophylactic surgery may affect the rates of obstetrical disorders during pregnancy and delivery of women with endometriosis. Therefore, there is a need to plan well designed studies (ideally, randomized controlled trials) to address this lack of knowledge.

REFERENCES

1. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 1997;68:585–96.
2. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril 2012;98:564–71.
3. Vercellini P, Frontino G, Pietropaolo G, Gattei U, Daguati R, Crosignani PG. Deep endometriosis: definition, pathogenesis, and clinical management. J Am Assoc Gynecol Laparosc 2004;11:153–61.
4. Brosens IA, Fusi L, Brosens JJ. Endometriosis is a risk factor for spontaneous hemoperitoneum during pregnancy. Fertil Steril 2009;92:1243–5.
5. Petraglia F, Arcuri F, de Ziegler D, Chapron C. Inflammation: a link between endometriosis and preterm birth. Fertil Steril 2012;98:36–40.
6. May K, Becker CM. Endometriosis and angiogenesis. Minerva Ginecol 2008;60:245–54.
7. Taylor RN, Yu J, Torres PB, Schickedanz AC, Park JK, Mueller MD, et al. Mechanistic and therapeutic implications of angiogenesis in endometriosis. Reprod Sci 2009;16:140–6.
8. Viganò P, Corti L, Berlanda N. Beyond infertility: obstetrical and postpartum complications associated with endometriosis and adenomyosis. Fertil Steril 2015;104:802–12.
9. Leone Roberti Maggiore U, Ferrero S, Mangili G, Bergamini A, Inversetti A, Giorgione V, et al. A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes. Hum Reprod Update 2016;22:70–103.
10. Clement PB. Perforation of the sigmoid colon during pregnancy: a rare complication of endometriosis. Case report. Br J Obstet Gynaecol 1977; 84:548–50.
11. Gini PC, Chukudebelu WO, Onuigbo WI. Perforation of the appendix during pregnancy: a rare complication of endometriosis. Case report. Br J Obstet Gynaecol 1981;88:456–8.
12. Floberg J, Bäckdahl M, Silferswärd C, Thomassen PA. Postpartum perforation of the colon due to endometriosis. Acta Obstet Gynecol Scand 1984; 63:183–4.
13. Nakatani Y, Hara M, Misugi K, Korehisa H. Appendiceal endometriosis in pregnancy. Report of a case with perforation and review of the literature. Acta Pathol Jpn 1987;37:1685–90.
14. Loverro G, Cormio G, Pantaleo G, Altomare D, Putignano G, Selvaggi L. Perforation of the sigmoid colon during pregnancy: a rare complication of endometriosis. J Gynecol Surg 1999;15:155–7.
15. Schweitzer KJ, van Bekkum E, de Groot CJM. Endometriosis with intestinal perforation in term pregnancy. Int J Gynaecol Obstet 2006;93: 152–3.
16. Faucheron J-L, Pasquier D, Voirin D. Endometriosis of the vermiform appendix as an exceptional cause of acute perforated appendicitis during pregnancy. Colorectal Dis 2008;10:518–9.
17. Beamish RE, Aslam R, Gilbert JM. Postpartum caecal perforation due to endometriosis. JRSM Short Rep 2010;1:61.
18. Pisanu A, Deplano D, Angioni S, Ambu R, Uccheddu A. Rectal perforation from endometriosis in pregnancy: case report and literature review. World J Gastroenterol 2010;16:648–51.
19. Boileau L, Borie F, Laporte S, Tailland ML, Mares P, de Tayrac R. Pelviperitonitis by colorectal perforation in the third trimester of pregnancy after surgery for deep pelvic endometriosis. Fertil Steril 2011;96:e42–4.
20. Lebastchi AH, Prieto PA, Chen C, Lui FY. Appendiceal endometriosis in a pregnant woman presenting with acute perforated appendicitis. J Surg Case Rep 2013;12:1–3.
21. Nishikawa A, Kondoh E, Hamanishi J, Yamaguchi K, Ueda A, Sato Y, et al. Ileal perforation and massive intestinal haemorrhage from endometriosis in pregnancy: case report and literature review. Eur J Obstet Gynecol Reprod Biol 2013;170:20–4.
22. Setúbal A, Sidiropoulou Z, Torgal M, Casal E, Lourenço C, Koninckx P. Bowel complications of deep endometriosis during pregnancy or in vitro fertilization. Fertil Steril 2014;101:442–6.
