Endometriosis and infertility: pathophysiology and management
Dominique de Ziegler, Bruno Borghese, Charles Chapron

Endometriosis and infertility are associated clinically. Medical and surgical treatments for endometriosis have different effects on a woman’s chances of conception, either spontaneously or via assisted reproductive technologies (ART). Medical treatments for endometriosis are contraceptive. Data, mostly uncontrolled, indicate that surgery at any stage of endometriosis enhances the chances of natural conception. Criteria for non-removal of endometriomas are: bilateral cysts, history of past surgery, and altered ovarian reserve. Fears that surgery can alter ovarian function that is already compromised can spark a rule of no surgery before ART. Exceptions to this guidance are pain, hydrosalpinges, and very large endometriomas. Medical treatment—eg, 3–6 months of gonadotropin-releasing hormone analogues—improves the outcome of ART. When age, ovarian reserve, and male and tubal status permit, surgery should be considered immediately so that time is dedicated to attempts to conceive naturally. In other cases, the preference is for administration of gonadotropin-releasing hormone analogues before ART, and no surgery beforehand. The strategy of early surgery, however, seems counterintuitive because of beliefs that milder non-surgical options should be offered first and surgery last (only if initial treatment attempts fail). Weighing up the relative advantages of surgery, medical treatment and ART are the foundations for a global approach to infertility associated with endometriosis.

Introduction
Endometriosis, an enigmatic disease characterised by development of endometrial tissue outside of the uterus, causes pain and infertility. A good correlation exists between amount, type, and location of endometriotic lesions and the painful symptoms encountered. By contrast, links between endometriosis and infertility are less clear, even though the association is clinically recognised. The prevailing vision today is that infertility in endometriosis is multifactorial, with many ways identified by which endometriosis possibly interferes with reproduction.

After touching on the pathophysiological background of endometriosis and infertility, we will assess the respective values of surgery and medical treatments. By medical treatments we mean the various agents proposed for treatment of endometriosis (all block ovarian function but by different means). Today, drugs mainly amount to agonists of gonadotropin-releasing hormone, oral contraceptives, and other hormone treatments (ie, progestins only). These, however, do not encompass the various assisted reproductive technologies (ART), such as ovarian stimulation, which is used for augmentation of fertility and is sometimes undertaken for endometriosis. When surgery and medical treatments fail, or natural conception is impossible because of coexisting tubal disease or altered male characteristics, reversion to ART is necessary. Such techniques include in-vitro fertilisation (IVF) and its variant for male factor infertility, intracytoplasmic sperm injection. Hence, we will also highlight how medical and surgical treatments of endometriosis affect the outcome of ART. Finally, having laid the foundation for a global approach to infertility associated with endometriosis, we will sketch a practical algorithm for guidance of clinical management.

Pathophysiology
Figure 1 summarises possible mechanisms by which endometriosis could affect fertility. These processes are described below, according to whether they take place in the pelvic cavity, ovaries, or uterus.

Pelvic cavity
Retrograde menstruation, first described by Sampson, remains the primary mechanism put forth to account for the pathogenesis of endometriosis. A participating role of the peritoneum—the coelomic metaplasia theory—has also been suggested. Ultimately, endometriotic lesions are associated with profound alterations of peritoneal fluid, which surrounds the pelvic organs. This fluid, an ultrafiltrate typically amounting to about 20 mL of serous fluid, contains ovarian secretions in women, including follicular fluid released at ovulation.
Fertilisation of human oocytes (natural conception) takes place at the distal end of the fallopian tube, the ampulla, in the vicinity of the ovaries. With a wide
opening into the pelvic cavity, the ampulla is exposed to peritoneal fluid, which thus contributes to the milieu in which fertilisation normally takes place. Logically, therefore, changes in the characteristics of peritoneal fluid might affect natural conception.

Pelvic inflammation, a classic feature of endometriosis, not only results from endometriotic lesions but also is a factor promoting ectopic proliferation and growth of endometrial tissue. Evidence for inflammatory changes in endometriosis that could affect peritoneal fluid includes: proliferation, activation, and phagocytic dysfunctions of macrophages; secretion of proinflammatory, growth, and angiogenic factors; and an increase in natural killer cells and T lymphocytes and their dysfunction, including a reduction in cytotoxic activity.

