Beyond infertility: obstetrical and postpartum complications associated with endometriosis and adenomyosis

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The risk of pregnancy and neonatal complications in women with endometriosis and adenomyosis is debatable. A literature review looking at rates, presentation, and management of spontaneous hemoperitoneum, enlargement, abscess, and rupture of an endometrioma, uterine rupture, and bowel perforation in pregnant women with endometriosis was conducted. Moreover, studies addressing differences in early pregnancy (miscarriage), late pregnancy (gestational diabetes mellitus, preeclampsia, prematurity, placenta previa, placental abruption, cesarean section, hemorrhages) and neonatal outcomes (weight at birth) between endometriosis and adenomyosis patients versus control subjects were reviewed. The overall prevalence of endometriosis-related spontaneous hemoperitoneum in pregnancy is estimated to be ~0.4%. Only four cases of endometrioma rupture in pregnancy have been reported. Although during pregnancy there is no way to anticipate the onset of complications from preexisting endometriosis, it is important, when a specific abdominal pain occurs, to suspect rare but potentially life-threating events. Population-based studies suggest a possible association of endometriosis with preterm birth and placenta previa. Limits of the published studies are noted and discussed. (Fertil Steril® 2015;104:802–12. ©2015 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, adenomyosis, pregnancy, complication, preterm birth, placenta previa

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Endometriosis, an estrogen-dependent disorder causing pain and affecting fertility through different mechanisms, is responsible for inflammatory alterations occurring not only in the peritoneal cavity but also at the endometrial level (1). Indeed, available evidence supports the concept that the endometrial microenvironment of women with endometriosis differs in some aspects from the endometrium of unaffected women. Important reviews have indeed focused on these differences, which mainly involve an abnormal expression of genes involved in local estrogen production and response to progesterone, an altered oxidative stress response, presence of cytokines, inflammatory mediators, and apoptotic markers (2, 3). Although these abnormalities are expected to affect fertility and in vitro fertilization (IVF) outcomes (1, 4), whether they might also affect pregnancy outcomes represents an emerging area of interest. It is important to emphasize in this context that an alteration of the dynamic cellular remodeling and the local immune response in the endometrium at the early stage of pregnancy is thought to have strong consequences later (2, 5, 6). Indeed, trophoblastic invasion into the "myometrial junctional zone" represents a critical event in determining the outcome of pregnancy because an inadequate placentation, characterized by abnormal spiral artery remodeling, inflammation, oxidative stress, and an imbalance in the angiogenic milieu is thought to be a common underlying contributing factor for various adverse fetal and maternal outcomes (7). On the basis of these premises, the general aim of the present review is to verify whether the altered endometrial or peritoneal environments characteristic of women with endometriosis might be reflected by a negative impact on pregnancy

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outcomes. More specifically, the wide spectrum of obstetrical events originating either in the ectopic implants or in the uterus will be described, and studies addressing the adverse pregnancy outcomes in women affected will be reviewed and discussed. Finally, because endometriosis and adenomyosis often coexist (8), and in both conditions the eutopic endometrium shows functional and structural abnormalities (7), the risk of poor pregnancy/neonatal outcomes in women with adenomyosis also will be elucidated. Limits of the published studies and cues for further investigations will be noted and discussed as well.

MATERIALS AND METHODS

We searched Pubmed for articles published in the English language from January 1950 to May 2015 with the use of the following MeSH search terms: "endometriosis" or "adenomyosis" combined with "pregnancy" with restriction to the human species. Data were extracted independently by the three authors, who also performed an initial screening of the title and abstract of all articles to exclude citations deemed to be irrelevant to all observers. 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. The review was divided into two sections. In the first section, divided into five subsections, complications associated with the presence of endometriotic lesions during pregnancy were considered. For this part, given the rarity of pregnancy complications, special care was given to studies addressing the prevalence of the events. In the second section, pregnancy and neonatal outcomes in patients with endometriosis and adenomyosis were reviewed. Limitations of the results of the specific studies were specifically addressed. No Institutional Review Board approval was required, because only published deidentified data were analyzed.

COMPLICATIONS OF ENDOMETRIOTIC LESIONS DURING PREGNANCY

Endometriosis affects ~10% of premenopausal women (9). Among them, as many as 50% may have ovarian endometriotic cysts (10), some 10% bowel endometriosis (11), and 1% ureteral or vesical endometriosis (12). Although endometriotic lesions usually regress during pregnancy owing to the favorable hormonal milieu (13), complications of preexisting endometriotic foci may rarely occur.

Peritoneal Endometriosis: Spontaneous Hemoperitoneum

Prevalence. The best-designed study for evaluating the prevalence of spontaneous hemoperitoneum in pregnancy (SHiP) is a retrospective review of 800 women attending the endometriosis clinic at the University of Tel Aviv over a 5-year period. This study reports of three (0.38%) women with significant intra-abdominal bleeding occurring during the third trimester that could be directly attributed to endometriosis (14). Interestingly, all three women conceived by means of IVF.

In another study undertaken at the University of Beijing, significant intra-abdominal bleeding during the third trimester of pregnancy was reported in three out of 573 women who conceived by means of IVF over a 3-year period. Two (0.35%) of these women had endometriosis and one had pelvic inflammatory disease. However, in this study, it was not known how many women in the study group had endometriosis (15).

In a review of 20 studies published over a 20-year period from 1987 to 2008, endometriosis was identified in 13 (52%) of the 25 women who experienced SHiP (16).

