Challenges & strategies of ovarian stimulation in endometriosis

- **Prof. Dr. Abha Majumdar**

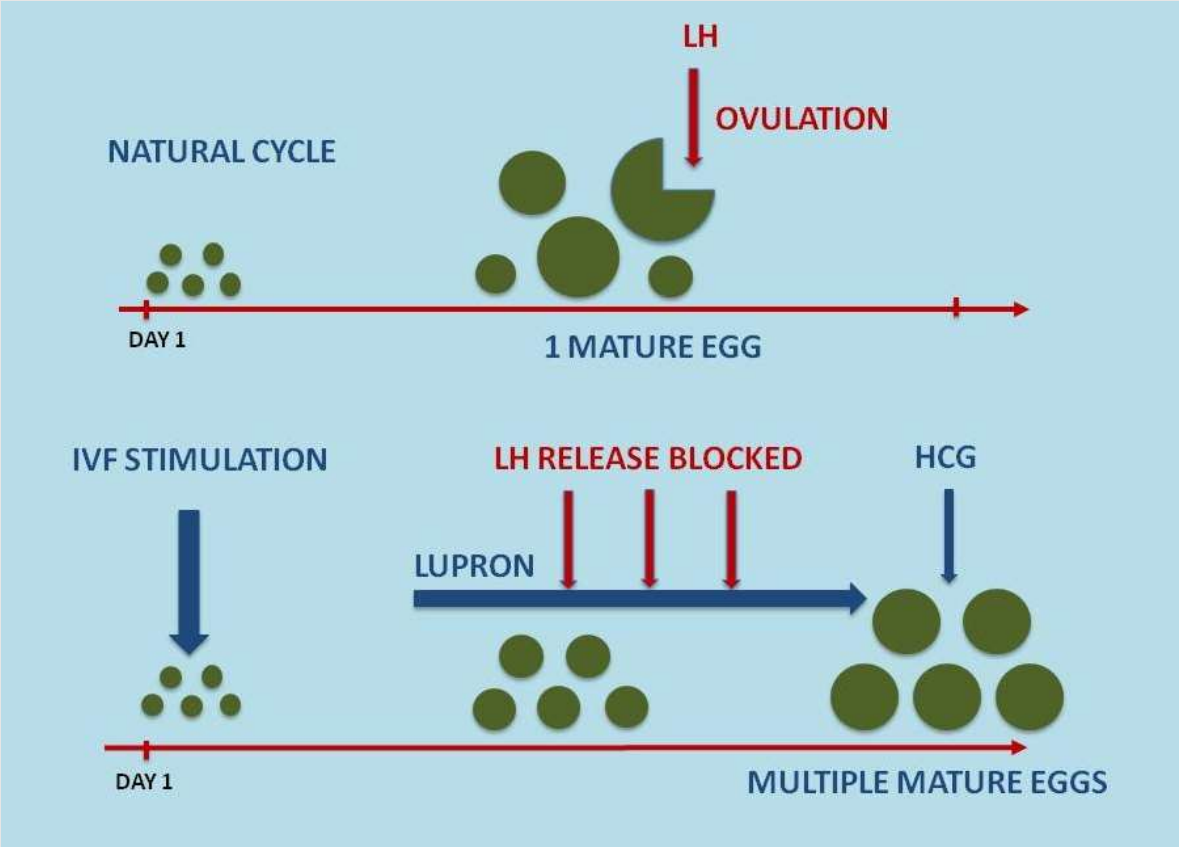
Why does one have to think differently for ovarian stimulation for women undergoing IVF with endometriosis

- Low ovarian reserve (ovarian disease and surgery)
- Poor oocyte/embryo quality
- Impaired endometrial receptivity (lower expression of HOXA 10 and qvβ3 integrins) or associated adenomyosis

What does one need to consider to develop an ideal protocol for IVF in endometriosis

- Age of the woman
- Ovarian reserve
- Duration of infertility
- Stage of endometriosis

Aim of ideal protocol?

