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THE OMINOUS ASSOCIATION BETWEEN SEVERE ENDOMETRIOSIS, IN-VITRO FERTILISATION, AND PLACENTA PRAEVIA: RAISING AWARENESS, LIMITING RISKS, INFORMING WOMEN

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Endometriosis is associated with several adverse pregnancy outcomes.[1] The most severe maternal complications are spontaneous haemoperitoneum in the second half of pregnancy and placenta praevia.[1] Spontaneous haemoperitoneum, mostly associated with endometriosis infiltrating the broad and uterosacral ligaments and the Douglas pouch, is a potentially fatal but rare event. Placenta praevia is more common,[1-3] and it is important to define its incidence, the association with different lesion types, the impact of additional risk factors, the potential obstetrical consequences, and the information that women should receive.

The association between endometriosis and placenta praevia

Reliable estimates of the risk of placenta praevia in women with endometriosis could be obtained investigating large population-based national cohorts. Harada *et al*. used data of the Japan Environment & Children Study to evaluate obstetrical outcomes in 9186 pregnant women with (*n*=330) or without (*n*=8856) a self-reported history of endometriosis. Placenta praevia was observed in 3.6% of women with endometriosis and 0.6% of those without the disease (adjusted OR, 6.4; 95% CI, 3.2-12.6).[2] Saraswat *et al*., using Scottish Record Linkage system data, compared late pregnancy outcomes in 4232 women with and 6707 without a diagnosis of endometriosis. The rate of placenta praevia was 1.7% in the former group and 0.8% in the latter (adjusted OR, 2.2; 95% CI, 1.5-3.3).[3] Berlac *et al*., extracting data from the Danish Health Register and the Medical Birth Register, observed a higher risk of several obstetrical and neonatal complications in the 11,739 patients with endometriosis compared with the 615,533 women without a diagnosis of endometriosis. The highest risk was observed

for pregnancies complicated by placenta praevia (2.1% versus 0.5%, respectively; OR 3.9; 95% CI, 3.5-4.3).[1]

The effect of severe forms of endometriosis and deep lesions on the incidence of placenta praevia

A dose-response relation of endometriosis severity with risk of placenta praevia has been observed. In the above Danish national cohort, pre-conceptional surgery considered as a surrogate marker of more severe endometriosis, was associated with a further increase in risk of placenta praevia (OR, 5.5; 95% CI, 4.6-6.5).[1] According to a Japanese cohort study conducted on women who conceived with assisted reproduction techniques (ART), the OR of placenta praevia in women with all endometriosis forms was 15.1 (95% CI, 4.4-61.7), but increased up to 39.8 (95% CI, 10.1-189.1) when only patients with severe endometriosis were considered.[4]

The specific effect attributable to deep endometriosis was firstly investigated on a large series of women with different disease forms who achieved a singleton pregnancy after natural attempts. The frequency of placenta praevia was 7.6% in 150 patients with rectovaginal lesions, but between 0 and 2.4% in 269 women with peritoneal and/or ovarian forms.[5] Compared with the latter patients, those with rectovaginal endometriosis had an almost six-fold increase in risk (OR 5.8; 95% CI 1.5–22.0). An increased prevalence of placenta praevia in association with deep endometriotic lesions within the posterior pelvic compartment was also reported in a subsequent cohort (17.1% (7/41) in women with ≥ 2cm nodules versus 0.3% (1/300) in women without a diagnosis of endometriosis (OR 61.6; 95% CI 7.4–515.5)).[6] One further series did not however, find a difference between deep and more superficial endometriosis in the rate of placenta praevia.[7] Several pathogenic

hypotheses have been formulated regarding the mechanisms underlying a possible association between deep endometriosis and placenta praevia.[1,5,6]

The additional effect of IVF, twinning, and blastocyst transfer on the incidence of placenta praevia

An almost fourfold increase in risk of placenta praevia was observed in singleton pregnancies after ART compared with those conceived naturally (RR, 3.7; 95% CI, 2.7-5.2).[8] A further systematic review, restricted to dichorionic twin pregnancies, showed an almost threefold increase in the risk of placenta praevia in conceptions achieved with ART compared with those achieved with natural attempts (RR 2.9; 95% CI, 1.5-5.9).[9] Therefore, ART appears to confer an increase in risk probably related to the manipulation involved in the in-vitro fertilisation and embryo transfer (IVF) technology, beyond the already observed increase in risk associated with twinning *per se*.

Among women achieving a conception with ART, Healy *et al.* were the first to report a significantly increased risk of placenta praevia in patients with endometriosis compared with those without the disease (OR 1.7; 95% CI, 1.2-2.4).[10] In the large cohort study conducted by Rombauts *et al*., endometriosis was shown to be an independent risk factor for placenta praevia (OR 2.0; 95% CI, 1.2-3.3).[11] In the population-based Japanese study,[2] the OR of placenta praevia in women with endometriosis was almost halved (from 6.4 to 3.3) when only women without infertility treatment were considered. Other investigators observed rates of placenta praevia ranging from 6.0% to 20.0% in women with endometriosis, but from 0.3% to 1.3% in women without the disease.[4,6,12] Unfortunately, with one exception,[6] within-study comparisons between women achieving conception naturally and with IVF are lacking.

The disease-specific risk of placenta praevia in women with endometriosis may be amplified by fertility treatments. This is particularly relevant, as the advent of oocyte donation programs has greatly increased the probability of pregnancy even in women with the most distorted anatomic condition and independently of previous ovarian surgical injury.

