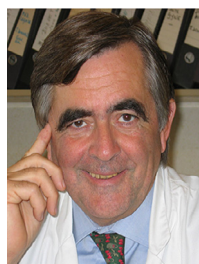


Could IVF replace reproductive surgery? No, reproductive surgery is still very much alive



BIOGRAPHY

Jacques Donnez is since 2012 Professor Emeritus at the Catholic University of Louvain. He published over 700 original articles in peer-review journals. He was the first and Founding President of the International Society for Fertility Preservation (ISFP) and World Endometriosis Society (WES).

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ABSTRACT

Could IVF replace reproductive surgery? The answer is no. Reproductive surgery still has a place, at least in some indications that will be explored in this contribution. While IVF can offer infertile couples the chance to have a healthy baby, it should be acknowledged that reproductive surgery can heal or harm the organs where reproduction takes place. This paper reviews different diseases and conditions with an impact on fertility, which may benefit from the technological innovations of recent decades, novel applications and the skill of reproductive surgeons. Reproductive surgery is certainly not dead. It lives on with the promise of restoring the functional anatomy to enhance the chances of pregnancy. It is our responsibility to train young residents adequately in this field to provide the right treatment at the right time.

When indications for reproductive surgery versus IVF are discussed, the fundamental question remains the same: could simply IVF replace reproductive surgery? The answer is no. Reproductive surgery still has a place, at least in some indications. This article will explore them one by one.

UTERINE SEPTUM RESECTION

The need or otherwise for uterine septum resection has been one of the most controversial issues of the last decade. Indeed, Rikken and colleagues reported that septum resection does not increase live birth rates or reduce pregnancy loss or preterm birth compared with expectant management (Rikken *et al.*, 2020) but a number of experts, in a letter to the journal's Editor, felt compelled to point out numerous sources of bias in Rikken and colleagues' study. First among

them were the many centres involved ($n = 21$) and the long recruiting time frame applied ($n = 19$ years), resulting in an average of just 0.37 cases per centre per year. Furthermore, the potential impact of the overdiagnosis of septate uterus needs to be taken into account. The diagnostic methods used in Rikken and colleagues' study do not reflect current gold standard diagnostic modalities, and the extension of the septum was not even defined.

Two recent meta-analysis and systematic reviews both support the notion that hysteroscopic metroplasty for uterine septum can lower the risk of miscarriage and increase the live birth rate. In experienced hands, the risk of complications is minimal and the risk–benefit balance weighs in favour of metroplasty, which is why experts should continue to offer the procedure to infertile women with a uterine septum.

ENDOMETRIOMAS: IVF VERSUS SURGERY

As stressed by Lessey and co-workers, women with endometrioma-related infertility face a dilemma when choosing the right approach to achieve their dream: surgery or IVF (Lessey *et al.*, 2018). One cannot overstate the concerns about the potential toxicity of the endometrioma content (iron and reactive oxygen species, among others), which may cause local inflammation culminating in the so-called burnout effect, responsible for a diminished ovarian reserve.

Despite misgivings about the impact of endometrioma surgery on the ovarian reserve, surgery does have a fundamental role to play, as the benefits in terms of pain relief and natural conception rates endorse this approach. Large series of women undergoing operative laparoscopy for the management of endometriomas

KEY WORDS

Caesarean scar defect
Fibroids
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Tubal re-anastomosis
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Uterine transplantation

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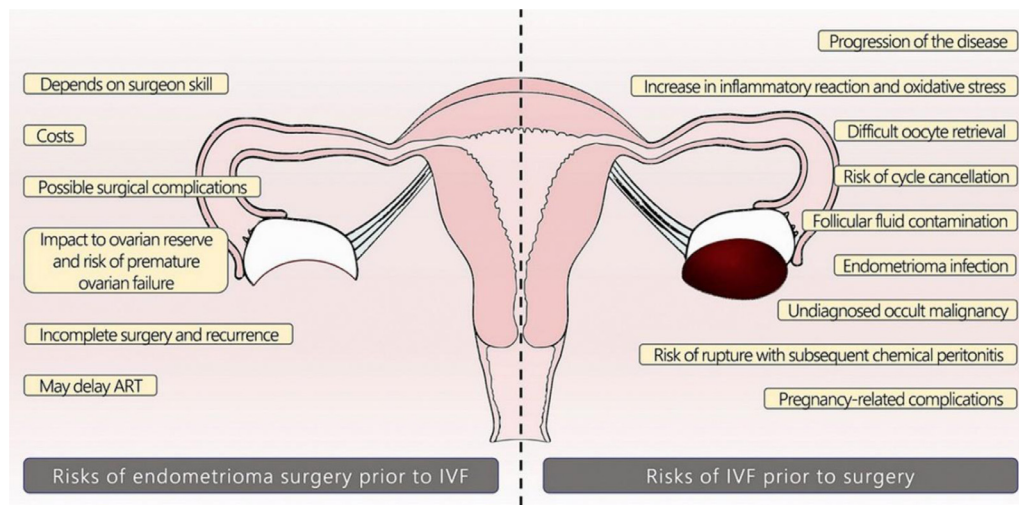


FIGURE 1 Risks of endometrioma-related infertility for surgery before IVF versus risks for IVF before surgery. Reprinted from *Fertility and Sterility*, 110 (7), J. Donnez, 'Women with endometrioma-related infertility face a dilemma when choosing the appropriate therapy: surgery or in vitro fertilization', pp. 1216–1217, © (2018), American Society for Reproductive Medicine, published by Elsevier.

achieved natural conception rates of >50% after surgery. Of course, to keep any damage to the ovary to a minimum, a

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knowledge of the appropriate technique and a certain level of expertise are required.

