

# Introduction:

## From pathogenesis to therapy, deep endometriosis remains a source of controversy

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Deep endometriosis remains a source of controversy. A number of theories may explain its pathogenesis and many arguments support the hypothesis that genetic or epigenetic changes are a prerequisite for development of lesions into deep endometriosis. Deep endometriosis is frequently responsible for pelvic pain, dysmenorrhea, and/or deep dyspareunia, but can also cause obstetrical complications. Diagnosis may be improved by high-quality imaging. Therapeutic approaches are a source of contention as well. In this issue's Views and Reviews, medical and surgical strategies are discussed, and it is emphasized that treatment should be designed according to a patient's symptoms and individual needs. It is also vital that referral centers have the knowledge and experience to treat deep endometriosis medically and/or surgically. The debate must continue because emerging trends in therapy need to be followed and investigated for optimal management. (*Fertil Steril*® 2017;108:869–71. ©2017 by American Society for Reproductive Medicine.)

**Key Words:** Deep endometriosis, pathogenesis, medical therapy, surgery, obstetrical complications

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The idea that peritoneal, ovarian, and rectovaginal endometriosis are three separate entities with a different pathogenesis was already suggested 20 years ago (1). However, deep (nodular/infiltrating) rectovaginal endometriosis has long been a source of controversy, from its pathogenesis to the medical and surgical approaches applied.

Defining deep endometriosis according to infiltration of more than 5 mm is actually misleading. Indeed, many peritoneal endometriotic lesions observed in the Douglas pouch or uterosacral ligaments infiltrate to a depth of more than 5 mm, but it would be inaccurate to term them deep endometriosis. As suggested by Gordts et al. (2) in this issue,

it is preferable to define deep endometriosis pathologically, as adenomyosis externa (2) or adenomyosis-like nodules (1). Most deep endometriotic nodules are unique, resulting in large (usually >2 cm) lesions extending to the bowel wall muscle and sometimes laterally to the ureters, but association with nodular bladder endometriosis is not infrequent. Their diagnosis may be improved by high-quality imaging, as advocated by Bazot and Daraï (3). They may also cause obstetrical complications (4).

### THE PATHOGENESIS REMAINS CONTROVERSIAL

There is increasing evidence that endometriosis exists because it bleeds. The concept of repeated tissue injury

and repair appears to be the driver, at least for peritoneal and ovarian endometriosis (2). Yet, even experts disagree. In the present issue, Gordts et al. (2) defends and supports the hypothesis of neonatal menstruation that occurs during the first week postpartum in approximately 5% of neonates, which could well account for some forms of peritoneal endometriosis. However, the presence of endometriosis in prepubertal girls is very rare, and neither neonatal menstruation nor Sampson's theory can explain progression from an early stage (endometrial attachment to the mesothelium) to a deep endometriotic nodule, 90% of which resides in the retroperitoneal space and consists of smooth muscle hyperplasia (1). The implantation theory may explain some forms of the disease (2), like peritoneal endometriosis and ovarian endometriosis, even if some authors favor the metaplasia theory for the latter (1). Nevertheless, evolution from a typical

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lesion to a deep lesion has never actually been observed and remains speculative (2).

Is deep endometriosis a progressive disease? According to Gordts et al. (2) this is debatable (2) but, on the other hand, progression occurs at a certain point in time (1). The first questions are “when and why” and then, “Why are we unable to diagnose this progressive step leading to establishment of a large nodular lesion?”

During reproductive life, different mechanisms could lead to implantation after reflux of desquamated endometrium. The presence of excess iron in the peritoneal cavity due to local bleeding of ectopic endometriotic lesions induces oxidative stress, resulting in macromolecular oxidative damage, tissue injury (local destruction of the peritoneal mesothelium) and chronic inflammation.

Another theory, the metaplasia theory, was proposed more than 50 years ago to explain endometriosis development in women without an endometrium (absent uterus). In these women, endometriosis could develop from stem cells, possibly following certain genetic or epigenetic changes triggering “abnormal growth of endometrium-like tissue” (2). It led Gordts et al. (2) to raise the question, “What is the original cell responsible for the development of deep endometriosis?”

As reviewed by Gordts et al. (2), there are many arguments supporting the hypothesis that genetic or epigenetic changes are a prerequisite for development of lesions into deep endometriosis. In their review, the authors obviously maintain two differing hypotheses (implantation vs metaplasia) (2). After more than a century of controversy, the pathogenesis of deep endometriosis remains a source of discussion and debate with no clear consensus.

Other theories should not be excluded either. Indeed, Müllerian rests remaining from embryonic development may constitute yet another hypothesis (2), and it cannot be ruled out that some forms of deep endometriosis are benign adenomyotic nodules originating from the cervix (1).

## THERAPEUTIC APPROACHES, WHETHER MEDICAL OR SURGICAL, ARE A SOURCE OF CONTENTION

The first point to emphasize is that treatment should be designed according to a patient's symptoms and individual needs (5). It is also vital that referral centers have the knowledge and experience to treat deep endometriosis medically and/or surgically (5, 6). Furthermore, there is a consensus that surgery should be first-line treatment if stenosis of the ureter or severe stenosis (50%–75%) of the rectosigmoid is observed. Both articles concur on these three points (5, 6).

For Vercellini et al. (5), medical therapy should be considered as first-line treatment in women with symptomatic deep endometriosis not seeking natural conception. Of course, this in no way contradicts the latter point, which remains wholly valid for the authors in the stated circumstances.

