

# Treatment of infertility associated with deep endometriosis: definition of therapeutic balances

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Deep endometriosis is a demanding condition that is associated with infertility. However, evidence supporting a direct link between deep endometriosis and infertility is weak. In fact, infertility in affected patients is more likely to be explained by the strong association between deep endometriosis and adhesions, superficial endometriotic implants, ovarian endometriomas, and adenomyosis. The purported beneficial effects of surgery on infertility are mainly based on the 40%–42% pregnancy rate (PR) after surgery observed in published case series. However, this level of evidence is questionable and overestimates the benefits of the intervention. Even if comparative studies are lacking, IVF may be a valid alternative. The procedure may be less effective in affected women compared with other indications and it is not without additional deep endometriosis-related risks. Some case reports suggest that lesions might progress during IVF causing ureteral or intestinal complications or can decidualize during pregnancy causing intestinal perforation, pneumothorax, and pelvic vessels rupture. Finally, in the decision-making process, physicians should also consider that women with a history of deep endometriosis may face an increased risk of pregnancy complications. In conclusion, clear recommendation for the management of infertile women with deep endometriosis cannot be extrapolated from the literature. The therapeutic decision should be based on a comprehensive evaluation that includes clinical history, instrumental findings, pain symptoms, risks of pregnancy complications, and the woman's wishes. (Fertil Steril® 2015;104:764–70. ©2015 by American Society for Reproductive Medicine.)

**Key Words:** Deep endometriosis, surgery, IVF, pregnancy

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**D**eep endometriosis is diagnosed when endometriotic lesions infiltrate the uterosacral ligaments, the rectovaginal pouch, the posterior vaginal fornix or the muscularis propria of the bladder, the intestine, or the ureter. Less frequently, these lesions may be found in sites distant from the pelvis (1). Deep endometriosis causes chronic pain whose characteristics may have a cyclic (catamenial) course and may be related to the location. Typical symptoms include dyspareunia, dyschezia, and dysuria. In most advanced cases, deep endometriosis may disrupt organ function causing in particular intestinal obstruction, rec-

torrhagia, hematuria, ureteral obstruction, and renal failure. Women with deep endometriosis may also be infertile (2).

Treatment of deep endometriosis includes hormonal agents and surgical excision and is aimed at alleviating symptoms or preventing imminent complications. Progestins are effective because they create a pseudopregnant state characterized by a steady hormonal condition without the physiological fluctuations in sex steroids, which are ultimately responsible for the endometriosis-related symptoms. Remarkable benefits may be obtained in most women but drugs have to be

assumed in the long term because symptoms typically and rapidly recur once treatment is discontinued (3). Surgery is also highly effective and typically recommended if medical therapy fails or if it cannot be ruled out that nodules may soon compromise the function of the adjacent organs (4). In some cases, surgery may definitely cure the woman. However, surgery can be demanding, requires utmost expertise and skillfulness, and exposes women to some risks (5). Removal of the lesions may cause organic or functional harm to the adjacent organs. Ureteral, bladder, and intestinal injury may occur during the intervention and can cause demanding short-term conditions, such as peritonitis, hemorrhagia, and ureteral damage, and long term complications such as fistulae, ureteral or rectal stenosis, or neurologic impairment of bladder or rectal function. Frequency of these complications

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varies from 1%–10% (5). In addition, surgery does not protect from recurrences. At least one in two operated women experience recurrence within 5 years (6, 7).

## AIMS AND METHODOLOGY

The pathogenesis and treatment of endometriosis remain debated. The relation between deep endometriosis and infertility and the beneficial effects of available treatments is a particularly intricate question. A definite conclusion is actually not at hand (2, 4). In this opinion article, we did not aim at a thorough review of the literature but, conversely, we aimed at discussing this multifaceted argument with the intent to provide some elements that may help the clinicians in interpreting the available evidence and in their decision-making process.

We searched PubMed for articles published in the English language between January 2000 and June 2015 using the following MeSH search terms: “deep” OR “invasive” OR “infiltrative” combined with “endometriosis” OR “endometriotic” and with “fertility” OR “infertility” OR “laparoscopy” OR “surgery” OR “surgical” OR “pregnancy” OR “Assisted Reproductive Technology” OR “ART” OR “in vitro fertilization” OR “IVF” OR “intracytoplasmic sperm injection” OR “ICSI” with restriction to the human species. Data were extracted independently by the two investigators who also performed an initial screening of the title and abstract of all articles to exclude citations deemed irrelevant. Manual search of review articles and cross references completed the search. Data presented exclusively as abstracts in national and international meetings were also excluded.