Based on the limited data available, endometriosis is a major risk factor for SHiP. The overall prevalence of endometriosis-related SHiP is estimated to be ~0.4%, and the risk of SHiP is increased among women with endometriosis who conceive by means of IVF.

Pathogenesis. The phenomenon of decidualization of endometriotic lesions during pregnancy under the influence of endogenous progesterone is well known (17). In one study, the absence of decidualization was observed in only 23% of endometriotic lesions in pregnant women (13). All studies that have histologically evaluated the site of bleeding in women who underwent surgery for SHiP have found decidualized and vascularized endometriotic lesions (16, 18–20).

The mechanisms through which decidualized endometriosis could lead to spontaneous hemoperitoneum in pregnancy are unknown. In one study, it has been hypothesized that the rupture of the vessel had been the consequence of increased back-pressure, because the intrusion of decidualized stroma into the vessel wall had been observed causing significant narrowing of the lumen (21).

A possible alternative explanation proposed by Brosens and Gellersen (22) is that the bleeding is triggered by the involution of the decidualized endometrium. In fact, decidualization represents "the point of no return" in the differentiation of mesenchymal cells, after which the cellular viability becomes strictly dependent on persistent progesterone signaling (22). Therefore, when progesterone levels fall, the necrosis of decidualized endometriotic lesions could lead to the rupture of adjacent blood vessels and consequently to spontaneous hemoperitoneum of unpredictable severity (16). However, one may object that because progesterone levels fall only at the time of delivery, it is unlikely that this fall is responsible for bleeding during pregnancy. More studies are needed to investigate the influence on ectopic endometrium of the hormonal milieu associated with pregnancy and its possible role in the pathogenesis of SHiP.

Clinical presentation. The vessels that rupture and cause hemoperitoneum may be the utero-ovarian vessels, which are dilated owing to the increased blood supply to the pregnant uterus (23), varicosities on the uterine surface, or the thin-walled blood vessels located in the decidualized stroma of endometriotic lesions (20).

In women experiencing SHiP, the origin of bleeding is venous in 80% of cases, arterial in 16%, and undetermined in 4% (16). When a massive hemorrhage occurs, the sudden onset of abdominal pain is associated with hypovolemic shock, a marked reduction of hemoglobin levels, and possible

intrauterine fetal death in the absence of vaginal bleeding. These cases require an immediate laparotomy to possibly prevent fetal and maternal death.

When the amount of bleeding is less severe, the symptoms of hemoperitoneum, i.e., abdominal pain, reduction of hemoglobin levels, fetal distress, and eventually hypovolemic shock, have a much more gradual onset. Accordingly, women may be hospitalized for days (18, 24) or even weeks (14) before becoming hemodynamically unstable and requiring surgical exploration.

Atypical clinical feature associated with SHiP may be hemothorax (25) and extensive decidualization mimicking malignancy (21).

Diagnosis and differential diagnosis. The most important imaging technique for the diagnosis of SHiP is ultrasonography. Sonography is readily available and cheap, and it can be performed at the bedside without major time loss or need for patient transfer. The sonographic preoperative diagnosis of SHiP may be difficult when hemoperitoneum is mostly made of blood clots, which at ultrasound are difficult to distinguish from the bowel, when gestational age is advanced, because visualization is impaired by the pregnant uterus, and in the presence of maternal obesity (26). Despite these limitations, a very high sensitivity of 92.7% has been reported for a transabdominal ultrasound evaluation specifically focused for the detection of intraperitoneal fluid, especially when performing serial examinations (27).

The preoperative differential diagnoses of massive hemorrhagic SHiP include rupture of the liver or spleen, uterine rupture, placental abruption, HELLP syndrome, and abdominal pregnancy. In cases of slowly progressing SHiP, abdominal or pelvic pain might be misinterpreted as uterine contractions, and the administration of analgesics may delay definite diagnosis and lead to life-threatening situations for the fetus and mother.

Management. The treatment of SHiP is surgical and consists of aspiration of the hemoperitoneum, identification of the source(s) of bleeding, and achievement of satisfactory hemostasis. A review of 20 SHiP cases over a 20-year period revealed that the bleeding site in 90% was either on the posterior side of the uterus or in the parametrium (16). Consequently, surgical access to the bleeding site may be difficult in the presence of a pregnant uterus, and a few authors report the need for hysterectomy, reporting one postpartum (21) and one after emergency cesarean section (28), to achieve hemostasis. After the surgical procedure for SHiP, the pregnancy may well progress normally to term without fetal or neonatal complications (29, 30). However, Katorza et al. (14) reported about four infants who suffered severe complications after surgery for SHiP performed between 26 and 29 weeks of gestation, including respiratory distress syndrome, cerebral palsy, and severe intrauterine hypoxia. The authors point out that a crucial factor that influences fetal outcome, together with gestational age, maternal hemodynamic status, and blood loss before and during surgery, is represented by uterine manipulation. Changes in uterine position during surgery, in fact, could alter the uteroplacental perfusion and thereby result in fetal distress. Furthermore, uterine exteriorization must be done very carefully in women with severe endometriosis or who had undergone extensive surgery for Douglas obliteration, because visceral lacerations and severe bleeding are possible owing to tearing of dense adhesions between the rectosigmoid, ileal loops, adnexa, and the posterior aspect of the uterus.