Some published data (but not all) suggest that peritoneal fluid from women with endometriosis leads to immobilisation of sperm, mainly through action of macrophages. Interleukins 1 and 6 directly affect sperm motility. Tumour necrosis factor (TNF) α causes DNA damage to sperm in a concentration-dependent and time-dependent manner, possibly through reactive oxygen species and apoptosis. Macrophage migration inhibitory factor, the amount of which is raised in peritoneal fluid of women with endometriosis, alters sperm motility in a dose-dependent manner. Also, migration inhibitory factor, TNFα, interleukin 6, and oxidative stress could hinder sperm capacitation. Furthermore, peritoneal fluid of patients with endometriosis hampers oocyte–sperm interactions. Peritoneal fluid decreases sperm binding to the zona pellucida through TNFα, interleukin 1, and the RANTES (regulated upon activation, normal T cell expressed and secreted) cytokine. Oxidative stress could also impair the acrosome reaction and sperm–oocyte fusion.

Overproduction of embryotoxic cytokines and prostaglandins in peritoneal fluid affects oocytes and ensuing embryos. In mice, TNFα inhibits cleavage of two-cell embryos and hinders implantation. In women, direct effects of endometriosis on oocyte quality and, in turn, embryo outcome have been proposed by some but questioned by others.

Ovaries

Endometriosis sometimes extends to the ovaries, forming cysts or endometriomas. By space-occupying effects, local reactions, or both, cysts can reduce the amount of functional ovarian tissue available, which could be aggravated further by surgery. Although the best surgical approach to endometriomas is uncertain, we now recognise that any type of surgery could cause additional damage to already compromised ovarian function.

Generally, the decline in ovarian follicles that happens throughout life does not hamper greatly the chance of conception before 37 years of age. However, this deterioration can take place at an earlier age in cases of ovarian endometriosis. Knowledge of the remainder of ovarian follicles and how this number predicts fecundity has led to the notion of ovarian reserve.

Several techniques have been proposed for assessment of ovarian reserve; all tests inform on the number (not the quality) of remaining oocytes. The two most frequent approaches are measurement of level of follicle-stimulating hormone on day 3 of the menstrual cycle and the number of antral ovarian follicles counted on ultrasound. Another proposed marker of ovarian reserve entails assessment of concentrations of antimullerian hormone produced by growing ovarian follicles. Concentrations of this hormone are not affected by the menstrual cycle or oral contraceptives, making measurement possible at any time in the cycle or during administration of hormonal treatments. Mean concentrations of antimullerian hormone were reduced in infertile women with endometriosis. When the fall in number of ovarian follicles is a result of ageing (ie, in women older than 40 years), data of ART indicate a parallel decrease in oocyte quality. This outcome does not arise when the number of ovarian follicles is reduced in younger women with endometriosis.

The possible effect of ovarian endometriosis on oocyte quality is still under debate. Some researchers say that

Figure 1: Effects of endometriosis on human reproduction

ART=assisted reproductive technologies.
fertilisation rates are reduced in women with endometriosis. Conversely, data of ART suggest that any effect of endometriosis on oocyte quality is probably minimal because pregnancy rates are preserved in women with endometriosis, even in those with poor response to controlled ovarian hyperstimulation.

**Uterus**

About 25 years of experience with ART has taught us how hormones control endometrial receptivity to embryo implantation. In particular, exogenous oestradiol and progesterone are sufficient for priming endometrial receptivity when ovaries are absent or non-functional—eg, in recipients of donor-egg IVF. However, findings suggest that the endometrium (ie, the eutopic endometrium lining the uterine cavity) is altered in women with endometriosis. These findings therefore question whether the endometrium is optimally receptive in endometriosis.

Endometrial alterations recorded in women with endometriosis are independent of circulating concentrations of oestradiol and progesterone (which are by and large normal); rather, they stem from local events. Anomalies are of two types: (1) abnormal, inflammation-related, in-situ production of oestradiol; and (2) overt resistance to the effects of progesterone.