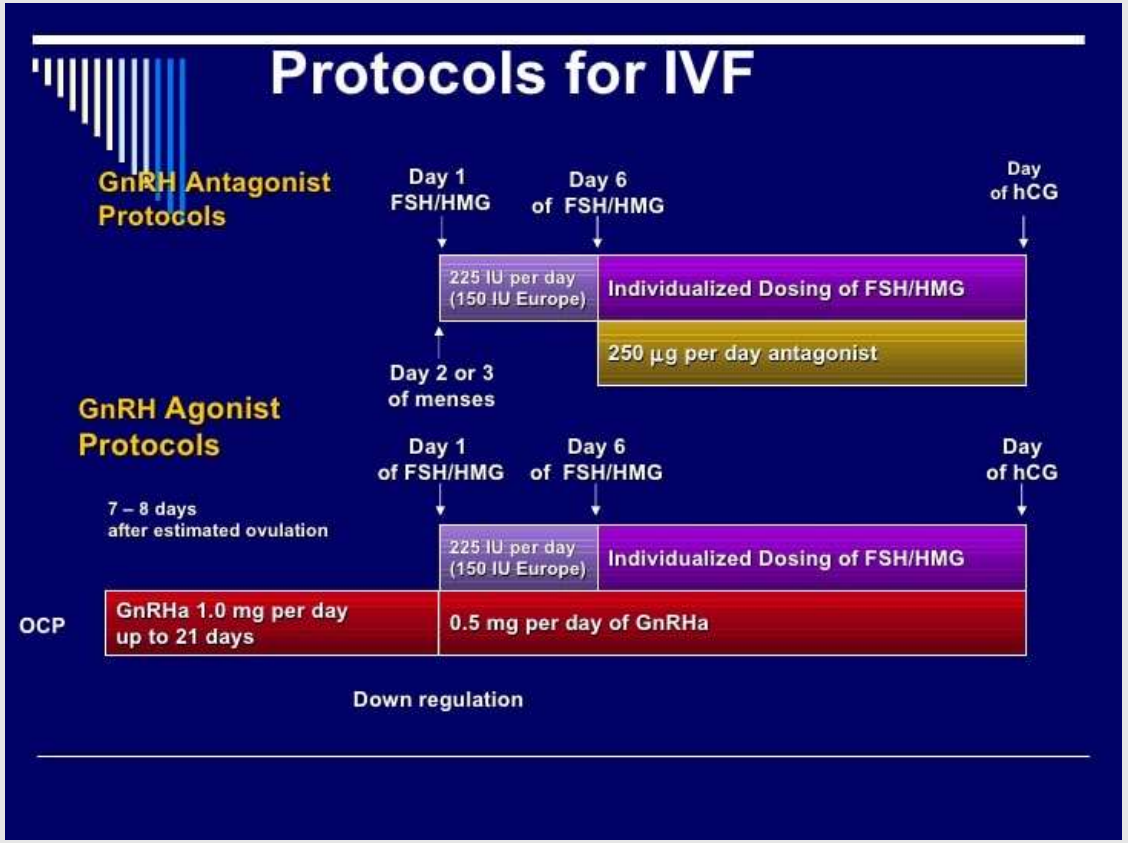


- Good number of high-quality oocytes
- Best endometrium for implantation

When do we need surgical pretreatment before COS for IVF in these patients with endometriomas?

- Diagnosis of endometrioma in doubt
- Follicles or ovarian cortex distal to cyst from the vaginal wall and probe
- Endometriomas with severe pelvic pain
- Large hydrosalpinx with bilaterality (if fresh transfer anticipated)
- Large endometriomas >4 cm with no previous surgery with normal ovarian reserve and young patient

