

## What is the role of surgery for endometriosis- associated infertility?

#### What is endometriosis?

The tissue lining the inside of the uterus is called **endometrium**. Menstruation comes from the shedding of this layer of tissue each month as a result of ovarian hormones.

**Endometriosis** develops from the backward flow of menstrual fluid (retrograde menstruation) and subsequent growth of endometriotic *implants* in locations outside the uterus.

# What is the evidence linking endometriosis to subfertility?

Ample evidence has linked endometriosis to subfertility:

- While endometriosis occurs in 5–10% of women with proven fertility, it may be found in up to 50% of infertile women.
- Infertility patients with untreated mild endometriosis conceive on their own at a rate of 2% to 5% per month, compared with a 15% to 20% monthly fertility rate in normal couples (ASRM 2016 Endometriosis a guide for patients).





 Evidence from artificial insemination donor (AID) program found women with minimalmild endometriosis have approximately half the chance of success of women without endometriosis (Jansen Fert Steri 196).



Image source: UpToDate

- IVF outcomes in women with tubal disease compared to women with endometriosis indicate that those with endometriosis have lower implantation rate, lower pregnancy rate per embryo transfer, lower pregnancy rate per cycle (Simon C. Human Repro 1994).
- Study using fertilised sibling oocytes transferred into women with or without endometriosis demonstrated reduced implantation, clinical pregnancy rate (PR), ongoing PR, and live birth rate in women with endometriosis, suggesting defects in endometrial receptivity as a cause of IVF failure.

#### Mechanisms of endometriosis- associated Infertility (1) Giudice L. Endometriosis. N Engl J Med 2010;362:2389-98. (2) Ziegler D et al. Lancet 2010; 376: 730-38 1. Pain: 2. Structural damage Uterus Pelvic and Adhesions Tubal blockage intercourse pain Affect normal sexual relationship 4. Peritoneal inflammation 3. Ovaries: Immunological Damage ovarian responses include function, egg cytokines, quality Ovar angiogenesis and Reduces ovarian cellular changes reserve (AMH) (natural killer cells) Poor response to ERFFI1 Affect sperm, egg **IVF** drugs MCP-1 function and Cyr 61 HoxA10, HoxA11 fertilisation αVβ3 TIMPs VEGE 5. Functional 6. Uterine cavity: EBAF Tubal, endometrial, Aberrant gene myometrial expression functions affected Progesterone PGE<sub>2</sub> Impairs gamete resistance transport and Impaired embryo embryo implantation implantation

#### How does endometriosis result in sub-fertility?

#### What is the role of surgery for endometriosis-associated subfertility?

- Reproductive surgery is indicated in infertile women with normal ovulation and normospermic partners, regardless of pain symptoms or transvaginal ultrasound results, since half of them have endometriosis and 40% of those without endometriosis have fertilityreducing pelvic pathology (Meuleman et al. Fertil Steril 2009)
- In infertile women with stage I/II endometriosis, operative laparoscopy to excise or ablate endometriosis lesions and adhesiolysis, rather than performing diagnostic laparoscopy only, is advised to increase ongoing pregnancy rates (Jacobson et al. 2010, Nowroozi et al. 1987).
- In infertile women with **ovarian endometrioma** undergoing surgery, **excision** of the endometrioma capsule is preferred to drainage and electrocoagulation of the endometrioma wall to **increase spontaneous pregnancy rates** (Hart et al. 2008).
- In infertile women with stage III/IV endometriosis, consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat, et al., 1989, Vercellini, et al., 2006a).

• Complete **surgical removal** of minimal to mild disease **prior to the start of ART** has been shown to improve reproductive outcome (Opoien et al. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. 2011).

### Should infertile women undergo surgical removal of ovarian endometrioma?

• The answer to this important question is contentious due to the lack of high-quality evidence and conflicting expert opinions.





- Endometriosis, particularly ovarian endometrioma, is detrimental to fertility due to several postulated mechanisms (Donnez J. Fertil Steri 2018):
  - Distortion of tubo-ovarian anatomy
  - Chronic inflammatory reaction diminishes ovarian reserve
  - Oxidative stress results in poor oocyte quality
- A recent review of impact of endometriomas on IVF outcomes found women with endometrioma (Hamdan M 2015):
  - have lower oocyte yield per cycle
  - higher cancellation rate
  - have similar live birth rates (LBR) compared to women with no endometriosis
  - surgical treatment of endometrioma did not alter the outcome of IVF compared to those with untreated endometrioma
- Surgical intervention for endometrioma may significantly reduce the ovarian reserve as represented by decreased serum AMH levels (Park 2019).
- Surgery for severe endometriosis, including endometrioma, may be considered before IVF in the following cases:
  - when the pain related to endometriosis is severe
  - when malignancy cannot be excluded
  - In patients with endometrioma ≥3 cm, laparoscopic ovarian cystectomy is recommended before IVF to reduce the risk of infection during oocyte retrieval and facilitate access to follicles, or to improve the ovarian response to controlled ovarian stimulation (2014 European Society of Human Reproduction and Embryology guidelines)

- when the qualities of the oocytes and embryos were found to be poor in IVF cycles before surgery, or in cases of recurrent implantation failure
- Restoration of a normal pelvic anatomy by surgical intervention could help improve natural and /or IVF outcomes in infertile women with severe endometriosis and repeated IVF failure.

Hence, individualisation of care for women with pelvic endometriosis and endometrioma-associated pain and subfertility is important to optimise outcomes.



Figure 1 Risks of surgical treatment of endometrioma before ART and risks of intact endometrioma during ART.

### References

- 1. American Society for Reproductive Medicine 2016 Endometriosis- A guide for patients.
- 2. Guideline of ESHRE Management of women with endometriosis September 2013
- 3. Kitajima M et al. Enhanced follicular recruitment and atresia in cortex derived from ovaries with endometrioma. Fert Steril 2014.
- 4. Hamdan M et al. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Repro Update 215.
- 5. Ovarian endometriosis and infertility: IVF or surgery as first approach. Fert Steri 2018.
- 6. Donnez J. Women with endometrioma-related infertility face a dilemma when choosing the appropriate therapy: surgery or IVF. Fert Steril 2018.
- 7. Park H et al. Could surgical management improve the IVF outcomes in infertile women with endometrioma? A review. Obstet & Gynecol Science 2019.