Uterine production of prostaglandins E2 and F2α is well known during menses. Increased manufacture of prostaglandin is a typical finding in dysmenorrhoea, a disorder that sometimes responds to cyclo-oxygenase (COX) inhibitors. In endometriosis, alterations of prostaglandin production in the eutopic endometrium have been identified. These include activation of COX2 and prostaglandin E2 manufactured by interleukin 1 and other cytokines made locally by developing macrophages. A key step identified in women with endometriosis is activation of steroidogenic factor 1. This transcription factor enables prostaglandin E2 to initiate expression of CYP19A1 (coding for aromatase, the enzyme that transforms testosterone into oestradiol) through stimulation of CYP19A1’s type IIa promoter. This process ultimately leads to in-situ production of oestradiol, which possibly disrupts peristaltic activity of the myometrium. Likewise, local production of oestradiol might cause resistance to progesterone. Usually, this inflammation-related loop is kept inactive in the endometrium by silencing of steroidogenic factor 1 by hypermethylation of its promoter.

In endometriosis, numbers of macrophages and dendritic cells are raised in the eutopic endometrium. These cells are the primary source of cytokines—interleukins 6, 8, and 10, transforming growth factor, and TNFα—that initiate COX2 activation and production of neurotrophic factors such as nerve growth factor and brain-derived neurotrophic factor. In women with endometriosis, brain-derived neurotrophic factor causes development of sensory Aδ adrenergic and cholinergic nerve fibres in the functional layer of the endometrium. This process parallels that seen in peritoneal and deep infiltrating endometriotic lesions. Ovarian suppression with gonadotropin-releasing hormone analogues or oral contraceptives corrects these endometrial alterations.

This effect might account for the improved outcome of ART after ovarian suppression with gonadotropin-releasing hormone analogues. The duration of treatment necessary for normalisation of the endometrium in endometriosis is not yet known precisely.

In the menstrual cycle, progesterone receptors develop in the endometrium during the follicular phase, under the effect of oestradiol. This process is necessary for expression of antiproliferative and differentiation-promoting properties of progesterone on the endometrial glands and stroma during the luteal phase. The situation in women with endometriosis departs from this normal physiological process. Data suggest overt resistance to both properties of progesterone in endometriosis. This resistance—a lack of full deployment of all normal biochemical effects of progesterone—might result from changes in isoforms of the progesterone receptor, in ways not unlike those identified during functional progesterone withdrawal that happens during labour.

**Genesis of endometriosis**

In summary, changes recorded in the eutopic endometrium in women with endometriosis alter the characteristics of endometrial cells. Endometrial debris collected in the pelvic cavity at the time of surgery implants and proliferates in vitro quicker when it originates from patients with endometriosis compared with unaffected women. Endometriosis, therefore, does not result solely from retrograde bleeding per se. Rather, the very properties of endometrial cells that are shed in the pelvic cavity, including their tendency to implant and proliferate, probably have a pivotal role as well. This novel idea refutes the longstanding objection to Sampson’s theory, that although most women have retrograde menstruation, only a few develop endometriosis.

**The compounding role of pain**

In women with endometriosis, pelvic pain and, particularly, dyspareunia affect a couple’s ability to have regular sexual intercourse and, thus, will compound infertility problems. The primary cause of pain is deep infiltrating endometriotic lesions that penetrate the muscularis propria of surrounding organs (such as the bladder or rectum). However, whether deep infiltrating endometriosis hinders fertility directly is unclear. Practically speaking, the presence of pain strongly weighs in favour of surgery, and findings show that surgery for deep infiltrating endometriosis improves fecundity. Therefore, thorough interrogation of patients about the presence and intensity of pelvic pain is important.
Specifically, the practical impact that pain can have on everyday activity and sex life needs to be assessed meticulously when contemplating surgery.

