EDITORIAL

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Bowel surgery for endometriosis-associated infertility: navigating amidst the certainty of the uncertainty

Paolo Vercellini[1,2], Nicola Berlanda[1], Edgardo Somigliana[1,2]

[1]Academic Centre for Research on Adenomyosis and Endometriosis, Department of Clinical Sciences and Community Health, Università degli Studi, Milan, Italy
[2]Gynecology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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Of Methodology, Bias, and Confounding: The Helter-skelter of the Available Evidence

The Authors of the review in this issue of Facts Views Vis Obgyn have done an excellent job of synthesising the published data on colorectal surgery for bowel endometriosis as a fertility-enhancing procedure.[1] They have also provided a comprehensive, objective, and balanced approach to this common and challenging clinical situation.[1] Indeed, even when prognostic factors such as radicality/residual disease, coexisting adenomyosis, age, and ovarian reserve are considered, quantifying the benefits of colorectal surgery based on largely inconsistent estimates is arduous.

Several confounding factors may here preclude a precise definition of the magnitude of the effect. Firstly, when assessing the impact on postoperative fertility, only preoperatively infertile patients should have been enrolled. However, in published studies available, it is not always easy to distinguish between infertile patients and those with an unknown fertility status who only sought to conceive after the procedure. Moreover, postoperative reproductive performance is often a secondary study outcome. This means that conclusions about the effect of surgery on fertility may be based on data from a population not selected to evaluate this outcome specifically. Secondly, since bowel lesions usually coexist with other endometriosis forms and infertility factors, how can the specific effect of intestinal endometriosis on the likelihood of conceiving after surgery be determined? Thirdly, colorectal endometriosis could be considered an indicator of advanced and progressive disease.[2] If this is true, the effect on fertility cannot be attributed exclusively to bowel lesions themselves, but rather to the extensive anatomical distortion, adhesions, and abdominopelvic inflammation associated with aggressive lesions. Fourthly, postoperative conceptions achieved after natural attempts or *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) were often grouped. This prevents the quantification of the additional benefit of colorectal procedures, as it is impossible to know what would have happened if IVF/ICSI had been resorted to upfront without prior surgery.[3] Fifthly, resection of bowel endometriosis is generally performed by highly skilled surgeons. How can we distinguish how much of the effect on fertility is due to the removal of colorectal lesions "per se" and

Corresponding Author: Paolo Vercellini, MD, Academic Centre for Research on Adenomyosis and Endometriosis, Department of Clinical Sciences and Community Health, Università degli Studi, Milan, Italy
E-mail: paolo.vercellini@unimi.it **ORCID ID:** orcid.org/0000-0003-4195-0996
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how much is due to the technical capability of radically removing "all" endometriotic lesions with limited tissue trauma, excising adhesions, and correcting additional coexisting anomalies according to precise reconstructive surgery criteria? Sixthly, non-comparative, observational studies generally overestimate the effect of any medical intervention for several reasons, including selecting the most favourable participants in terms of age and co-occurring infertility factors in addition to endometriosis, and excluding patients lost to follow-up (i.e., those with the worst prognosis). Seventhly, publication bias is highly likely, as no surgeon would reasonably be willing to report suboptimal post-surgical reproductive outcomes and complication rates.

The Role of Adenomyosis and Age

Adenomyosis and endometriosis are strongly associated "sister entities", particularly in cases of severe, infiltrating lesions such as colorectal endometriosis.[4] Several studies included in the present review clearly demonstrated the detrimental impact of adenomyosis on the reproductive performance of infertile patients, whether conception was sought naturally or via IVF/ICSI.[1] This is expected and can be explained by the reduction in implantation likelihood associated with adenomyosis.[4] Therefore, the removal of bowel endometriosis, along with all coexisting extraintestinal lesions, may reduce local inflammation, theoretically favouring gamete interactions and thus fecundation (i.e., the pelvic phase of reproduction). However, as adenomyosis is generally left untreated, it is unclear how colorectal surgery might influence implantation, i.e., the intrauterine phase, which is the limiting step in the conception process.

Thus, adenomyosis and age are independent factors that reduce the likelihood of a live birth, regardless of the presence of bowel endometriosis or any type of colorectal procedure performed.[4] This is important to consider when counselling individual patients, as the reported mean postoperative pregnancy rates should be contextualised. Appropriately, the Authors suggest that IVF/ICSI should be considered without prior surgery for women over 35 years of age, especially if adenomyosis is present.[1]

Risk of Progression of Unoperated Bowel Lesions and Obstetric Complications with and without Colorectal Surgery

A potential drawback of upfront IVF/ICSI is the risk of colorectal endometriosis progression and bowel occlusion or perforation during ovarian stimulation or pregnancy. Although anecdotal reports have been published,[5] the overall risk of occlusion seems low, unless the degree of lumen stenosis is ≥60% or subocclusive symptoms are reported at baseline evaluation. Indeed, these patients should undergo surgery anyway, regardless of their desire for conception.

