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Current opinion

Defective myometrial spiral artery remodelling as a cause of major obstetrical syndromes in endometriosis and adenomyosis

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ABSTRACT

Endometriosis and adenomyosis are characterized by the presence of ectopic endometrium, but are also associated with functional and structural changes in the eutopic endometrium and inner myometrium. Alterations in the inner myometrium occurring in women with endometriosis and adenomyosis may be at the root of a defective remodelling 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 remodelling of the myometrial spiral arteries has been well documented. The possibility of a link between both endometriosis and adenomyosis and some major obstetric syndromes remains controversial because of at least two factors: first, changes of the inner myometrium are frequently present in women with endometriosis but the diagnosis requires high-resolution imaging such as magnetic resonance which is not routinely performed and second, patients with endometriosis are frequently subjected to prolonged hormone suppressive therapy. Indeed, there is evidence that pre-treatment with a Gonadotropin Releasing-Hormone analogue can improve the uterine microenvironment and implantation rate following IVF in infertile patients with endometriosis.

1. Introduction

Endometriosis and adenomyosis are defined by the presence of ectopic endometrium, respectively outside the uterus and in the myometrial wall. Recent morphological studies have demonstrated that under both conditions the eutopic endometrium, as well as the inner myometrium, shows functional and structural abnormalities [1]. Major obstetrical syndromes have been described in association with endometriosis and adenomyosis and it is today well known that they are associated with different types of defective remodelling of the myometrial spiral arteries [2–4]. High-resolution imaging studies, particularly by Magnetic Resonance (MR) imaging, have demonstrated the presence of functional and structural changes in the inner myometrium in young women with endometriosis [5]. Recently, it has been suggested that the process of defective deep placentation starts in the late menstrual cycle by disruption of the decidualization process and triggers a cascade of events resulting in defective transformation of the myometrial spiral arteries [6]. Therefore, the question arises whether alterations in the inner myometrium present in subjects with endometriosis and adenomyosis are at the root of defective remodelling of the myometrial spiral arteries and cause an increase in the risk of major obstetrical syndromes. Thus, a non-invasive assessment of the myometrial JZ prior to conception may turn out to be useful in identifying women at risk of major obstetrical complications and offer a window for preventive treatment.

2. Risk of major obstetrical syndromes in endometriosis and adenomyosis

Recent findings have suggested a link between both endometriosis and adenomyosis and some major obstetric syndromes including spontaneous late miscarriage, preterm birth, small for gestational age (SGA), pre-eclampsia and obstetric haemorrhages, such as abruptio placentae and postpartum bleeding.

2.1. Miscarriage

Youm et al. [7] evaluated the effects of myometrial thickening on the outcomes of in vitro fertilization and embryo transfer (IVF-ET). Four hundred thirteen patients for a total of 551 IVF-ET cycles were

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divided into group A (<2.00 cm), group B (2.00–2.49 cm), and group C (≥2.50 cm) based on total myometrial thickness. Following the criteria of Kido et al. [8], they considered a diffusely enlarged uterus in the absence of a well circumscribed mass as adenomyosis and found that a myometrial thickening of more than 2.50 cm on trans-vaginal ultrasonography (TVUS) exerted an overall adverse effect on IVF-ET outcomes. Even with mild thickening (2.00–2.49 cm), the presence of sonographic findings suggestive of adenomyosis was associated with adverse outcomes of IVF-ET: lower implantation, clinical pregnancy and live birth rates, and higher abortion rates. Martinez-Conejero et al. [9] evaluated in a retrospective, matched cohort study the impact of adenomyosis on pregnancy outcome in oocyte donation cycles. Whereas clinical and molecular data showed that implantation was not affected by adenomyosis, the higher miscarriage rates associated with this condition lead to lower term pregnancy rates, indicating a clear negative effect on the final outcome of oocyte donation.

2.2. Preterm birth, preterm premature rupture of membranes and small for gestational age

In a matched case–control study Kortelahti et al. [10] analysed obstetric outcome among 137 women with endometriosis and 137 controls matched in terms of IVF procedures. They observed that the overall pregnancy characteristics and outcome measures (birth weight) were similar in women affected or not by endometriosis. It should be noted that in this study only 19% of the women had severe endometriosis and that the endometriosis group included significantly older women than the control group. From a 1:2 nested case–control study, Juang et al. [11] concluded that gravid women with adenomyosis had an increased risk of both spontaneous preterm delivery and preterm premature rupture of the membranes.