Pregnancy outcome. Three reviews have reported fetal and neonatal outcome after SHiP. In 1950, a review of 75 cases reported an overall maternal mortality rate of 49.3% (23). Although maternal mortality associated with SHiP dropped dramatically to 4% from 1950 to 1987 owing to improvement of intensive care, fetal mortality remained high at 31%, with 44% of the deaths attributable to maternal shock (31). In a recent review, no maternal deaths were reported (16). However, fetal or neonatal death occurred in ten out of 28 cases, resulting in a perinatal mortality rate of 36%, which compares unfavorably to the 31% reported by Ginsburg et al. in 1987 (31).

Ovarian Endometriosis: Enlargement, Abscess, and Rupture

Prevalence. In a retrospective study evaluating 7,157 women who delivered in a single institution over an 11-year period, ovarian endometriosis in pregnancy was detected in 24 women (0.34%). In five of these women (20%; 0.1% of overall total), cysts increased in size during the second trimester. Three of these five enlarging cysts were suspicious for malignancy; two were surgically removed with histologic evidence of decidualized endometrioma, whereas the third cyst decreased in size during the third trimester after the woman had refused the operation. Both of the remaining two women with enlarging cysts required surgery, one for a tubo-ovarian abscess and one for a ruptured endometrioma (32).

In comparison, another study observing 40 endometriotic cysts in 24 women reported that at postpartum follow-up ultrasound, only two (5%) of the endometriotic cysts were increased in size compared with before pregnancy; moreover, no complications were observed during pregnancy, and no women underwent surgery. In this study, 46% of the cysts diagnosed before pregnancy were sonographically undetectable postpartum (33). The different prevalence of enlarging endometrioma observed by the two studies may reflect the different inclusion criteria. In one study (33), the diagnosis of endometriotic cyst was obtained before pregnancy by means of at least two sonographic evaluations performed at least two menstrual cycles apart, and in the other (32) all adnexal masses sonographically suggestive of endometrioma identified in the first trimester of pregnancy were retrospectively included. The hypothetic recruitment bias of the latter study may be represented by the possible erroneous inclusion of women with luteal cyst and the possible selection of women with more "evident" endometrioma (i.e., bigger endometrioma or endometrioma associated with pain symptoms).

Pathogenesis

Enlargement and vanishing of endometrioma. The suggested pathogenesis of the enlargement and vanishing of endometriotic cysts during pregnancy is the same as proposed

by Brosens et al. (16) for the genesis of spontaneous hemoperitoneum. Briefly, decidualization during early pregnancy may cause an increase in the size of the cyst. During the third trimester, however, an extensive necrosis of the endometrium covering the internal layer of the cyst occurs in most cases. Consequently the cyst, empty of viable endometrium, ultimately shrinks or disappears (33–35).

Abscess. The possible causes for the infection of an endometriotic cyst include the direct extension of the infection from the bowel wall and the hematogenous or lymphatic spread of infection (36–38).

Rupture. A possible mechanism for the rupture of an ovarian endometriotic cyst in pregnancy is the stretching of dense utero-ovarian adhesions caused by the enlarging uterus (39–41).

Clinical presentation

Enlargement of endometrioma. The enlargement of an endometrioma is usually an asymptomatic sonographic diagnosis.

Abscess. Symptoms of an infected endometrioma are those of an acute abdomen, i.e., lower abdominal pain, high fever, vomiting, and elevated white blood cell count. Interestingly, Dogan et al. (42) reported the case of a 30-year-old woman who underwent appendectomy at 24 weeks' gestation for acute appendicitis due to decidualized endometriosis. Subsequently, at 28 weeks' gestation, she underwent a second laparotomy with left salpingectomy owing to a tubo-ovarian abscess arising from a decidualized ovarian endometrioma.

Rupture. Possible clinical presentations include lower abdominal pain without signs of infection due to the presence of "chocolate" fluid within the peritoneal cavity (39, 40, 43). In more rare cases, when rupture involves an ovarian vessel, a spontaneous hemoperitoneum can develop (26), determining the clinical picture previously described in the SHiP section.

Diagnosis and differential diagnosis. The diagnosis of adnexal pathologies in pregnancy is more common during the first trimester, when ovarian scanning should be a second focus of attention of transvaginal ultrasonography after the obstetrical evaluation. Conversely, the ovaries are seldom visualized with the use of obstetrical ultrasound of the second and third trimester. The most challenging diagnostic dilemma associated with ovarian endometriosis in pregnancy, fortunately occurring in rare cases, is the presence of rapidly growing and abundantly vascularized intraluminal vegetations that are thought to be consequent to a decidual modification of ovarian endometriotic implants (34, 44). In such cases, the differential diagnosis between decidualized ovarian endometrioma and ovarian cancer is difficult with the use of both ultrasonography and magnetic resonance imaging (MRI) (35). Of some help might be the fact that decidualized endometriomas, compared with malignant masses, present neither septations nor free abdominal fluid (34).

The sensitivity and specificity of transvaginal ultrasonography in the diagnosis of tubo-ovarian abscess in nonpregnant women have been reported to be 81% and 86%, respectively. Undoubtedly, these figures should be reduced for the second and third trimester of pregnancy, when the pregnant uterus limits the accuracy of a transabdominal scan. In such cases, MRI is the most accurate imaging technique, with sensitivity and specificity of 100% and 90%, respectively (45). The differential diagnosis for tubo-ovarian abscess is mainly with ovarian tumors and appendicitis, depending on the presence or absence of symptoms and signs of infection.

Management

Enlargement of endometrioma. Because it has been reported that endometriotic cysts that increase in size in early pregnancy might subsequently decrease in size in the third trimester, systematic intervention for enlarging cysts in the second trimester of pregnancy could result in overtreatment. Watchful waiting seems to be the best approach in these cases, possibly limiting surgery to cysts complicated by rupture or infection or when the appearance of the cyst suggests ovarian malignancy rather than the much more frequent decidualization.