The potential obstetrical consequences of placenta praevia in association with deep endometriosis

Placenta praevia, especially when morbidly adherent, may cause postpartum haemorrhage and require emergency caesarean hysterectomy. However, in patients with extensively infiltrating endometriosis, and especially in those who underwent previous complex procedures such as colorectal resection and ureteral-bladder re-implantation, even the access to the abdominal cavity may be cumbersome. The development of the utero-vesical space in order to incise the lower uterine segment may reveal impracticable in cases of bladder endometriosis, which generally causes firm adhesion to the uterine anterior wall and fundus. The pelvis may be obliterated in women with rectovaginal lesions, with the rectosigmoid stuck to the posterior uterine wall. Complications during caesarean section, including haemorrhage and bladder injuries, were significantly more frequent in women with deep posterior compartment endometriosis than in those without endometriosis.[6]

In cases of uncontrolled haemorrhage due to placenta praevia, an emergency caesarean hysterectomy will be more technically demanding, potentially threatening maternal safety. In fact, placenta previa requires total rather than sub-total hysterectomy, but the bleeding lower uterine segment is precisely the anatomical site most severely involved by infiltrating endometriotic lesions and dense adhesions with surrounding organs. In addition, surgery must be performed rapidly in order to limit blood loss.

Raising awareness, limiting risks and informing women

The available data suggest that women with severe and deep endometriosis are at an increased risk of placenta previa after natural conceptions compared not only with women without endometriosis, but also with patients with milder disease forms. Undergoing IVF may allow an otherwise unlikely conception, thus exposing these women to the endometriosis-attributable risk. Moreover, patients are additionally exposed to the increase in risk attributable to ART.

The apparent association between endometriosis and placenta praevia are derived from large population-based studies and are broadly consistent. In contrast, data on the specific effect of severe forms or endometriosis and deeply infiltrating lesions are mostly derived from small and heterogeneous retrospective cohort studies. Furthermore, the available evidence does not clarify whether the increased risk observed after ART is due to the disease itself or a synergistic effect of IVF. Large multicentre studies are warranted to define the magnitude of the impact of the two factors and their individual contribution to the overall risk of placenta praevia. What is apparent and worrying is that the effects are in the same direction.

Is there something that we can and should do to minimise the risk of placenta praevia in women with severe forms of endometriosis whilst awaiting further and better quality data? It seems unlikely that excisional surgery might have any appreciable influence, as the association with placenta praevia was observed in both operated[5] and non-operated[6] women. The biological rationale to directly link deep endometriosis outside the uterus to an altered implantation process inside the uterine cavity appears to lack plausibility. Overall, evidence supporting removal of deep lesions prior to IVF is insufficient and of low quality, and caution is needed, particularly considering the potential complications of this demanding surgery.

Can we reduce the non-specific risk of placenta praevia attributable to ART? In an IVF setting, elective single embryo transfer (eSET) is mandatory in cases of severe and deep endometriosis, as multiplicity would translate not only in an increased risk of prematurity, but also of placenta praevia. The indication to eSET is even more important when undergoing oocyte donation programs. In particular, transfer at blastocyst stage of two embryos obtained with oocyte donation should never be contemplated. Moreover, albeit evidence is not yet conclusive, physicians may consider cleavage rather than blastocyst transfer, and could implement freeze-all policies.[11] Indeed, recent data suggests an increased likelihood of placenta praevia associated with transfer of a day 5 embryo and a lower risk in women undergoing elective frozen embryo transfer in a natural cycle.[11]

When pregnant women with rectovaginal lesions are diagnosed with placenta praevia, they should be referred to tertiary care centres with experience in both deep endometriosis and surgically complex obstetrical cases. To limit the risk of major intra- and postoperative complications, elective caesarean sections must be undertaken exclusively in hospitals with a blood bank, an interventional radiology unit, and availability of skilled obstetricians, colorectal surgeons, and urologists.

Information regarding the increased risk of placenta praevia should be disseminated among gynaecologists in charge of women with severe endometriosis and particularly among those providing ART. Both clinicians should also understand that the surgical implications of a placenta praevia in these women are different from those in the general pregnant population, and that a caesarean hysterectomy may pose the woman's safety at risk. A strict collaboration between the caring physicians, the personnel performing IVF, and the obstetricians that follow the pregnancy and carry out the delivery is mandatory. In fact, the objective of the ART process in this particular group of patients is not only a healthy singleton, but also a healthy mother after delivery. The short-term goal of maximising

reproductive success per embryo transfer, which is rewarding for both doctors and patients, appears here particularly short-sighted. In women with deep infiltrating endometriosis, the safety of the ART procedure is certainly no less important than its efficacy. Providers of IVF treatments must minimise late-pregnancy complications and safeguard the long-term health of the mother in addition to that of the baby. Incidentally, doctors who have to manage the consequences of multiple embryo replacement generally are not those who performed the IVF procedure.

Women must be allowed to make informed choices regarding their health based on their priorities and preferences. Thus, counselling patients is of utmost importance. The possibility of developing a placenta praevia and the potential obstetrical consequences should be described in detail to women with severe and deep endometriosis, whether operated or not. They should also know that IVF further increases the risk, and should be strongly invited to undergo exclusively eSET independently of age, ovarian reserve status, overall burden of treatment, and costs. Once adequately informed and fully aware, women may choose differently; some may decide to take the risk, but others may consider refraining from fertility treatments. It is their decision, not ours, and once pregnant they cannot turn back time.

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CONTRIBUTION TO AUTHORSHIP

Conception and design: PV. Acquisition of data: MPF, GB, and LB. Analysis and interpretation of data: PV and ES. Drafting of the article: PV. Critical revision of the article for intellectual content: PV, MPF, GB, LB, and ES. All the authors approved the final version of the manuscript.

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