23. Menzlova E, Zahumensky J, Gürlich R, Kucera E. Rectal injury following delivery as a possible consequence of endometriosis of the rectovaginal septum. Int J Gynaecol Obstet 2014;124:85–6.
24. Costa A, Sartini A, Garibaldi S, Cencini M. Deep endometriosis induced spontaneous colon rectal perforation in pregnancy: laparoscopy is advanced tool to confirm diagnosis. Case Rep Obstet Gynecol 2014; 2014:907150.
25. Sriganeshan V, Willis IH, Zarate LA, Howard L, Robinson MJ. Colouterine fistula secondary to endometriosis with associated chorioamnionitis. Obstet Gynecol 2006;107(2 Pt 2):451–3.
26. Lane RE. Endometriosis of the vermiform appendix. Am J Obstet Gynecol 1960;79:372–7.
27. Tedeschi LG, Masand GP. Endometriosis of the intestines: a report of seven cases. Dis Colon Rectum 1971;14:360–5.
28. Finch DR, Lee E. Acute appendicitis complicating pregnancy in the Oxford region. Br J Surg 1974;61:129–32.
29. Nielsen M, Lykke J, Thomsen JL. Endometriosis of the vermiform appendix. Acta Pathol Microbiol Immunol Scand A 1983;91:253–6.

30. Silvestrini IE, Marcial MA. Endometriosis of the appendix with decidual polyp formation: a rare cause of acute appendicitis during pregnancy. P R Health Sci J 1995;14:223–5.
31. Stefanidis K, Kontostolis S, Pappa L, Kontostolis E. Endometriosis of the appendix with symptoms of acute appendicitis in pregnancy. Obstet Gynecol 1999;93:850.
32. Perez CM, Minimo C, Margolin G, Orris J. Appendiceal endometriosis presenting as acute appendicitis during pregnancy. Int J Gynaecol Obstet 2007;98:164–7.
33. Giorgakis E, Karydakis V, Farghaly A. Perforated endometrial appendicitis in pregnancy. Hippokratia 2012;16:181–3.
34. Dimitriadis PA, Makar RR, Kingston G, Farouk R. Appendiceal endometriosis and carcinoid presented as acute appendicitis in pregnancy: a rare case report and review of the literature. Case Rep Obstet Gynecol 2013; 2013:360459.
35. Murphy SJ, Kaur A, Wullschleger ME. Endometrial decidualization: a rare cause of acute appendicitis during pregnancy. J Surg Case Rep 2016; 2016:rjw053.
36. Inoue T, Moriwaki T, Niki I. Endometriosis and spontaneous rupture of utero-ovarian vessels during pregnancy. Lancet 1992;340:240–1.
37. Mizumoto Y, Furuya K, Kikuchi Y, Aida S, Hyakutake K, Tamai S, et al. Spontaneous rupture of the uterine vessels in a pregnancy complicated by endometriosis. Acta Obstet Gynecol Scand 1996;75:860–2.
38. Leung WC, Leung TW, Lam YH. Haemoperitoneum due to cornual endometriosis during pregnancy resulting in intrauterine death. Aust N Z J Obstet Gynaecol 1998;38:156–7.
39. Ismail KMK, Shervington J. Hemoperitoneum secondary to pelvic endometriosis in pregnancy. Int J Gynaecol Obstet 1999;67:107–8.
40. Aziz U, Kulkarni A, Kulkarni A, Lazic D, Cullimore JE. Spontaneous rupture of the uterine vessels in pregnancy. Obstet Gynecol 2004;103:1089–91.
41. O'Leary SM. Ectopic decidualization causing massive postpartum intraperitoneal hemorrhage. Obstet Gynecol 2006;108:776–9.
42. Wu C-Y, Hwang J-L, Lin Y-H, Hsieh B-C, Seow K-M, Huang L-W. Spontaneous hemoperitoneum in pregnancy from a ruptured superficial uterine vessel. Taiwan J Obstet Gynecol 2007;46:77–80.
43. Kirkinen P, Keski-Nisula L, Kuoppala T, Tommola S, Uotila J. Spontaneous bleeding from the uterine arteries during pregnancy problems in diagnosis and therapy bleeding from uterine arteries during pregnancy. Ultraschall Med 2007;28:212–5.