**Practical benefit of medical treatment and surgery on conception chances**

**Natural conception**

To date, all forms of medical treatment available for endometriosis block ovarian function and are, thus, contraceptive (eg, danazol, gonadotropin-releasing hormone analogues, progestins, and oral contraceptives). These agents are effective on pain and reduce the risk of recurrence of symptoms after surgery. Contrary to earlier beliefs, however, fecundity does not rebound on termination of treatment. Medical treatments are, thus, not indicated for infertility associated with endometriosis, either as a standalone option or after surgery.

The issue of whether surgical removal of endometriotic lesions—either by laparoscopy or laparotomy—improves a woman’s chances of spontaneous (natural) conception is complex. Confusion stems from the different forms of endometriosis (superficial endometriosis extending according to American Fertility Society score, endometriomas, and deep infiltrating endometriosis), types of surgery undertaken, and modes of fertility assessed (in vivo or in vitro). The propounded effect through which surgery would enhance the chances of natural conception is by reduction of pelvic inflammation, but this suggestion was never verified.

First-line evidence in support of surgery for superficial endometriosis came from a randomised trial reported by Marcoux and colleagues and the ensuing meta-analysis. These authors accounted for co-interventions—ie, ovarian stimulation—that took place in fewer than 10% of participants, cases and controls alike. They reported an increased odds ratio for spontaneous conception of 1.66 (95% CI 1.09–2.51) after surgical removal of superficial endometriosis.

Unfortunately, as far as we know, all other studies of pregnancy chances after surgery for various stages of endometriosis are either open or not prospective, and many are uncontrolled. In a trial looking at 222 women who underwent surgery for various-stage endometriosis with no other cause for infertility, cumulative rates of pregnancy were about 30% and 50% at 18 and 36 months, respectively. Probability of conception did not differ according to stage of endometriosis. In a meta-analysis, the same team reviewed results of 14 trials of pregnancy chances after laparoscopic treatment of endometriotic cysts. Postoperative rates of conception varied from 30% to 67%, with a weighted mean of about 50% (webappendix). According to Hart and colleagues, excision by laparoscopy of endometriomas larger than 3 cm offered better chances of subsequent conception in vivo compared with drainage or vaporisation.

Surgery for deep infiltrating endometriosis is mainly aimed at alleviation of pain classically associated with these lesions. Information on subsequent pregnancies is not always available. Reported pregnancy rates range from 24% to 54% (webappendix). In their review, Vercellini and colleagues stress that reported data are probably overestimates. A possible bias is that some patients did not actively try to conceive before surgery. Furthermore, suboptimum and negative results are less likely to be published, which is referred to as publication bias.

During more than 25 years of experience with ART, a trend for treatments other than IVF has been noted, consisting of controlled ovarian hyperstimulation with or without intrauterine insemination as intermediary therapeutic option. These so-called middle-ground measures have been proposed generally to all couples capable of conception in vivo, according to their tubal and semen characteristics. However, the soundness of middle-ground treatments was challenged in unexplained infertility, for which these strategies were not superior to a wait-and-see approach and were not cost effective. Their effectiveness in endometriosis is questionable further, since Oml and colleagues reported diminished results in women with this disorder versus unexplained infertility. In a study with a seemingly different outcome, Werbrouck and coworkers indicated that pregnancy rates of controlled ovarian hyperstimulation with intrauterine insemination were similar in women with mild or minimal endometriosis and unexplained infertility. However, all endometriosis patients had undergone surgery (diagnostic and curative) within the previous 6 months. Therefore, the findings might actually show that it is surgery that may have provided a similar if not greater effect on in-vivo fertilisation than controlled ovarian hyperstimulation with intrauterine insemination alone. Until additional data are available and evidence of effectiveness of controlled ovarian hyperstimulation with intrauterine insemination is provided, we do not recommend this middle-ground approach in women with endometriosis, either before or after surgery.