An important issue to discuss when deciding whether to resort to surgery is how it may modify the risk of major obstetrical complications. Placenta praevia is the condition more consistently and robustly associated with severe endometriosis.[6,7] However, this adverse outcome is most likely due to coexisting adenomyosis,[4] rather than bowel endometriosis. As expected, resorting to excisional colorectal procedures does not seem to reduce the risk.[6,7] Spontaneous haemoperitoneum in pregnancy is another rare but life-threatening complication affecting patients with severely infiltrating endometriosis. In theory, pseudo-normalisation of the pelvic anatomy could reduce this risk; however, the rarity of the event makes it difficult to assess the effect of bowel surgery, if any.

Balancing Trade-Offs, Communicating Uncertainties, and Setting Thresholds

In addition to the above factors impacting the assessment of the potential benefits of colorectal surgery for bowel endometriosis, factors influencing the potential harms should also be evaluated.[8,9] Above all, a surgeon's expertise in dealing with difficult procedures for extensive and infiltrating disease forms influences the risk of major complications. According to a large French survey of 56 hospital facilities, 82 out of 1,135 patients (7.6%) with colorectal endometriosis who underwent surgery in 2015 developed Clavien-Dindo grade III-V complications (rectovaginal fistula, 2.7%; anastomotic leakage, 0.8%; pelvic abscess, 3.4%; ureteral fistula, 0.7%). The proportion was highest for segmental resection, lowest for shaving, and intermediate for disc excision. Importantly, an inverse relationship was observed between the number of procedures performed per year, both at the institutional and individual levels, and the probability of complications.[10] Therefore, the type of referral centre and the experience and technical capabilities of the surgeon affect the risk of severe complications.

This has methodological and practical implications. On the one hand, the reported complication rate reflects the best possible clinical scenario and is not generalisable. Indeed, the likelihood of potential harm may be higher

when colorectal procedures are performed by surgeons with average experience and capability. In this regard, choosing shaving instead of disc excision or segmental resection to limit surgical risk is often not feasible because, as the authors correctly highlight, "the decision to perform one technique over another is largely based on the characteristics of the endometriotic bowel lesions".[1]

On the other hand, these aspects contribute to shaping the overall therapeutic balance that each patient should ponder based on comprehensive, detailed, and balanced information, including the disclosure of personal and institutional volumes and performance.[8] Moreover, in a framework of truly shared medical decision-making, it must be disclosed whether both surgery and ART can be provided with the same level of expertise. In other words, offering one of the two options simply because it is more readily available at one's hospital without disclosing this does not seem ethically appropriate, as it infringes the fiduciary pact of trust between a patient and doctor.

The probability of major complications that is acceptable for a given magnitude of the expected additional benefit of bowel surgery over expectant management or upfront IVF/ICSI is a matter of patient choice, not healthcare provider choice. The issue is complicated by the fact that, while potential harms can now be quantified with an adequate degree of precision,[10] quantifying the potential benefits in different conditions is difficult, as the quality of the evidence is low and the clinical variables are many.[1] Thus, another ethically crucial aspect of counselling is open communication about uncertainties.[8,9] Uncertainty is part of everyday medical practice and is particularly important here. If an individual patient is aware of the uncertainty surrounding the communicated estimates of the potential benefits of surgery, she may be more inclined to opt for upfront IVF/ICSI. Otherwise, she may choose to undergo a colorectal procedure even in the absence of severe bowel symptoms.

Counselling involves weighing up the quantified benefits and harms of the two options. Even when based on robust evidence, weights have a relative impact on the final decision, as different patients may attribute different weights to the same estimate.[8,9]

Actually, as offering precise estimates of the potential benefits of colorectal surgery for endometriosis as a fertility-enhancing procedure in different clinical conditions is complicated, when in doubt, the less invasive option, i.e., upfront IVF/ICSI, can be suggested,[3] unless i) the patient reports subocclusive complaints; ii) examinations demonstrate a degree of bowel lumen stenosis ≥60% regardless of symptoms; iii) the woman has severe abdominopelvic pain and/or is willing to conceive through natural attempts only; iv) repeated IVF/ICSI cycles have failed.

Interestingly, the Authors have also provided an update on ongoing randomised, controlled trials investigating the effect of colorectal surgery for bowel endometriosis in diverse infertile populations.[1] Considering the methodological limitations of the available observational evidence,[1] women with endometriosis and healthcare providers are eagerly awaiting the results of these high-quality trials.

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