44. Katorza E, Soriano D, Stockheim D, Mashiach R, Zolti M, Seidman DS, et al. Severe intraabdominal bleeding caused by endometriotic lesions during the third trimester of pregnancy. Am J Obstet Gynecol 2007;197: 501.e1–4.
45. 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;21:924–6.
46. Passos F, Calhaz-Jorge C, Graça LM. Endometriosis is a possible risk factor for spontaneous hemoperitoneum in the third trimester of pregnancy. Fertil Steril 2008;89:251–2.
47. Chiodo I, Somigliana E, Dousset B, Chapron C. Urohemoperitoneum during pregnancy with consequent fetal death in a patient with deep endometriosis. J Minim Invasive Gynecol 2008;15:202–4.
48. Bouet P-E, 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;144:95–6.
49. 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;16:510–2.
50. 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;92:395.e13–6.
51. 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;148:204–5.
52. Gao JL, Lortie K, Singh SS. Laparoscopic internal iliac artery ligation for postpartum spontaneous hemoperitoneum. J Obstet Gynaecol Can 2010;32:1172–5.
53. Brouckaert OM, Oostenveld E, Quartero H. Spontaneous hemoperitoneum and fetal demisein a nulliparous woman requiring hysterectomy with fetus in situ. Int J Gynaecol Obstet 2010;110:273.
54. 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.
55. Aggarwal I, Tan P, Mathur M. Decidualised fallopian tube endometriotic implant causing spontaneous haemoperitoneum in a twin pregnancy. BMJ Case Rep 2014:2014.
56. 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;15:262–4.
57. Petresin J, Wolf J, Emir S, Müller A, Boosz AS. Endometriosis-associated maternal pregnancy complications—case report and literature. Geburtshilfe Frauenheilkd 2016;76:902–5.
58. Ploteau S, Lopes P. Regarding "recurrent hemoperitoneum during pregnancy in large deep endometriosis infiltrating the parametrium". J Minim Invasive Gynecol 2016;23:1200–1.
59. 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 Minim Invasive Gynecol 2016;23:643–6.
60. Lier M, Malik RF, van Waesberghe J, Maas JW, van Rumpt-van de Geest DA, Coppus SF, et al. Spontaneous haemoperitoneum in pregnancy and endometriosis: a case series. BJOG 2017;124:306–12.
61. Yaqub U, Hassan S-E, Yusaf Z, Yusuf AW. Endometriosis in the renal area. J Coll Physicians Surg Pak 2008;18:174–5.
62. Pezzuto A, Pomini P, Steinkasserer M, Nardelli GB, Minelli L. Patient with pelvic pains: retroperitoneal fibrosis or pelvic endometriosis? A case report and review of literature. Fertil Steril 2009;92:1497.e9–12.
63. Leone Roberti Maggiore U, Remorgida V, Sala P, Vellone VG, Biscaldi E, Ferrero S. Spontaneous uroperitoneum and preterm delivery in a patient with bladder endometriosis. J Minim Invasive Gynecol 2015;22:701–2.
64. van de Putte I, Campo R, Gordts S, Brosens I. Uterine rupture following laparoscopic resection of rectovaginal endometriosis: a new risk factor? Br J Obstet Gynaecol 1999;106:608–9.
65. Sholapurkar SL, Sharp NC, Hirschowitz L. Life-threatening uterine haemorrhage six weeks after cesarean section due to uterine scar endometriosis: case report and review of literature. Aust N Z J Obstet Gynaecol 2005; 45:256–8.
66. Villa G, Mabrouk M, Guerrini M, Mignemi G, Colleoni GG, Venturoli S, et al. Uterine rupture in a primigravida with adenomyosis recently subjected to laparoscopic resection of rectovaginal endometriosis: case report. J Minim Invasive Gynecol 2008;15:360–1.
67. Dim CC, Agu PU, Dim NR, Ikeme AC. Adenomyosis and uterine rupture during labour in a primigravida: an unusual obstetric emergency in Nigeria. Trop Doct 2009;39:250–1.
68. Granese R. Acute abdomen in pregnancy with endometriosis. Acta Obstet Gynecol Scand 2010;89:844–5.
69. Chen ZHY, Chen M, Tsai H-D, Wu C-H. Intrapartum uterine rupture associated with a scarred cervix because of a previous rupture of cystic cervical endometriosis. Taiwan J Obstet Gynecol 2011;50:95–7.