**Conception by ART**

Timely medical pretreatment—ovarian suppression with a gonadotropin-releasing hormone analogue—has favourable effects on ART outcome in women with endometriosis. In a classic randomised trial, women who were diagnosed surgically with endometriosis within 60 months had better pregnancy rates if they were pretreated with analogues of gonadotropin-releasing hormone for 3 months before ART. These findings also showed that pretreatment did not impair the ovarian response to controlled ovarian hyperstimulation. A meta-analysis of three randomised trials containing a total of 165 women confirmed the benefit of 3–6 months’ administration of gonadotropin-releasing hormone analogues before initiation of ART. The optimum duration of pretreatment is unknown, however, because...
testing was only done for 3–6 months. Whether other means of ovarian suppression (eg, with oral contraceptives) might be similarly effective is currently unknown.

The mechanism by which pretreatment with gonadotropin-releasing hormone analogues improves ART outcome is uncertain and can be only speculated. However, we can postulate reasonably that ovarian suppression before ART augments outcome by correction of endometrial alterations encountered in endometriosis, thus, amplifying receptivity. In support of this hypothesis, endometrial alterations noted in women with endometriosis disappeared after ovarian suppression with oral contraceptives or analogues of gonadotropin-releasing hormone. Admittedly, the reduction of nerve bundles recorded in women receiving oral contraceptives does not necessarily indicate that the endometrium truly returns to normal once it proliferates again after discontinuation of oral contraceptives.

Reports of the effects of surgery on outcome of ART are divergent. Some show a benefit in cases of deep endometriosis; others looking at the effects of surgery on endometriomas record no effect, and some provide evidence of harm. These reports concur, however, to indicate that any adverse effect of surgery on ART outcome probably stems from ovarian surgery for endometriomas further reducing the amounts of ovarian tissue remaining. In a classic case–control report, Garcia-Velasco and colleagues showed that surgery for ovarian endometriosis failed to augment outcome of ART versus expectant management. In other studies, surgery for endometriomas could cause harm, particularly in women with bilateral disease, impaired ovarian reserve, or who had previous surgery for endometriomas. Aboulghar and coworkers stressed that surgery for ovarian endometriosis could hamper ovarian response to the point of causing cycle cancellation. Importantly, cessation of cycles is not necessarily recognised when only the pregnancy rates per retrieval are assessed. In an analysis of the pros and cons of surgery for endometriomas, criteria in favour were an intact ovarian reserve, no previous ovarian surgery, unilateral disease, and rapid growth. Conversely, past surgery, altered ovarian reserve, and bilateral endometriomas favoured abstinence. Finally, following a rule of no surgery before ART, non-removal of endometriomas might have drawbacks. Endometriomas kept in place could increase the risk of infection at the time of oocyte retrieval.

The rule of no surgery before ART comes with exceptions, however. One of them is the need to remove hydrosalpinges, which reduce outcome of ART by about 50%. When salpingectomy is surgically challenging because of the extent of endometriotic disease, preferences include proximal resection, clipping, or even aspiration at the time of IVF. Surgery before ART should also be considered in cases of pain, because pain by itself can be associated with infertility. Likewise, surgery might be advisable when endometriomas are excessively large or doubts exist about their exact nature.

Some observations do not support the general contention that surgery is best avoided before ART to prevent hindrance of ovarian reserve. Bianchi and colleagues reported that thorough laparoscopic excision of deep infiltrating endometriosis improves IVF outcome, which departs from the notion that this form of the disease only affects ART outcome minimally. Also, Littman and coworkers noted that surgery was still helpful for women in whom ART had failed, with 22 of 29 who underwent surgery after ART managing to conceive, most (76%) naturally. No information is provided to exclude the suspicion that original ART might have been undertaken too promptly in these women.

**Management of infertility**

Figure 2 outlines primary variables to be taken into account during treatment of infertility associated with endometriosis. The proposed strategy represents the essence of a global approach that combines respective advantages of surgery and ART, and it accords with guidelines of the European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine. Surgery should be offered early in the course of endometriosis, when infertility is at the workup stage, because the primary benefit of surgery is to enhance the chances of natural conception.

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**Figure 2: Algorithm for management of infertility associated with endometriosis**

From work of Vercellini and colleagues, we know that surgery augments the probability of natural conception irrespective of disease stage. Therefore, when weighing up the advantages of surgery, considerations should include availability of time, ovarian reserve, and capacity to conceive naturally (tubal and sperm status) rather than disease stage. Indeed, sufficient time (at least 12 months) needs to be allocated after surgery to maximise the chances of a natural pregnancy. Conversely, surgery undertaken just before ART offers, in principle, little benefit.