There is no doubt that deep endometriosis provokes pain in a great majority of cases, involving many mechanisms that may explain its prevalence, like inflammation, activation, or encapsulation (by endometriotic tissue) of sensory nerve fibers, and traction of adjacent ligaments or organs fixed by

dense adhesions. Endocrine pharmacotherapy can also be administered as neoadjuvant or adjuvant therapy to treat recurrences, and there is a rationale for use of hormone therapy (5) to manage inflammatory and neuropathic pain. However, as stressed by Vercellini et al. (3), medical therapy can control but not eradicate deep endometriosis. This explains why symptoms may recur at variable times after drug withdrawal, an argument frequently used by gynecologists to prove that hormone therapy is ineffective.

The contentious debate between proponents of radical surgery and hormone therapy is still ongoing and, like Vercellini et al. (3), I would like to cite Pellicer and Zuppi, “Excellent speakers have promoted the efficacy of hormone treatments without knowing the benefits of surgical approaches; talented surgeons are explaining the benefits of radical removal of lesions without any experience with medical treatment options.” This rather sums it up.

Recommendations for endocrine therapy include the following options (5):

- Oral contraceptives (OCs)
- Gestagens (nortestosterone or progesterone derivatives)
- Gonadotropin-releasing hormone agonists/antagonists
- Painkillers, including anti-inflammatory drugs

There is no consensus between use of OCs or progestogens as first-line treatment. Vercellini and colleagues (5) favor OCs while Casper, as discussed by Vercellini and colleagues, prefers progestogens, but there are arguments in support of both approaches (7). Other options, like the combination of aromatase inhibitors with gestagens or gonadotropin-releasing hormone agonists, have also demonstrated some degree of efficacy. Nevertheless, the absence of response when aromatase inhibitors are administered alone, as well as their cost, make this option highly dubious (5, 7). Moreover, as stated by Vercellini et al. (5) in their article, the association of letrozole to norethisterone acetate gives a similar level of satisfaction to monotherapy with norethisterone acetate. It is therefore clear that even experts and pioneers in medical therapy have reached no consensus on the type of drugs that should be used.

Finally, the most important thing is to fully explain all aspects (pros and cons) of treatment (medical, surgical, or medico-surgical) during counseling, like the duration of medical therapy (until pregnancy is sought or menopause reached), side effects of drugs, and complications of surgery (5). During discussion of all options, not only improvements but also recurrence rates should be clearly communicated to patients.

## SURGERY FOR DEEP ENDOMETRIOSIS: ALSO CONTROVERSIAL?

There are, in fact, two types of possible surgery, a more aggressive approach (known as radical) that involves bowel resection, and a less aggressive approach (known as conservative) that entails use of the shaving technique and/or disc excision. In their manuscript, Donnez and Roman (6) clearly state, “Even if infiltration up to the rectal mucosa and invasion of >50% of the circumference have been suggested as

an indication for bowel resection, this remains a subject of debate.” Indeed it does because on one hand, surgeons in favor of a conservative approach claim that peri- and postoperative complications are much less frequent after shaving and/or disc excision, while on the other hand, those in favor of bowel resection claim that the more radical procedure yields lower recurrence rates.

But are these claims really well balanced? When shaving surgery is performed by highly skilled and experienced surgeons familiar with the procedure, the recurrence rate is as low as after bowel resection (6). However, the risk of severe complications (like rectovaginal fistula or leakage) is, without doubt, higher after bowel resection, particularly when the lesion is located  $\leq 8$  cm from the anal verge (6).

Are functional outcomes important? In recent years, more and more articles (6) have underlined the importance of functional outcomes. Bowel resection may lead to bowel denervation and subsequent incontinence and fecal urgency, or bladder denervation with resulting urinary retention. In the majority of cases, these unfavorable functional outcomes may only be temporary, but in some cases, they are permanent. In any case, patients need to be informed of these risks.

### The Debate Goes on...and Probably with Good Reason

The debate needs to continue because emerging trends in therapy have to be followed and managed. Indeed, ‘shaving’ enthusiasts are shaving ever more and do not hesitate to open the rectum to resect a small disc, while ‘resection’ advocates are actually resecting increasingly smaller parts of the bowel, taking care to preserve nerves.

Performing a large resection with a view to a radical approach is not actually requisite, as it was demonstrated that being ‘radical’ in endometriosis treatment is almost impossible (6). Finding residual lesions after bowel resection is not so uncommon, with positive margins observed in 10%–22% of cases (6). Moreover, occult microscopic bowel implants have been identified as far as 3 cm from macroscopic nodules (6). Of course, indications for bowel resection exist, but in our opinion, they are steadily declining.

As stressed by Donnez and Roman (6), in the overall context of colorectal surgery, there is a general tendency towards more conservative surgical techniques in diseases as varied as rectal cancer, Crohn’s disease and rectocolitis, and it is inevitable that this tendency also extends to deep endometriosis. There is no doubt that experts in deep endometriosis are now moving towards a consensual approach involving: shaving (associated with posterior vaginal fornix resection) as the first-line approach; disc excision when the results of rectal shaving are unsatisfactory; and segmental bowel resection in case of major bowel stenosis (50%–75%) or multiple nodules infiltrating the rectosigmoid junction and/or sigmoid colon.

In conclusion, deep nodular (rectovaginal) endometriosis remains a source of controversy, throwing up numerous challenges, but experts are exploring all options for medical and surgical strategies in their resolve to arrive at a unanimous and universally accepted approach. The future may well see the discovery or development of a drug able to very significantly (>50%) reduce the volume of nodules to facilitate their elective resection, avoiding the need for segmental bowel resection altogether (7).

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