2 protocols used for Ovarian stimulation for IVF in endometriosis



I. Long GnRh agonist protocol

II. GnRh Antagonist protocol

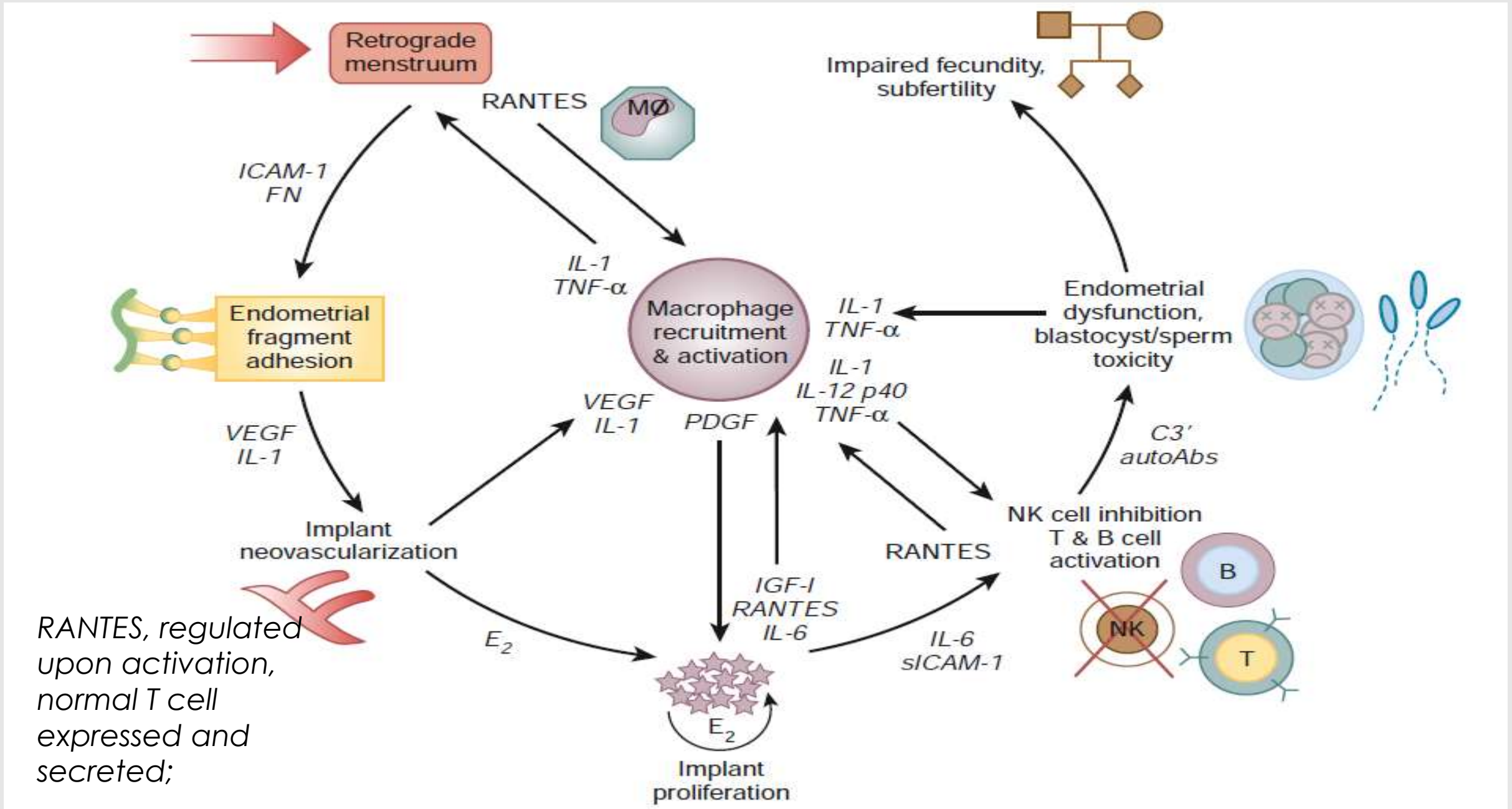
Ideal protocol which one?

Long GnRH-agonist vs. Short GnRH-antagonist in Endometriosis

Long GnRH-a protocol and GnRH antagonist protocol in endometriosis have similar IVF outcomes

Actual impact of GnRH analogues is on ovarian hormonal control and not on oocyte and embryo quality.

Bastu E et al. JSLS 2014 : 18(3)



RANTES, regulated upon activation, normal T cell expressed and secreted;

Novel mechanisms of action of prolong use of GnRH agonist in endometriosis

- Suppression of ovulation reduces exposure of endometriotic implants to a growth factor (midkine) in follicular fluid involved in proliferation of endometriotic cells
- Direct inhibition of proliferation of endometriotic cells by regulation of apoptotic and angiogenic mechanisms
- Inhibition of menstruation reduces exposure to thrombin and its protease activated receptor; factor which leads to cell inflammation
- Inhibition of uterine contractions: blocks mechanical stress

Omega Y, Gynecol Obstetric Invest. 2004

Cochrane Database Systemic Review .2006(Jan);1:CD004635. Salem et al;

Ultra- long protocol: Ideal for endometriosis

Suppression of endometriosis by prolonged administration of GnRH agonist may improve the oocyte quality, embryo quality and thus indirectly also the implantation rates.