Infertile women have on average about a 30% chance of having endometriosis if surgically investigated, which rises to roughly 50% if moderate-to-severe dysmenorrhoea is present. Pelvic imaging, including ultrasound and MRI, is increasingly sharp at singling out deep infiltrating endometriotic lesions but notoriously fails to identify superficial disease. Data reviewed above (see Practical benefit of medical treatment and surgery on conception chances) indicate that women treated surgically for any stage of endometriosis have about a 50% chance of spontaneous conception 1–2 years after surgery. Although biases could have inflated these numbers artificially, we believe that the clinical benefit of surgery is worth considering.

A recommendation for surgery early in the course of endometriosis for management of associated infertility goes against common wisdom that favours progressive approaches. A progressive strategy would favour simple options first (medical treatment, non-IVF methods, etc) while reverting to complex measures (surgery and IVF) last, if the simple ideas fail. Hence, the rationale for consideration of surgery early on in the therapeutic strategy for infertility associated with endometriosis should be explained thoroughly to patients, because it is counterintuitive.

Before surgery is contemplated, some verification is needed. Ovarian reserve should be tested upfront during infertility workup; if it is altered, the patient is older than 38 years, or infertility is longlasting, direct ART should be envisioned, thus making surgery (in principle) unnecessary. Likewise, semen characteristics or tubal status that are incompatible with natural conception mandate going straight to ART. Surgery should be considered in all other cases, because endometriosis is possible and surgery improves chances of natural conception. After surgery, couples must attempt to conceive naturally in principle, for at least 1 year. If this attempt fails, we recommend going directly to IVF. We advise against undertaking cycles of controlled ovarian hyperstimulation with intrauterine insemination, which are sometimes recommended before ART. Data indicate that these middle measures are not cost effective in general infertility and have poor results in women with endometriosis. Moreover, individuals for whom surgery seems appropriate should nonetheless be offered the alternative of immediate ART. In all cases, patients should be made fully aware of the respective advantages and inconvenience of each option.

When ART is necessary, surgery is generally of little value. Medical pretreatment—in principle, 3 months of gonadotropin-releasing hormone analogues—is recommended. Data indicating that oral contraceptives correct endometrial anomalies seen in endometriosis suggest that short oral contraceptive treatment could be as effective as gonadotropin-releasing hormone analogues for optimisation of ART outcome in endometriosis. Clinical trials are awaited.

The rule of no surgery before ART comes with exceptions, including pelvic pain (possibly intensifying during controlled ovarian hyperstimulation), presence of hydrosalpinges, and large endometriomas (especially when doubts exist about their exact nature). In all these cases, ART is undertaken directly after surgery.

Conclusion

The cause of infertility associated with endometriosis remains elusive, with current findings suggesting a multifactorial mechanism. The respective advantages of surgery, medical treatment, and ART intertwine complexly in women with these disorders. This intricate medley mandates a global approach to optimise every option. Indeed, only such a strategy can oppose a situation that still too often prevails, when the main reason for choice of surgery or ART stems from the primary activity of the doctor who is first consulted.

Contributors

All authors contributed equally to the literature review in preparation for writing this report. CC mainly concentrated on references pertinent to surgical treatment, whereas BB focused on pelvic and DiDZ on ovarian and endometrial alterations encountered in endometriosis. DiDZ coordinated writing of the report.

Conflicts of interest

DdZ holds stocks in Ultrast (device developing company), has served as a consultant for IBISA, and has sat on advisory boards of IBISA and MerckSerono. These companies have no product for treatment or diagnosis of endometriosis. DiDZ also sat on a data and safety monitoring board for Preglem Pharmaceuticals, supervising two trials unrelated to endometriosis, and sat on advisory boards of Ferring Pharmaceuticals and Schering-Plough. CC has sat on an advisory board for Bayer. BB has nothing to disclose.


