FIRST-LINE IVF OR SURGERY FOR INFERTILE WOMEN WITH BOWEL ENDOMETRIOSIS?

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Reportedly, endometriosis infiltrates the colorectal muscularis propria in about one-tenth of patients with the disease (1, 2). When women with bowel endometriosis are infertile, it is unclear whether first-line IVF or surgery including intestinal procedures is the most effective treatment. By definition, bowel endometriosis must not cause severe subocclusive symptoms here, otherwise, surgery would be mandatory independently of infertility.

In addition to increasing the chances of natural pregnancy and preventing fetal exposure to the limited but established risks of IVF, surgical excision of all pelvic endometriotic lesions may reduce the frequency and severity of pain symptoms. On the other hand, colorectal resection, the still most frequently performed procedure, is associated with major complications in 5-10% of patients, may need a temporary ileostomy or colostomy, and cause de-novo intestinal dysfunctions or anastomotic stenosis.

First-line IVF avoids the risk of surgical harms and may speed up pregnancy achievement. However, some cases of endometriosis worsening after ovarian stimulation have been reported, with resulting intestinal occlusion or perforation. Nevertheless, it is unclear if a bowel lumen stenosis ≥ 50% was systematically ruled out in these women before proceeding with ART. In fact, the incidence of severe complications specifically due to the progression of infiltrating colorectal lesions in women without pre-existing sub-occlusion seems limited, despite the temporary hyper-estrogenism typical of IVF (3).

It is currently undetermined if the pathophysiology of infertility associated with bowel endometriosis differs from that of ovarian and superficial peritoneal lesions. An even more important issue is whether the reproductive prognosis varies if infiltrating intestinal endometriosis is left or removed. Owing to the extremely frequent co-existence of other pelvic lesion types, the available observational studies may not discriminate the specific impact of colorectal endometriosis on the likelihood of pregnancy achievement.

Presumably because the definition of the effects of surgery or ART as fertility-enhancing procedures for this condition remains problematic, the positions of experts diverge and the

recommendations issued by major reproductive medicine scientific societies are not conclusive. In this scenario, the results of the study by Maignien, Santulli and co-workers (1) are particularly welcome, as 64/101 women with unoperated advanced endometriosis, including infiltrating bowel lesions, achieved a live birth after first-line IVF.

The 101 participants were prospectively selected from a population of 336 infertile patients with intestinal endometriosis and, overall, complained of moderate pain symptoms. Included women were at fairly good reproductive prognosis, as their mean age was 32 years, mean serum AMH level 3 ng/mL, and mean AFC 15. One-fifth of them conceived before the index IVF cycles. A single embryo/blastocyst was transferred in the vast majority of participants, and a minority of them underwent more than two cycles. As expected, infertility of long duration and low ovarian reserve parameters were independent negative live birth predictors. No complications due to endometriosis were observed after ovarian stimulation, during pregnancy, and at delivery.

The authors agree that "*the impact of bowel endometriosis per se on fertility remains controversial, as bowel lesions are frequently associated with other anatomical endometriotic lesions*". Indeed, almost all the participants had several other endometriotic lesions in addition to intestinal ones. In particular, ovarian endometriomas were diagnosed in three-quarters of them. Moreover, the favorable results observed question the purported detrimental impact of adenomyosis, given that the condition was identified in about nine out of ten patients.

This study is remarkable, as only women with an imaging diagnosis of bowel endometriosis and without previous surgery were selected, thus limiting the potential confounding resulting from the effect of removal of endometriotic lesions and selection of the worse cases, i.e., those who did not conceive naturally after surgery. Importantly, patients lost to follow-up were not excluded and, in one of the analyses, were assumed to have not achieved a live birth. This should have prevented overestimation of the treatment effect.

Interestingly, among 46 patients originally excluded from the study as they underwent IVF after radical surgery for bowel endometriosis, a lower live birth rate of 41.3% was observed. This is

at odds with the results of Bendifallah *et al*. (4), who reported significantly higher live-birth rates in infertile women with colorectal endometriosis who underwent IVF after radical excision of intestinal lesions compared with those who underwent first-line IVF. At the third cycle, the live birth rates were 70.6% versus 54.9%, respectively. However, when surgery and IVF are combined, it seems arduous to distinguish between the impact of the two interventions without conducting an RCT comparing surgery plus postoperative IVF versus IVF only. This type of evidence should be available by 2025 (https://www.clinicaltrials.gov/ct2/show/NCT02948972?term=endometriosis+AND+France&dra=2&rank=8. Accessed on 4 January 2021).