70. Nikolaou M, Kourea HP, Antonopoulos K, Geronatsiou K, Adonakis G, Decavalas G. Spontaneous uterine rupture in a primigravid woman in the early third trimester attributed to adenomyosis: a case report and review of the literature. J Obstet Gynaecol Res 2013;39:727–32.
71. Fettback PB, Pereira RM, Domingues TS, Zacharias KG, Chamié LP, Serafini PC. Uterine rupture before the onset of labor following extensive resection of deeply infiltrating endometriosis with myometrial invasion. Int J Gynaecol Obstet 2015;129:268–70.
72. Otsubo Y, Nishida M, Arai Y, Ichikawa R, Taneichi A, Sakanaka M. Association of uterine wall thickness with pregnancy outcome following

uterine-sparing surgery for diffuse uterine adenomyosis. Aust N Z J Obstet Gynaecol 2016;56:88–91.
73. Berlac JF, Hartwell D, Skovlund CW, Langhoff-Roos J, Lidegaard Ø. Endometriosis increases the risk of obstetrical and neonatal complications. Acta Obstet Gynecol Scand 2017;96:751–60.
74. Kortelahti M, Anttila MA, Hippeläinen MI, Heinonen ST. Obstetric outcome in women with endometriosis—a matched case control study. Gynecol Obstet Invest 2003;56:207–12.
75. Brosens IA, de Sutter P, Hamerlynck T, Imeraj L, Yao Z, Cloke B, et al. Endometriosis is associated with a decreased risk of pre-eclampsia. Hum Reprod 2007;22:1725–9.
76. Hadfield RM, Lain SJ, Raynes-Greenow CH, Morris JM, Roberts CL. Is there an association between endometriosis and the risk of pre-eclampsia? A population based study. Hum Reprod 2009;24:2348–52.
77. Stephansson O, Kieler H, Granath F, Falconer H. Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome. Hum Reprod 2009;24:2341–7.
78. Fernando S, Breheny S, Jaques AM, Halliday JL, Baker G, Healy D. Preterm birth, ovarian endometriomata, and assisted reproduction technologies. Fertil Steril 2009;91:325–30.
79. Healy DL, Breheny S, Halliday J, Jaques A, Rushford D, Garrett C, et al. Prevalence and risk factors for obstetrics haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia. Hum Reprod 2010;25:265–74.
80. Vercellini P, Parazzini F, Pietropaolo G, Cipriani S, Frattaruolo M, Fedele L. Pregnancy outcome in women with peritoneal, ovarian and rectovaginal endometriosis: a retrospective cohort study. BJOG 2012;119:1538–43.
81. Kuivasaari-Pirinen P, Raatikainen K, Hippeläinen M, Heinonen S. Adverse outcomes of IVF/ICSI pregnancies vary depending on aetiology of infertility. ISRN Obstet Gynecol 2012;2012:451915.
82. Tobias DK, Chavarro JE, Williams MA, Buck Louis GM, Hu FB, Rich-Edwards J, et al. History of infertility and risk of gestational diabetes mellitus: a prospective analysis of 40,773 pregnancies. Am J Epidemiol 2013;178:1219–25.
83. Takemura Y, Osuga Y, Fujimoto A, Oi N, Tsutsumi R, Koizumi M, et al. Increased risk of placenta previa is associated with endometriosis and tubal factor infertility in assisted reproductive technology pregnancy. Gynecol Endocrinol 2013;29:113–5.
84. Aris A. A 12-year cohort study on adverse pregnancy outcomes in Eastern Townships of Canada: impact of endometriosis. Gynecol Endocrinol 2014;30:34.
85. Conti N, Cevenini G, Vannuccini S, Orlandini C, Valensise H, Gervasi MT, et al. Women with endometriosis at first pregnancy have an increased risk of adverse obstetric outcome. J Matern Fetal Neonatal Med 2014;9:1–4.
86. Mekaru K, Masamoto H, Sugiyama H, Asato K, Heshiki C, Kinjyo T, et al. Endometriosis and pregnancy outcome: are pregnancies complicated by endometriosis a high-risk group? Eur J Obstet Gynecol Reprod Biol 2014;172:36–9.
87. Uccella S, Cromi A, Casarin J, Bogani G, Pinelli C, Serati M, et al. Laparoscopy for ureteral endometriosis: surgical details, long-term follow-up, and fertility outcomes. Fertil Steril 2014;102:160–6.e2.