Administration of GnRH agonists for period of 3-6 months prior to IVF or ICSI increases the odds of clinical pregnancy four fold & live birth rate 9 fold

- 3 RCTs with 165 women
- Live Birth Rate/ woman OR 9.19
- Clinical Pregnancy Rate: OR 4.28

Authors' conclusions

- **Cochrane Database of Systematic Reviews 2019.**


Cochrane Library

Cochrane Database of Systematic Reviews

Long-term GnRH agonist therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis (Review)

Georgiou EX, Melo P, Baker PE, Sallam HN, Arici A, Garcia-Velasco JA, Abou-Setta AM, Becker C, Granne IE

Background

Endometriosis is known to have an impact on fertility and it is common for women affected by endometriosis to require fertility treatments, including in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), to improve the chance of pregnancy. It has been postulated that long-term gonadotrophin-releasing hormone (GnRH) agonist therapy prior to IVF or ICSI can improve pregnancy outcomes. This systematic review supersedes the previous Cochrane Review on this topic (Sallam 2006).

Contrary to previous findings, we are uncertain as to whether long-term GnRH agonist therapy impacts on the live birth rate or indeed the complication rate compared to standard IVF/ICSI.

In light of the paucity and very low quality of existing data, particularly for the primary outcomes examined, further high-quality trials are required to definitively determine the impact of long-term GnRH agonist therapy on IVF/ICSI outcomes in women with endometriosis.

Reproductive Biology and Endocrinology

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The effectiveness of different down-regulating protocols on in vitro fertilization-embryo transfer in endometriosis: a meta-analysis

Xue Cao, Hong-yang Chang, Jun-yan Xu, Yi Zheng, Yun-qai Xiang, Bing Xiao, Xu-jing Geng, Li-li Ni, Xi-

Only studies that met the following criteria were included in this meta-analysis, including cohort studies and RCT's;

(1) clinical study of the efficacy of IVF/ICSI-ET in the treatment of endometriosis infertility patients
    (1) GnRH-a ultra-long protocol,
    (2) GnRH-a long protocol,
    (3) GnRH-a short protocol
(2) Subjects of study were women diagnosed with endometriosis by laparoscopy, laparotomy, or transvaginal aspiration of the ovarian endometrial cyst combined with pathology

Results

In this meta-analysis total of 21 studies in compliance with the standard literature were included, and RCT and non-RCT studies were analyzed separately.

1. GnRH-a ultra-long protocol could **improve the clinical pregnancy** rate of infertile patients in **RCT studies**, especially in patients with stages III–IV endometriosis (RR = 2.04, 95% CI: 1.37~3.04, $P < 0.05$).
2. Subgroup analysis found the different down-regulation protocols provided **no significant difference** in improving clinical outcomes in patients with endometriosis in the **non-RCT studies.**

Limitations of Prolonged Down-regulation

Time consuming

Diminished response
especially in poor responders

Medical methods to minimize negative effect of endometriosis on oocytes

PRE-TREATMENT WITH OCP'S FOR 6 TO 8 WEEKS

LETROZOLE WITH DEPOT GNRH AGONIST FOR 8 WEEKS

DIENOGEST PRE TREATMENT FOR 3 MONTHS

Human Reproduction Open, pp. 1–8, 2019
doi:10.1093/hropen/hoz001

human reproduction open

PROTOCOL

Continuous oral contraceptives versus long-term pituitary desensitization prior to IVF/ICSI in moderate to severe endometriosis: study protocol of a non-inferiority randomized controlled trial

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What is known already: Long-term pituitary desensitization with a GnRH agonist for 3-6 months prior to IVF/ICSI improves clinical pregnancy rates in women suffering from endometriosis. Alternatively, IVF/ICSI pre-treatment with continuous OCP's may offer fewer side-effects and lower costs, as well as encouraging IVF outcomes in women with endometriosis. To date, these two different IVF/ICSI pre-treatment strategies in women with endometriosis have not been directly compared.