Abscess. The treatment of a tubo-ovarian abscess includes peritoneal washing followed by cyst drainage, cystectomy, or salpingo-oophorectomy (46).

Rupture. Endometrioma rupture in pregnancy is usually an intraoperative diagnosis. To our knowledge, only four cases have been reported in the English-language literature (26, 39, 40, 43), of which three involved cystectomy (26, 39, 43) and one salpingo-oophorectomy (40).

Pregnancy outcome

Enlarging endometrioma. The two largest series of endometriotic cysts in pregnancy did not report adverse effects of enlarging endometriomas on pregnancy outcome (32, 33).

Abscess. Dogan et al. (42) reported a single case of preterm delivery at 28 weeks' gestation on the 5th day after surgery for infected ovarian endometrioma.

Rupture. In the case in which a cesarean section was deemed to be necessary during the emergency procedure for hemoperitoneum at 27 weeks, two healthy twins were delivered (26). In the other three women, pregnancies progressed uneventfully until term (39, 40, 43).

Bowel Endometriosis: Spontaneous Perforation

The prevalence of spontaneous bowel perforation in pregnancy is unknown. Recently, Setúbal et al. (47) reviewed the literature on this topic. Among 12 cases of bowel perforation during pregnancy caused by endometriosis, only three women had a history of endometriosis. Regarding the pathogenesis of this complication, the authors hypothesized that extensive decidualization might weaken the bowel wall and that the associated adhesions might cause traumas during uterine growth. Six spontaneous bowel perforations involved the rectosigmoid colon, three the appendix, two the small intestine, and one the cecum. Because most women do not have histories suggesting endometriosis and symptoms are nonspecific, usually consisting in severe acute abdominal pain, the diagnosis of a bowel perforation can be difficult. Clinical and laboratory signs of peritonitis and a chest

radiograph showing free air below the diaphragm should orient the clinician toward the correct diagnosis of bowel perforation (48). However, such clinical information is often lacking and, according to the review by Setúbal et al., in the majority of cases bowel perforation is not diagnosed even during exploratory laparotomy, necessitating a subsequent repeated laparotomy (47). Eventually, all women underwent emergency surgery for an acute abdomen, and a Hartman operation and/or segmental resection was performed. The timing of spontaneous bowel perforation was reported for ten women; among them, seven perforations occurred between 26 and 37 weeks of gestation and three occurred in the immediate postpartum period. Five women were reported to have delivered with the use of cesarean section and three women vaginally. Healthy babies were born in all cases. The creation of an international database for spontaneous bowel perforation in pregnancy is needed to better understanding and possibly prevent this rare but severe complication.

Uterine Rupture

Uterine rupture has been observed in three women who had undergone surgery for endometriosis before pregnancy (49–51). In the first patient, who had undergone the excision of a rectovaginal nodule, the uterine rupture was detected on the posterior wall of the lower uterine segment for fetal distress signs during labor at 37 weeks' gestation (49). In the second woman, thick adhesions between the rectosigmoid and the posterior wall of the uterus had been excised while taking care not to create damage to the intestinal loop by cutting closer to the uterine wall. Five years later, at 32 weeks' gestation, an emergency cesarean section was performed and a hemoperitoneum of 4 liters was evacuated. A loss of integrity involving two-thirds of myometrium was observed in the posterior wall of the uterus, at the level of the lower segment (50). In these cases where a cleavage plane is lacking, the attempt of a complete lesion excision may result in damage to the cervix or the uterine isthmus, possibly predisposing to uterine rupture owing to the stretching of weakened myometrium during pregnancy. The third patient underwent excision of a rare cervical endometriotic cyst. The uterine rupture was revealed by manual exploration of the uterine cavity because of a retained placenta after a vaginal delivery at term (51). Fetal outcome was excellent in two cases and not reported in one case (50).

Parametrial Endometriosis: Ureter Rupture

A case of urohemoperitoneum with hemorrhagic shock and intrauterine fetal death at 31 weeks' gestation has been reported. This woman had previously undergone surgery for stage IV endometriosis without treatment of a deep nodule at the basis of the right broad ligament. At emergency surgery during pregnancy, interruption of the right ureter at the level of the deep nodule and bleeding from the right uterine artery were observed. Ureterovesical reimplantation was performed and hemostasis obtained (52).

ENDOMETRIOSIS AND ADENOMYOSIS AND PREGNANCY/NEONATAL OUTCOMES

Miscarriage

From the early 1980s great attention was devoted to try to assess a possible relationship between endometriosis and miscarriage, but the first studies were characterized by very critical limitations severely hampering their value in evaluating the risk of miscarriage in women affected (53–56). The two major problems encountered were the following:

- Many of these studies evaluated the pre- and post-treatment incidence of abortion. No control groups were enrolled for this kind of analysis.
- A selection bias is often present in these studies because they enrolled a population of women with endometriosis from a pool of infertile women. Because infertility is a condition that leads to further analysis and potential diagnosis of endometriosis, the frequency of infertile women among the cases was therefore increased (57).

Some retrospective studies on the relationship between miscarriage and endometriosis regardless of the treatment have been published (57–63), and only two of them observed an association. In the studies finding an association, pregnancies obtained with the use of assisted reproduction technology (ART) procedures were not excluded (59, 63). Vercellini et al. retrospectively recruited nulligravid women who obtained a natural conception dividing them into 4 groups according to the type of endometriosis. A higher miscarriage rate was observed in women with ovarian endometriomas associated or not with the peritoneal disease (adjusted odds ratio [OR] 1.70, 95% confidence interval [CI] 1.04–2.8) (61).