88. Carassou-Maillan A, Pouly JL, Mulliez A, Dejou-Bouillet L, Gremeau AS, Brugnon F, et al. Adverse pregnancy outcomes after assisted reproduction technology in women with endometriosis. Gynecol Obstet Fertil 2014;42:210–5.
89. Stern JE, Luke B, Tobias M, Gopal D, Hornstein MD, Diop H. Adverse pregnancy and birth outcome associated with underlying diagnosis with and without assisted reproductive technology treatment. Fertil Steril 2015;103:1438–45.
90. Lin H, Leng JH, Liu JT, Lang JH. Obstetric outcomes in Chinese women with endometriosis: a retrospective cohort study. Chin Med J 2015;128:455–8.
91. Kmietowicz Z. Endometriosis is linked to greater risk of complications in pregnancy and birth, study finds. BMJ 2015;350:h3252.
92. Leonardi M, Papaleo E, Reschini M, Pagliardini L, Benaglia L, Candotti G, et al. Risk of miscarriage in women with endometriosis: insights from in vitro fertilization cycles. Fertil Steril 2016;106:386–92.e3.
93. Allerstorfer C, Oppelt P, Enzelsberger SH, Shamiyeh A, Schimetta W, Shebl OJ, et al. Delivery after operation for deeply infiltrating endometriosis. Biomed Res Int 2016;2016:8271452.
94. Exacoustos C, Lauriola I, Lazzeri L, de Felice G, Zupi E. Complications during pregnancy and delivery in women with untreated rectovaginal deep infiltrating endometriosis. Fertil Steril 2016;106:1129–35.e1.
95. Saavalainen L, Heikinheimo O, Tiitinen A, Härkki P. Deep infiltrating endometriosis affecting the urinary tract—surgical treatment and fertility outcomes in 2004–2013. Gynecol Surg 2016;13:435–44.
96. Jacques M, Freour T, Barriere P, Ploteau S. Adverse pregnancy and neonatal outcomes after assisted reproductive treatment in patients with pelvic endometriosis: a case-control study. Reprod Biomed Online 2016;32:626–34.
97. Santulli P, Marcellin L, Menard S, Thubert T, Khoshnood B, Gayet V, et al. Increased rate of spontaneous miscarriages in endometriosis-affected women. Hum Reprod 2016;31:1014–23.
98. Kim SC, Lee NK, Yun KY, Joo JK, Suh DS, Kim KH. A rapidly growing adenomyosis associated with preterm delivery and postpartum abscess formation. Taiwan J Obstet Gynecol 2016;55:620–2.
99. Harada T, Taniguchi F, Onishi K, Kurozawa Y, Hayashi K, Harada T, et al. Obstetrical Complications in women with endometriosis: a cohort study in Japan. PLoS One 2016;11:e0168476.
100. Fujii T, Wada-Hiraike O, Nagamatsu T, Harada M, Hirata T, Koga K, et al. Assisted reproductive technology pregnancy complications are significantly associated with endometriosis severity before conception: a retrospective cohort study. Reprod Biol Endocrinol 2016;14:73.
101. Benaglia L, Candotti G, Papaleo E, Pagliardini L, Leonardi M, Reschini M, et al. Pregnancy outcome in women with endometriosis achieving pregnancy with IVF. Hum Reprod 2016;31:2730–6.
102. Uccella S, Cromi A, Agosti M, Casarin J, Pinelli C, Marconi N, et al. Fertility rates, course of pregnancy and perinatal outcomes after laparoscopic ureterolysis for deep endometriosis: a long-term follow-up study. J Obstet Gynaecol 2016;36:800–5.
103. Thomin A, Belghiti J, David C, Marty O, Bornes M, Ballester M, et al. Maternal and neonatal outcomes in women with colorectal endometriosis. BJOG, Published online 2016.
104. Mannini L, Sorbi F, Noci I, Ghizzoni V, Perelli F, Di Tommaso M, et al. New adverse obstetrics outcomes associated with endometriosis: a retrospective cohort study. Arch Gynecol Obstet 2017;295:141–51.
105. Glavind MT, Forman A, Arendt LH, Nielsen K, Henriksen TB. Endometriosis and pregnancy complications: a Danish cohort study. Fertil Steril 2017;107:160–6.
106. Pallacks C, Hirchenhain J, Krüssel JS, Fehm TN, Fehr D. Endometriosis doubles odds for miscarriage in patients undergoing IVF or ICSI. Eur J Obstet Gynecol Reprod Biol 2017;213:33–8.
