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