Two prospective cohort studies were conducted on this topic (64, 65). Matorras et al. (1998) aimed to assess if infertile women with endometriosis (n = 174) had an increased risk of abortion compared with a control group of infertile women in whom endometriosis was laparoscopically ruled out (n = 174). No difference was found between the two groups (64). Opposite conclusions were drawn by Hjordt Hansen et al. (65). With the use of data from Danish national registries, 24,667 subjects with a diagnosis of endometriosis were age-matched with a population of subjects without endometriosis (n = 98,668). A higher rate of miscarriage was found in the endometriosis group (relative risk [RR] 1.2, 95% CI 1.2–1.29). The RRs were 1.21 (95% CI 1.17–1.26) for natural pregnancies and 4.34 (95% CI 3.42–5.50) for the ART subgroup. Ectopic pregnancy risk was also significantly increased in affected women (RR 1.9, 95% CI 1.8–2.1) (65).

A meta-analysis published in 2014 by Barbosa et al. with the aim to compare ART outcomes in women with and without endometriosis was compatible with a small to moderate increase in the risk of miscarriage among pregnant women with endometriosis (RR 1.31, 95% CI 1.07–1.59) (66). Conversely, no difference in miscarriage rate per woman

was found in a meta-analysis by Hamdam et al. conducted with a similar aim (4).

For adenomyosis, the meta-analysis published by Vercellini et al. in 2014 (67) including seven studies and 928 IVF pregnancies, reported a rate of miscarriages of 31% in women with adenomyosis and 14.1% in nonaffected women (RR 2.12, 95% CI 1.20–3.75), suggesting a causal relationship.

In conclusion, according to the current literature, there is controversial evidence supporting an association between endometriosis and miscarriage. Moreover, based on the more recent findings (8) and on the coexistence of adenomyosis and endometriosis, adenomyosis could have acted as a confounder in studies on endometriosis.

Further well conducted studies are needed to disentangle this issue.

Second- and Third-trimester Pregnancy Outcomes

Sixteen studies have addressed the effect of endometriosis on late pregnancy outcomes, most of them published in the past 10 years (61–63, 68–80) (Table 1). These studies have been divided into three groups according to the populations considered and the mode of diagnosis of the disease. Indeed, whereas in most studies diagnosis has been laparoscopically-proven, in those enrolling endometriosis patients requiring ART, diagnosis could be also based on clinical evidence (68) or imaging techniques (69, 70). Even in some population-based studies, the diagnosis could be clinical (71, 72).

Only two studies have addressed the effect of adenomyosis on late pregnancy outcomes (81, 82) (Table 2).

Endometriosis and ART. Most of the published studies suffer from several methodologic limits. The most important problem refers to the fact that endometriosis women are more likely to receive ART procedures, which themselves are a risk factor for adverse pregnancy outcomes, and many of the studies refer to or consider pregnancies obtained by IVF.

Fernando et al. tested the hypothesis that preterm birth and small-for-gestational-age (SGA) birth rates were increased in patients with endometriosis requiring ART, evaluating these rates among 535 ART singleton babies from patients with nonovarian endometriosis and 95 ART singleton babies from patients with ovarian endometriosis. Control groups included ART patients without endometriosis (n = 1,201), subfertile women (n = 156), community-based fertile control subjects for all forms of endometriosis matched for maternal age and year of birth (n = 1,260) and fertile control subjects for ovarian endometriosis matched for maternal age and year of birth (n = 1,140). No difference was found for ART babies from women with any form of endometriosis compared with ART patients with other causes of infertility. Preterm birth rate was increased only for babies from ART women with ovarian endometriosis compared with the corresponding fertile group (adjusted OR 1.98, 95% CI 1.09–3.63). Moreover, statistically increased risks for an SGA baby were found in the ovarian endometriosis ART group compared with the ART group without endometriosis (adjusted OR 1.95, 95% CI 1.06–3.60) and with the ART group with other forms of the disease (adjusted OR 1.99, 95% CI 1.04–3.81) (68). A total of 318 ART patients were examined by Takemura et al. for the risk of placenta previa. Ten variables, including maternal age, parity, previous abortion, previous cesarean section, endometriosis, male infertility, and tubal disease, were evaluated for association with placenta previa, and endometriosis was found to be significantly associated (OR 15.1, 95% CI 7.6–500.0) (69). In comparing first singleton ART pregnancies from 255 women with spontaneous singleton pregnancies from the general population (n = 26,870) in the period 1996–2007 in Kuopio, Finland, Kuivasaari-Pirinen et al. found an increased risk of preterm birth among ART women with endometriosis (n = 49) after adjustment for confounding factors such as age, parity, body mass index, and smoking (adjusted OR 3.25, 95% CI 1.50–7.07) (73). ART women with endometriosis were not compared with ART women without the disease. In contrast with these results, Benaglia et al. did not find differences in late pregnancy and neonatal outcomes between women with ovarian endometriosis at the time of ART procedure and age-matched ART patients without endometriomas (70). Overall, a nonconsistent association with placenta previa and preterm birth has been observed in these studies performed in ART patients. As a matter of fact, it can not be excluded that associations found might be restricted to ART pregnancies. Finally, another limit of most of these studies is the relatively small sample size preventing definitive conclusions.