## DEEP ENDOMETRIOSIS AND INFERTILITY: THE CRITICAL ROLE OF CONFOUNDERS

Interpretation on the available evidence linking deep endometriosis to infertility is challenging. A crucial point is the association between deep endometriosis with other forms of endometriosis that may affect fertility on their own. The presence of superficial endometriotic implants, endometriomas, and pelvic adhesions was documented in 61%, 50%, and 74% of patients with deep endometriotic nodules, respectively. Overall, deep peritoneal endometriosis was isolated in only 6% of patients (8). Similar findings were observed when considering specifically deep nodules of the bladder (9). Noteworthy, even if specific data on the independent impact of all the different forms of endometriosis on fertility are lacking and cannot be obtained, deep endometriosis is intuitively less likely to affect fertility. Superficial implants may release inflammatory mediators in the peritoneal fluid that may be detrimental to the released oocyte and its fertilization in the distal part of the tube (10). Adhesions may distort pelvic anatomy interfering with the tubal function (11). Endometriomas may affect folliculogenesis and oocytes quality (12). In contrast, deep peritoneal lesions are generally buried under adhesions and the associated local inflammation is thus unlikely to reach the peritoneal cavity and thus interfering with the conception process. On theoretical bases, one may thus question whether these lesions may independently have any impact on fertility (13). On the other hand, there is

evidence for an indirect effect mediated by the reduction in sexual function consequent to deep endometriosis-related dyspareunia (14).

The scenario is even more intricate if we consider the well-known association between endometriosis and adenomyosis (15–17) and the possible relationship between the latter and infertility (18, 19). Of particular interest is the growing evidence that adenomyosis is more frequently diagnosed in women with deep endometriosis compared with other forms of the disease (15, 16, 20, 21). Based on a large series of 1,618 women with endometriosis, Di Donato et al. (21) highlighted that the most significant factor associated to adenomyosis was the presence of deep lesions. The adjusted odds ratio (OR) was 3.1 (95% confidence interval [CI] 2.4–4.1). In a systematic review of the literature, Vercellini et al. (22) showed that the chances of pregnancy after surgery for deep endometriosis are markedly lower if concomitant adenomyosis is diagnosed. The common relative risk of pregnancy in women with adenomyosis was 0.3 (95% CI 0.2–0.7).

## THE IMPACT OF DEEP ENDOMETRIOSIS ON NATURAL FERTILITY AND THE BENEFITS OF SURGERY

Endometriosis can cause infertility but the magnitude of this effect and the independent role of the different forms of the disease remain uncertain. In addition, as the main symptom of deep endometriosis is pain, the wish for a child only emerges once pain has been reduced and it is obviously very intricate to dissect how many women with asymptomatic deep endometriosis are fertile or the percentage of infertile women not seeking pregnancy as they have pelvic pain or dyspareunia.

Studies reporting on the natural fecundity in not operated women with endometriosis are scanty and tend to support the view that, even if subfertile, affected women can conceive naturally even without surgery. In the control arm of the two randomized controlled trials investigating the benefits of surgery in infertile women with endometriosis stage I–II (23, 24), the pregnancy rate (PR) was 18%, thus significantly lower but not markedly different from the 26% observed in operated women (7). Recently, Leone Roberti Maggiore et al. (25) observed that the 6-month cumulative PR in a large cohort ( $n = 244$ ) of women with unoperated unilateral endometriomas and who did not previously seek pregnancy was 43% (95% CI 37%–50%), thus lower than the expected theoretical 74% rate for fertile women (26) but still relevant from a clinical perspective. In the subgroup of women who were diagnosed also with concomitant deep endometriosis ( $n = 184$ ), 76 conceived (41%, 95% CI 34%–49%) (25).

Vercellini et al. (27) compared the chances of pregnancy in infertile women with rectovaginal endometriosis who did and did not undergo surgery. A total of 150 infertile women with this form of the disease but without other concomitant factors of infertility were given the possibility to choose between expectant management and surgery after an in-depth discussion of the pros and cons of the two options. At 24-month

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