Q4 In 2018, a Fertile Battle (*Lessey et al., 2018*) on the pro and cons of surgery versus IVF opposed surgery as the first-line approach in cases of infertility (**FIGURE 1**). However, even IVF advocates consider surgery to be indicated when the woman is in pain that interferes with her daily life, or when rapid growth or features of malignancy are detected on ultrasonography. Surgery also improves follicle accessibility.

There are therefore strict indications for surgery, and the most recent European Society for Human Reproduction and Embryology guidelines state that operative laparoscopy may increase the chances of natural pregnancy, albeit in the absence of data from comparative studies (*Becker et al., 2022*). Overall, there is a broad consensus that for endometriomas over 4 cm in size, the clinical balance tips more towards surgery, especially as it has been demonstrated that endometriomas measuring more than 4 cm interfere with the ovarian response to ovarian stimulation (*Somigliana et al., 2020*). The woman's age and preferences (co-sharing the decision), a history of previous surgery (recurrence), the ovarian reserve and the physician's expertise are factors that should guide the decision.

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DEEP ENDOMETRIOSIS

The treatment of infertility related to deep endometriosis is still challenging. In an extensive review, Donnez concluded that rectal shaving should be considered the primary surgical approach in most women and reported natural conception in more than 50% of participants after surgery for deep endometriosis (*Donnez, 2021*).

On the other hand, some teams favour performing IVF before surgery, but starting IVF in a woman with a deep endometriosis nodule left in place is somewhat questionable. It is even more questionable in women suffering from severe dysmenorrhoea, dyspareunia and chronic pelvic pain, which are frequent symptoms. Several studies have shown that IVF procedures do not have a positive impact on pain symptoms, while others point out the difficulty of oocyte retrieval in the presence of a large nodule.

A recent systematic review and meta-analysis (*Casals et al., 2021*) revealed significant benefits of surgery for deep endometriosis nodules before IVF. Indeed, the live birth rate was 2.22 times higher in patients with previous surgery than in those undergoing IVF without previous surgery. Although the debate is not settled, there are some absolute indications for surgery (preferably the shaving approach) in cases of: (i) painful nodules of 3 cm or more in size; (ii) ureteral involvement (occurring in more than 10% of cases if the nodule is over 3 cm in size); (iii) an

association with bladder endometriosis; (iv) bowel involvement with severe substenosis (80%); and (v) an association with an endometrioma $\geq 3/4$ cm (*Donnez, 2021*). Although it is suspected that infertility and deep endometriosis are strongly related, the choice of surgery versus first-line assisted reproductive technology (ART) for infertile women with deep endometriosis is still a matter of debate.

UTERINE FIBROIDS

Infertility related to uterine fibroids may be explained by uterine cavity distortion, impaired endometrial/myometrial blood supply, defective endometrial receptivity and HOXA-10 (homeobox A10) expression and, finally, greater uterine contractility (*Dolmans et al., 2021*).

For fibroids classified as 0-1-2 by the International Federation of Gynecology and Obstetrics classifications, hysteroscopic myomectomy is the standard minimally invasive procedure. Additionally for type 2 fibroids, or if the myoma exceeds 3 cm in size, the use of a preoperative gonadotrophin-releasing hormone (GnRH) agonist/antagonist may facilitate surgery by reducing the fibroid size.

In the case of intramural fibroids that do not distort the endometrial lining (type 3–4), several meta-analyses have concluded that their removal is indicated

in infertile woman seeking to conceive through ART. Indeed, it is suggested that type 3 fibroids measuring more than 2.5 cm should be removed before ART, as they exert a negative effect on implantation, clinical pregnancy and live birth rates in women undergoing IVF. Concerning the surgical approach, the decision to perform a laparoscopy should take into account the experience of the surgeon and their ability to achieve an appropriate suturing of the uterine wall.

CAESAREAN SCAR

The presence of blood and endometrial debris in the Caesarean scar defect may impair fertility through several mechanisms, including the flow of bloody fluid or bleeding from the defect and the cytotoxicity of iron. Excess iron in the uterine cavity is toxic to embryos and may impair their implantation by disrupting the endometrial receptivity or uterine microbiota ([Donnez, 2020](#)). It was very recently reported that the presence of a Caesarean scar defect could negatively impact reproductive outcomes after IVF with frozen embryo transfer ([Zhang et al., 2022](#)).