When trying to assess the specific fertility-enhancing effect of intestinal endometriosis removal, exclusively natural conceptions should be considered. Moreover, to allow a meaningful comparison with first-line IVF, the pregnancy rate after surgery should be calculated including infertile women only. Roman *et al*. (2) reported a conception rate of 81% in 36 patients who sought a pregnancy after surgery for colorectal endometriosis. However, the rate halved when considering exclusively the 23 women who were infertile before the procedure and who conceived naturally.

Also, the effectiveness of ART should be evaluated in an unselected population at average reproductive prognosis. In fact, in case a randomized comparison between first-line IVF and surgery is planned, it would seem little plausible to postulate a clinically important additional benefit of surgery if the expected live-birth rate in the IVF arm is already about 65% (1). A superiority trial with a hypothesized incremental benefit of 15% in favor of surgery (a smaller difference would not seem reasonable, given the morbidity of colorectal endometriosis excision), would mean recruiting almost 300 participants, at the usual levels of α=5% and β=20%. However, such estimates of success might reveal excessively optimistic in an infertile population with severe endometriosis. In fact, the magnitude of the effects observed when RCTs are eventually conducted is usually smaller than that reported in observational studies. Several methodological drawbacks may explain this common discrepancy, selection bias generally having the largest impact.

Indeed, a further issue to consider is the generalizability of the reported results when they represent the maximum effect achievable under ideal clinical settings. Findings may reveal much less encouraging in the hands of less experienced surgeons or infertility laboratory teams. In the present study on first-line IVF, "*the MRI examinations were performed by a single experienced radiologist who is a referring practitioner for image-based diagnosis of endometriosis*". This might be considered a strength in terms of diagnostic performance and, consequently, accuracy of the selection process, but a limit in terms of generalizability. In surgical studies, performance of difficult bowel procedures may be an indicator of overall technical capabilities. Thus, the promising outcomes observed after colorectal surgery might not necessarily reflect the effect of specific intestinal procedures, but rather the excellent management of pelvic endometriosis as a whole.

Finally, an often-downplayed aspect when treating infertility in women with deep endometriosis is the risk of severe complications during pregnancy and delivery (5). Pre-conceptional information must include explanation of the risk of placenta previa, spontaneous hemoperitoneum and, in case a cesarean section is performed, visceral lesions and hemorrhage. In this regard, IVF appears ethically more challenging than surgery, as it is an active medical measure specifically aimed at obtaining a pregnancy that would not have occurred otherwise, whereas surgery implies removal of lesions but, afterwards, conception is sought naturally.

Given the quality of the available evidence, it appears uncertain how infertile women with non-sub-occlusive bowel endometriosis should be counselled. If the results of the study by Maignien, Santulli and co-workers will be confirmed by independent groups, the combination of first-line surgery plus postoperative ART should probably be considered with caution, as the additional benefit of excisional bowel procedures before IVF might not be sufficiently large to justify the associated morbidity and increased costs. First-line surgery as a sole measure, could be favored in patients with severe pain symptoms, without tubal factors and with a normozoospermic partner. A benefit of prophylactic surgery to prevent the obstetrical complications associated with colorectal endometriosis has not yet been proven (5). In the end, patients should be enabled to

choose the alternative that most fits their preferences and priorities, as different women may show variable acceptance thresholds for a given surgical complication risk, or reveal diverse psychological attitudes toward ART conceptions.

After decades of intense research on endometriosis, clinicians still have to rely on observational and often non-comparative data when counselling their infertile patients with non-sub-occlusive colorectal lesions. Multicenter, pragmatic trials, aimed at generating real-world evidence generalizable to routine practice are long awaited, and could eventually clarify whether the very notion of infertility associated specifically with bowel endometriosis is well-founded or ill-conceived.

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