Endometriosis and population-based studies. More reliable results can probably to be deduced from published population-based studies, because most of them were quite attentive in stratifying results for some variables, including maternal age, year of birth, and ART procedures. No evidence of association between endometriosis and pregnancy hypertension or preeclampsia was found by Hadfield et al., who considered 208,879 women with a singleton first birth in the period 2000–2005 in the Australian state of New South Wales, of whom 3,239 had an earlier diagnosis of endometriosis (74). Stratification for ART procedures did not change the result. The large Swedish study by Stephansson et al., including 1,442,675 singleton births of which 13,090 were from women affected by endometriosis, found some associations but stratified the analysis by ART only for the preterm birth outcome and found an unchanged result (ART women with endometriosis: adjusted OR 1.24, 95% CI 0.99–1.57; non-ART women with endometriosis: adjusted OR 1.37, CI 1.25–1.50) (72). An Australian study by Healy et al. evaluated the prevalence of obstetrical hemorrhagic complications in singleton pregnancies of 6,730 IVF/intracytoplasmic sperm injection (ICSI) patients in the state of Victoria from 1991 to 2004. Control groups included infertile patients who did not conceive by ART (n = 2,167), women who conceived by gamete intrafallopian transfer (n = 779), and community-based control subjects (n = 24,619) (75). The IVF/ICSI group had higher rates of all of the hemorrhagic complications than the general population. Having confirmed an increase in obstetrical hemorrhage specific to IVF/ICSI, that group was explored on its own to investigate which factors were related to these findings. The diagnosis

TABLE 1

Studies addressing late pregnancy outcomes in endometriosis patients divided according to the populations considered and the mode of diagnosis of the disease.

Study	Population	Type of study	Pregnancy outcomes
ART			
Fernando et al., 2009 (67)	535 ART endometriosis, 95 ART endometrioma, 1,201 ART infertile, 156 subfertile women, 1,260 fertile non-ART control subjects for all forms of endometriosis, 1,140 fertile non-ART control subjects for ovarian endometriomata	Retrospective cohort	Increased preterm birth risk for ART women with ovarian endometriosis compared with corresponding fertile group (adjusted OR 1.98, 95% CI 1.09–3.63). Increased risks for SGA baby in the ovarian endometriosis ART group compared with ART group without endometriosis (adjusted OR 1.95, 95% CI 1.06–3.60) and with ART group with other forms of the disease (adjusted OR 1.99, 95% CI 1.04–3.81).
Benaglia et al., 2012 (69)	78 ART endometrioma vs. 156 ART control subjects	Retrospective cohort	No associations
Kuivasaari-Pirinen et al., 2012 (72)	49 ART endometriosis vs. 26,870 pregnancies from general population	Retrospective cohort	Increased preterm birth risk (adjusted OR 3.25, 95% CI 1.50–7.07)
Takemura et al., 2013 (68)	53 ART endometriosis vs. 265 ART nonendometriosis	Retrospective cohort	Increased risk for placenta previa (OR 15.1, 95% CI 7.6–500.0).
Population-based			
Hadfield et al., 2009 (73)	3,239 endometriosis vs. 205,640 non-endometriosis	Retrospective	No association with preeclampsia or hypertension in pregnancy
Stephansson et al., 2009 (71)	13,090 endometriosis vs. 1,429,585 nonendometriosis	Retrospective	Increased preterm birth risk (adjusted OR 1.33, 95% CI 1.23–1.44)
Healy et al., 2010 (74)	1,265 ART endometriosis, 5,465 ART nonendometriosis, 2,167 infertile patients who did not conceive with ART, 779 women who conceived with GIFT, 24,619 community-based control subjects	Retrospective cohort	Increased risk of placenta previa (adjusted OR 1.65, 95% CI 1.18–2.32) and postpartum hemorrhage (adjusted OR 1.28, 95% CI 1.06–1.56) in ART endometriosis group versus ART non-endometriosis group
Aris et al., 2014 (62)	784 endometriosis vs. 30,284 general population	Retrospective cohort	Increased risk of stillbirth (OR = 2.29; 95% CI, 1.24–5.22)
Tobias et al., 2013 (75)	388 endometriosis vs. 40,385 incident pregnancies	Prospective cohort	No association with gestational diabetes
Stern et al., 2015 (70)	406 ART endometriosis, 590 non-ART endometriosis, 297,987 fertile non-ART control subjects	Retrospective	Increased hospital admissions and cesarean section in both ART and non-ART endometriosis groups. Increased risk of prematurity (adjusted OR 1.46, 95% CI 1.07–1.99) and preterm birth (adjusted OR 1.66, 95% CI 1.26–2.18) in non-ART endometriosis group compared with fertile non-ART group.
Laparoscopically proven diagnosis			
Kortelhati et al., 2003 (76)	137 cases vs. 137 controls	Case-control	No associations
Brosens et al., 2007 (77)	245 cases vs. 274 controls	Case-control	Reduced risk of preeclampsia (OR 7.5, 95% CI 1.7–33.3) and hypertension (OR 2.6, 95% CI 1.2–6.0)
Vercellini et al., 2012 (61)	419 cases (150 rectovaginal, 69 ovarian and peritoneum, 100 ovarian, 100 peritoneal)	Retrospective cohort	Increased risk of placenta previa in deep endometriosis compared with other forms (OR 5.81, 95% CI 1.53–22.03)
Conti et al., 2014 (78)	316 endometriosis and 1,923 fertile control subjects	Retrospective cohort	Increased risk of preterm birth (OR 2.24, 95% CI 1.46–3.44), SGA fetus (OR 2.72, 95% CI 1.46–5.06), gestational diabetes (OR 2.13, 95% CI 1.32–3.44), and preterm premature rupture of membranes (OR 2.93, 95% CI 1.24–6.87)
Mekaru et al., 2014 (63)	49 cases vs. 59 controls	Retrospective cohort	No associations
Lin et al., 2015 (80)	249 cases vs. 249 controls	Retrospective cohort	Increased risk of preterm birth (adjusted OR 2.44, 95% CI 1.05–5.57), placenta previa (adjusted OR 4.51, 95% CI 1.23–16.50), and cesarean section (adjusted OR 1.93, 95% CI 1.31–2.84)