It is therefore both logical and appropriate to propose surgery before contemplating IVF in these women, and also in infertile and symptomatic patients wishing to conceive. Laparoscopic repair should be considered if there is a residual myometrial thickness of less than 3 mm, in which case repair is essential, while hysteroscopic resection should be carried out if the thickness is over 3 mm. The live birth rate after surgery was found to range from 21.8% to 75% ([Donnez et al., 2020](#)).

TUBAL RE-ANASTOMOSIS

Approximately 1–3% of women who have undergone tubal ligation request a reversal as they are looking to conceive, but the debate is ongoing between surgery and IVF. We favour surgery because, according to a review of 15 studies ([Sato et al., 2021](#)), there is at least a 60% chance of giving birth within the following 5 years if tubal reversal is performed before 40 years of age. After age 40, the rate falls to half that number. The next most important prognostic factors after patient age are the remaining tubal length and the integrity of the ampulla, which is the site of fertilization and early embryo development.

In our clinical experience the live birth rate following laparoscopic tubal re-anastomosis after ligation by clips or rings is more than 90% in women aged less than 40 years. What about women over the age of 40? A study found delivery rates to be 27.3% in women over 42 years. This good prognosis for women of advanced reproductive age compared with outcomes in women undergoing IVF at the same age also endorses surgery, even in this age group.

UTERINE TRANSPLANTATION

Uterine factor infertility affects up to 1 in 500 reproductive-age women, Mayer–Rokitansky–Küster–Hauser syndrome being the predominant congenital cause. Uterine transplantation gives these women the chance to become pregnant, avoiding the need for surrogacy or adoption.

Conditions for surgery are: (i) a vagina that is over 5 cm in length and wide enough to receive a parous cervix; and (ii) a sufficient number of frozen embryos (minimum 6 blastocysts). In transplant recipients, spontaneous menstruation was achieved in 100% of cases. To date (2023), 92 uterine transplantations and 49 live births (mostly in Sweden and the USA) have been recorded, perfectly illustrating the successful collaboration between IVF and surgery.

One key issue is the risk–benefit ratio of living versus deceased donors. In the first series published by Brännström, the operating time for living donors was more than 10 h ([Brännström et al., 2019](#)). Efforts are being made to reduce this time, possibly by using robotic assistance.

UTERINE ADENOMYOSIS

Two systematic reviews and meta-analysis found women with adenomyosis to exhibit lower pregnancy and higher miscarriage rates than unaffected women. Inflammatory factors, endometrial receptivity alterations and macrophages linked to the presence of adenomyotic lesions could be responsible for the decreased fertility in these women ([Donnez et al., 2022](#); [Stratopoulou et al., 2023](#)).

Focal adenomyosis can be resected (adenomyomectomy) by laparoscopy.

Surgery is similar to myomectomy, but the plane of dissection between the adenomyoma and the healthy myometrium is relatively difficult to identify.

In case of diffuse adenomyosis, the triple-flap method is best carried out by laparotomy, as this surgical procedure is extremely difficult to perform laparoscopically. Indeed, diffuse adenomyotic tissue should be removed by finger palpation and delicate suturing by hand. This surgery requires a light touch, and the risk of rupture during pregnancy is real. For severe adenomyosis in an enlarged uterus, we would advocate medical therapy such as an oral GnRH antagonist for 3 months to first reduce the size of the uterus and the severity of the lesions; 2 weeks after the end of therapy, frozen embryos, collected before starting the medical therapy, can then be transferred ([Donnez et al., 2022](#)).

INTRAUTERINE ADHESIONS

Hysteroscopy remains the gold standard to confirm how far intrauterine adhesions extend and is an effective tool for treatment, seeking to restore the functional anatomy and endometrial activity to boost the chances of pregnancy. The likelihood of pregnancy depends on the extension of the lesions and whether the remaining endometrial lining covers at least 50% of the surface ([Santamaria et al., 2020](#)). Postoperative pregnancy rates range from 35% to 60% depending on the severity of the lesions. When there is no endometrial lining and no chance of it being regenerated, the likelihood of pregnancy is, of course, very low ([Santamaria et al., 2020](#)). Studies are urgently needed to find ways of regenerating the injured endometrium (e.g. barriers or stem cell therapy).

CONCLUSION

Quo vadis, reproductive surgery? This is surely a pertinent question for the 21st century, even if most reproductive endocrinology and fertility specialists are either inadequately trained or not interested in this field ([Gargiulo and Bhagavath, 2019](#)). While IVF can offer infertile couples the chance to have a healthy baby, it should be acknowledged that reproductive surgery can heal or harm

the organs where reproduction takes place.

Different diseases and conditions responsible for infertility may benefit from the technological innovations of recent decades, novel applications and the skill of reproductive surgeons. Reproductive surgery is certainly not dead. It lives on with the promise of restoring the functional anatomy to enhance the chances of pregnancy. It is our responsibility to train young residents adequately in this field to provide the right treatment at the right time.

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DATA AVAILABILITY

No data was used for the research described in the article.

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