107. Pan ML, Chen LR, Tsao HM, Chen KH. Risk of gestational hypertension-preeclampsia in women with preceding endometriosis: a nationwide population-based study. PLoS One 2017;12:e0181261.
108. Li H, Zhu HL, Chang XH, Li Y, Wang Y, Guan J, et al. Effects of previous laparoscopic surgical diagnosis of endometriosis on pregnancy outcomes. Chin Med J (Engl) 2017;130:428–33.
109. Saraswat L, Ayansina DT, Cooper KG, Bhattacharya S, Miligkos D, Horne AW, et al. Pregnancy outcomes in women with endometriosis: a national record linkage study. BJOG 2017;124:444–52.
110. Stirrat GM. Recurrent miscarriage. Lancet 1990;336:673–5.
111. Juang CM, Chou P, Yen MS, Twu NF, Horng HC, Hsu WL. Adenomyosis and risk of preterm delivery. BJOG 2007;114:165–9.
112. Centini G, Afors K, Murtada R, Argay IM, Lazzeri L, Akladios CY, et al. Impact of laparoscopic surgical management of deep endometriosis on pregnancy rate. J Minim Invasive Gynecol 2016;23:113–9.
113. Mochimaru A, Aoki S, Oba MS, Kurasawa K, Takahashi T, Hirahara F. Adverse pregnancy outcomes associated with adenomyosis with uterine enlargement. J Obstet Gynaecol Res 2015;41:529–33.

114. Benaglia L, Bermejo A, Somigliana E, Scarduelli C, Ragni G, Fedele L, et al. Pregnancy outcome in women with endometriomas achieving pregnancy through IVF. Hum Reprod 2012;27:1663–7.
115. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, d'Hooghe T, de Bie B, et al. European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.
116. Kunz G, Beil D, Huppert P, Noe M, Kissler S, Leyendecker G. Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging. Hum Reprod 2005;20:2309–16.
117. di Donato N, Montanari G, Benfenati A, Leonardi D, Bertoldo V, Monti G, et al. Prevalence of adenomyosis in women undergoing surgery for endometriosis. Eur J Obstet Gynecol Reprod Biol 2014;181:289–93.
118. Leyendecker G, Bilgicyildirim A, Inacker M, Stalf T, Huppert P, Mall G, et al. Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. Arch Gynecol Obstet 2015;291:917–32.
119. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod 2014b;29:964–77.
120. Brosens I, Pijnenborg R, Benagiano G. Defective myometrial spiral artery remodelling as a cause of major obstetrical syndromes in endometriosis and adenomyosis. Placenta 2013;34:100–5.
121. Benagiano G, Brosens I, Habiba M. Adenomyosis: a life-cycle approach. Reprod Biomed Online 2015;30:220–32.
122. Minkoff HL, Berkowitz R. The myth of the precious baby. Obstet Gynecol 2005;106:607–9.
123. Kunz G, Beil D, Huppert P, Leyendecker G. Structural abnormalities of the uterine wall in women with endometriosis and infertility visualised by vaginal sonography and magnetic resonance imaging. Hum Reprod 2000;15:76–82.
124. Leone Roberti Maggiore U, Scala C, Tafi E, Racca A, Biscaldi E, Vellone VG, et al. Spontaneous fertility after expectant or surgical management of rectovaginal endometriosis in women with or without ovarian endometrioma: a retrospective analysis. Fertil Steril 2017;107:969–76.e5.
125. Brosens I, Brosens JJ, Benagiano G. The eutopic endometrium in endometriosis: are the changes of clinical significance? Reprod Biomed Online 2012;24:496–502.
126. Gentilini D, Perino A, Viganò P, Chiodo I, Cucinella G, Vignali M, et al. Gene expression profiling of peripheral blood mononuclear cells in endometriosis identifies genes altered in nongynaecologic chronic inflammatory diseases. Hum Reprod 2011;26:3109–17.
127. Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update 2014;20:386–402.
128. Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. Fertil Steril 2016;106:1011–7.
129. Exacoustos C, Luciano D, Corbett B, DeFelice G, di Feliciantonio M, Luciano A, et al. The uterine junctional zone: a 3-dimensional ultrasound study of patients with endometriosis. Am J Obstet Gynecol 2013;209:248.e1–7.
130. Aguilar HN, Mitchell BF. Physiological pathways and molecular mechanisms regulating uterine contractility. Hum Reprod Update 2010;16:725–44.