Note: ART = assisted reproductive technology; CI = confidence interval; GIFT = gamete intrafallopian transfer; OR = odds ratio; SGA = small for gestational age.

Vigano. Pregnancy in endometriosis and adenomyosis. Fertil Steril 2015.

TABLE 2

Studies addressing late pregnancy outcomes in adenomyosis patients.

Study	Population	Type of study	Pregnancy outcomes
Juang et al., 2006 (81)	104 women with preterm labor vs. 208 women who delivered after 37 weeks' gestation	Nested case-control	Increased risk for preterm birth (adjusted OR 1.84, 95% CI 1.32–4.31) and preterm premature rupture of membranes (adjusted OR 1.98, 95% CI 1.39–3.15)
Mochimaru et al., 2015 (82)	36 women with adenomyosis diagnosed by ultrasound or MRI before pregnancy vs. 144 women without adenomyosis	Retrospective cohort	Increased risk for preterm birth (OR 5.0, 95% CI 2.2–11.4), preterm premature rupture of membranes (OR 5.5, 95% CI 1.7–17.7), cesarean delivery (OR 4.5, 95% CI 2.1–9.7), SGA (OR 4.3, 95% CI 1.8–10.3), postpartum hemorrhage (OR 6.5, 95% CI 2.2–19.0), and malpresentation (OR 4.2, 95% CI 1.6–10.8)

Note: Abbreviations as in Table 1.

Vigano. Pregnancy in endometriosis and adenomyosis. Fertil Steril 2015.

of endometriosis was found to be associated with a higher risk of placenta previa (adjusted OR 1.65, CI 1.18–2.32, compared with the nonendometriosis group) and postpartum hemorrhage (adjusted OR 1.28; 95% CI 1.06–1.56, compared with the nonendometriosis group) (75). Endometriosis has been shown to increase the incidence of stillbirth (OR 2.29, 95% CI 1.24–5.22) and not of other adverse pregnancy outcomes in an uncontrolled cohort study by Aris including 31,068 women who had a pregnancy from 1997 to 2008 in the Eastern Townships of Canada. Among these women, 784 had a hospital diagnosis of endometriosis (62). Endometriosis was not associated with gestational diabetes mellitus in a prospective analysis by Tobias et al. of pregnancies in the United States Nurses' Health Study II cohort. The association between a history of infertility and gestational diabetes mellitus was assessed and the primary reasons for infertility evaluated (76). Finally, the recent study by Stern et al. aimed to compare the risks for adverse pregnancy and birth outcomes according to infertility-related diagnoses with and without ART treatments and with pregnancies in a fertile population. The study population included pregnancies from 3,689 women who underwent ART procedures, pregnancies from 4,098 women who did not undergo ART treatments but with a diagnosis of ovulation disorders, endometriosis, or reproductive inflammation, and 297,987 pregnancies from fertile women. The results indicated an increase of perinatal morbidities associated with infertility diagnosis in both ART-treated and non–ART-treated women (71) (Table 1). Overall, an increased risk of obstetrical hemorrhage and preterm birth has been suggested by these population-based studies. Conversely, an association with preeclampsia, SGA babies, and cesarean section was less consistently supported.

Case-control and cohort studies with laparoscopically proven diagnosis of endometriosis. Some studies specifically focused on pregnancies from women with a surgical confirmation of endometriosis and eventually adjusted for confounding factors. Women with endometriosis were all operated on for the disease. Kortelahti et al. did not find significant differences in pregnancy outcomes between 137 women with laparoscopically proven endometriosis and 137 control subjects matched for age and ART procedures who had undergone laparoscopy for infertility or tubal sterilization (77). The negative results can not be completely trusted owing to the small sample size. A similar limitation can be found in a recent study that examined effects of endometriosis on pregnancy outcomes by comparing 49 women with and 59 without endometriosis detected by a definitive laparoscopic diagnosis. No significant difference in both obstetrical and neonatal outcomes was found (63). Brosens et al. evaluated incidence of preeclampsia and pregnancy-related hypertension in 245 women with a diagnosis of endometriosis-associated infertility matched for age, parity, and multiple pregnancies with 274 women who underwent treatment for male infertility (78). This is the only study that found a reduced risk of both preeclampsia (OR 7.5, 95% CI 1.7–33.3) and hypertension (OR 2.6, 95% CI 1.2–6.0) in the endometriosis group. A major problem of this study was the use of postal questionnaires that may have introduced potential biases, including subjective over- or underestimation of complications (78). Vercellini et al. retrospectively evaluated pregnancy outcomes in 419 nulligravid women who underwent conservative surgical treatment for different forms of endometriosis and who achieved their first conception without ART procedures (61). A control group of women without visually excluded endometriosis was not included. The risk of SGA and low-birth-weight babies was not significantly different among the different forms of endometriosis and results were apparently similar to the national population-based estimates. No cases of placenta previa were observed in patients with ovarian endometriomas only, whereas an almost sixfold increase in risk was found in women with rectovaginal endometriosis compared with all women with ovarian and peritoneal lesions (OR 5.81, 95% CI 1.53–22.03) (61). A multicentric cohort study evaluated women with a diagnosis of endometriosis confirmed surgically before pregnancy (n = 316) compared with 1,923 women who were hospitalized for their delivery. Women with endometriosis at first pregnancy showed significantly higher incidence of SGA fetuses (OR 2.72, 95% CI 1.46–5.06), gestational diabetes (OR 2.13, 95% CI 1.32–3.44),