A retrospective cohort study by Fernando et al. [12] included 95 singleton IVF babies from patients with ovarian endometriomata and 535 IVF singleton babies from patients who had endometriosis but no ovarian endometriomata. The control groups included 1201 singleton babies from IVF patients without endometriosis and 2400 randomly selected women from the Perinatal Data Collection Unit database of 850,000 births. The authors found that the rates of preterm birth and SGA babies doubled in infertility patients with ovarian endometriomata who required IVF. In a nationwide Swedish study including 1,442,675 singleton births Stephansson et al. [13] assessed the association between adverse pregnancy outcome, IVF and a previous diagnosis of endometriosis. They also found that endometriosis represents a risk factor for preterm birth, irrespective of IVF. Women with endometriosis were also more likely to be delivered by Caesarean section and to suffer from antepartum haemorrhage/placental complications. In contradistinction to these data, a recent multicentre retrospective cohort study found that women with endometriomas achieving pregnancy through IVF-ET do not seem to be exposed to a significant increased risk of obstetrical complications, such as preterm birth and small for gestational age, in comparison with patients who achieved pregnancy through IVF without endometriomas [14]. It is interesting to note that the authors used a long protocol for controlled ovarian hyper-stimulation to achieve pituitary desensitization.

2.3. Pre-eclampsia

Three studies have attempted an estimation of the risk of pre-eclampsia in women with endometriosis. In a retrospective case–control study set at the University of Ghent IVF centre, Brosens et al. [15] found no evidence that endometriosis predisposes for pre-eclampsia. Instead, the risk of hypertensive disorder in pregnancy was significantly reduced in women with endometriosis-associated infertility. In a population-based, longitudinal study of all women in the Australian state of New South Wales, aged 15–45 years of age with a singleton birth during the period 2000–2005 Hadfield et al. [16] determined whether women with a history of endometriosis were at modified risk for pregnancy hypertension or pre-eclampsia. In this large population-based dataset, they found no evidence for an association between endometriosis and a subsequent risk of either pregnancy hypertension or pre-eclampsia. Finally, the above-mentioned study by Stephansson et al. [13] found that women with endometriosis were more likely to suffer from pre-eclampsia. These inconsistent results indicate that the evaluation of the risk of pre-eclampsia in women with endometriosis remains problematic.

3. Changes in the inner myometrium in women with endometriosis and adenomyosis

The inner myometrium is a distinct, hormone-dependent myometrial compartment underlying the endometrium that was first visualized by MR imaging (Fig. 1a). This zone has been cited in the literature by many names, including archimetrium, myometrial junctional zone (JZ) and endomyometrial junction. Despite the apparent lack of histological distinction, the JZ and the outer myometrium are in reality structurally and biologically different [17].

Several studies have investigated changes of the JZ in women with endometriosis. The MR studies by Kunz et al. [5] have shown that the mean thickness of the dorsal JZ is already increased in very young women with endometriosis, as compared with healthy controls; however, the difference only reaches statistical significance in women 30 years of age and older. Xavier et al. [18] found a higher sub-endometrial and intra-endometrial perfusion in patients with ovarian endometrioma in the late secretory phase of the cycle, close to menstrual shedding and formulated the hypothesis that endometriosis may increase endometrial vasodilatation. Another explanation is that the increased blood flow in patients with endometriosis may have resulted from endometrial progesterone resistance [19]. Indeed, it has been shown that there is a significant, positive correlation between unopposed circulating oestradiol levels and the rate of endometrial blood flow, and that when progesterone levels are elevated, this correlation is lost [20]. Thomassin-Naggara et al. [21] evaluated the ability of dynamic contrast-enhanced magnetic resonance imaging to assess physiological microvascular states in normal myometrium and observed that in women of reproductive age, the inner myometrium displays higher tissue blood flow than the outer myometrium. The inner myometrium presented microvascular variations during the menstrual cycle with a pre-ovulatory peak followed by a fall reaching a nadir of blood flow about 4 days after ovulation.

Although there are clear differences between inner and outer myometrium, the transition in healthy subjects is gradual with no distinct zonation in morphometric features between the inner and outer myometrium. In contradistinction to this, in adenomyosis patients a reduced cell density, increased nuclear size and features of hyperplasia and hypertrophy can be observed [22]. Interesting results have been obtained by extending the study of the distribution of oestrogen (ER) and progesterone (PR) receptors and their isoforms from the endometrium to the myometrium. Noe et al. [23] found that the JZ exhibits a cyclic pattern of ER and PR expression that parallels that of the endometrium, whereas the outer myometrium does not exhibit a cyclic pattern of receptor expression. In a case–control, blinded study Mehasseb et al. [24] found that the