preterm premature rupture of membranes (OR 2.93, 95% CI 1.24–6.87), and preterm birth (OR = 2.24, 95% CI 1.46–3.44). Multiparous women with endometriosis delivered SGA fetuses significantly more often than nonendometriosis patients (OR 2.93, 95% CI 1.28–6.67). Data adjusted for ART procedures were not provided (79). Finally, Lin et al. evaluated 249 pregnant women with surgically confirmed endometriosis and 249 control women without previous clinical or surgical diagnosis of the disease. ART conceptions were excluded. After controlling for maternal age, affected women showed an increased risk of preterm birth (adjusted OR 2.44, 95% CI 1.05–5.57), placenta previa (adjusted OR 4.51, 95% CI 1.23–16.50), and cesarean section (adjusted OR 1.93, 95% CI 1.31–2.84) (80). These studies are all characterized by a limited number of patients, suggesting caution in interpreting their data. As a matter of fact, results from these studies tend to suggest associations of endometriosis with several pregnancy and neonatal complications, even a reduced risk of preeclampia and an increased risk of gestational diabetes, which were not observed in the other groups of studies. These results require verification.

Adenomyosis. Of the two studies addressing the relationship between adenomyosis and pregnancy/neonatal outcomes, one evaluated specifically the risk of preterm birth in a nested case-control study and the more recent aimed at retrospectively elucidating the risk of poor pregnancy outcomes in women with adenomyosis with uterine enlargement identified in medical records at the Perinatal Center for Maternity and Neonates of Yokohama University. Results of these studies are presented in Table 2, and both suggested an increased risk of preterm birth in these patients (81, 82).

CONCLUSION

Owing to the rarity of complications of preexisting endometriosis in pregnancy, the surgical treatment of endometriosis before pregnancy to prevent such complications does not seem to be justified. At the same time, surgery may be indicated to increase the chances of getting pregnant. Preventive surgery for endometriosis could be beneficial because lysis of adhesions may reduce the risk of spontaneous rupture of viscera. On the other hand, in very rare cases, the treatment of endometriosis located at the level of the uterine isthmus may weaken the posterior uterine wall, predisposing it to uterine rupture during pregnancy or delivery. Because there is no correlation between the stage of endometriosis and the prevalence of complications, there is no way to anticipate complications of endometriosis during pregnancy; therefore, additional imaging evaluations during pregnancy do not seem to be warranted.

Presently, the only reliable measures for possibly preventing the complications of endometriosis during pregnancy are represented by adequate preconception counseling and by the awareness of such possibilities by physicians. All women with endometriosis should be informed about the risk associated with a future pregnancy, and those who are affected by—or underwent surgery for—severe disease involving the bowel, bladder, or ureter should also be informed about the potential technical difficulties in case of abdominal delivery. Moreover, in a woman with endometriosis it is important, when nonspecific abdominal pain occurs during pregnancy, to suspect possible intraperitoneal bleeding, infected or ruptured endometrioma, or uterine rupture, to undertake proper management for achieving the best possible outcome for both mother and fetus.

For neonatal and maternal outcomes, studies that have recruited patients who underwent ART procedures or that specifically focused on pregnancies from women with a surgical confirmation of endometriosis are characterized by several limitations, including small sample size, lack of adjustment for confounders, and lack of adequate control subjects. Population-based studies, on the other hand, tend to suggest that endometriosis can result in adverse pregnancy outcomes and that these occur even in the absence of ART treatment. Placenta previa and preterm birth seem to occur at higher risk for affected women. Most of the studies failed to analyze associations in relation to the various forms of the disease, but when this was done, risk for placenta previa was mostly observed in relation to deep endometriosis (61) and risk for preterm birth was found to be both directly and inversely related to ovarian endometriosis (61, 68). Further studies are needed to clarify these findings and to investigate the mechanisms underlying these effects. It should be also emphasized that none of the studies reported here considered the association between endometriosis and adenomyosis as a possible confounding factor. Indeed, most of the studies cited herein for endometriosis did not exclude the contemporary presence of adenomyosis that coexists in a consistent proportion of cases (8). Given the reported possible causal relationship between adenomyosis and abortion (67) and between adenomyosis and preterm birth (81), this aspect should be taken into consideration when addressing future studies on this topic.

Several explanations have been suggested to clarify the pathogenetic link between endometriosis and adenomyosis and late-pregnancy obstetrical complications. Most of them support the idea that dysfunctional critical uterine changes during the implantation process can trigger a defective process of decidualization and placentation, with a cascade of events resulting in defective remodeling of the spiral arteries (7). These dysfunctional uterine changes may be based on an alteration of the myometrial junctional zone, the local inflammation-based response, the consequences of progesterone resistance, or inadequate uterine contractility. The further elucidation of these mechanisms promises to become more and more an interesting area of research in the future.

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