Study design size duration: An open-label, parallel two-arm multicenter RCT is planned, including patients with moderate to severe endometriosis. the sample size calculation is rounded off to 165 patients per group; 330 patients in total will be included. After informed consent, web-based block randomization will be stratified per center. Study inclusion is expected to be complete in 3-5 years. **However, the final results of this specific trial are not yet published.**

RBMO

ARTICLE

A comparison of two months pretreatment with GnRH agonists with or without an aromatase inhibitor in women with ultrasound-diagnosed ovarian endometriomas undergoing IVF

Abstract

Research question: Does the addition of an aromatase inhibitor improve IVF outcomes in women with endometriomas when pretreating them with gonadotrophin-releasing hormone agonists?

Design: Retrospective two-centre cohort study involving 126 women aged 21-39 years who failed a previous IVF cycle and all subsequent embryo transfers and had sonographic evidence of endometriomas. Women were non-randomly assigned to either 3.75 mg intramuscular depo-leuprolide treatment alone or in combination with 5 mg of oral letrozole daily for 60 days prior to undergoing a fresh IVF cycle. Main outcome measures included clinical pregnancy rate and ongoing pregnancy rate after 24 weeks' gestation.

Conclusions: The combination of depo-leuprolide acetate monthly for 60 days combined with daily letrozole has better clinical outcomes at IVF in women with endometriomas than depo-leuprolide acetate treatment alone.

Results: Eighty-eight (58.3%) patients underwent IVF without previous hormonal treatment, and 63 (41.7%) received pretreatment with DNG.
The cumulative implantation, clinical pregnancy and live birth rates were significantly higher in the DNG-treated group.
Largest diameter of endometriomas significantly decreased by DNG pretreatment ($P < 0.001$).
Use of DNG increased significantly the number of oocytes retrieved ($P = 0.031$), two-pronuclear embryos ($P = 0.039$) and blastocysts ($P = 0.005$) in women with endometriomas of diameter ≥4 cm.
Conclusions: This study suggest that in patients with endometriosis, IVF outcomes can be improved by pretreatment with DNG. In particular, the use of DNG allows for better oocyte retrieval and blastocysts in patients with large endometriomas.

Meta-Analysis > Gynecol Obstet Invest. 2023;88(3):135-142. doi: 10.1159/000529400.
Epub 2023 Feb 3.

Pretreatment of Dienogest for Women with Endometriosis in in vitro Fertilization: A Systematic Review and Meta-Analysis

Xueying Li [1 2], Jinli Lin [3], Linhao Zhang [4], Yao Liu [5]

Results: Four articles with 422 patients were included.
No significant differences were found on the following prameters between the DNG group and the control group.

Number of mature oocytes (MD = -1.27, 95% CI: -3.63 to 1.09, I2 = 91%),
Rate of clinical pregnancies (odds ratio = 1.07, 95% CI: 0.33-3.47, I2 = 84%),
Rate of live births (odds ratio = 1.09, 95% CI: 0.34-3.46, I2 = 84%)

Conclusion: Pretreatment with DNG for women with endometriosis who underwent IVF could not improve the number of mature oocytes, the rate of clinical pregnancies, or the rate of live births.

Personalized information should be patient centric

Favors direct IVF

- Previous surgery for endometriosis*
- Bilaterality (risk of severe impairment of OR after surgery as risk of additional damage to a weak ovarian reserve could cause definitive exhaustion***
- Older age, and reduced ovarian reserve
- Male partner/ tubal block.

Favors surgery before IVF

- Dimension and USG appearance of larger cysts and doubtful diagnosis**
- Concomitant severe pain if resistant to medical treatment
- Antral follicles away from vaginal wall

Vercellini P, et al. The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review. Acta Obstet Gynecol Scand 2009;88:1074-82.

Ferrero S,et al. Second surgery for recurrent unilateral endometriomas and impact on ovarian reserve: a case-control study. Fertil Steril 2015;103:1236-43.

**Ferrero S,et al. Impact of large ovarian endometriomas on the response to superovulation for in vitro fertilization: A retrospective study. Eur J Obstet Gynecol Reprod Biol 2017;213:17-21.*

***Guerriero S, et al. Systematic approach to sonographic evaluation of the pelvis: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol 2016;48: 318-32.*

****Somigliana E, et al. IVF-ICSI outcome in women operated on for bilateral endometriomas. Hum Re-prod 2008;23:1526-30.*

Specific risks of stage 3 & 4 with IVF

1. A low risk of tubo-ovarian abscess secondary to oocyte retrieval
2. Theoretical risk of disease progression. Although rare cases have been reported, cohort studies have demonstrated that ART does not exacerbate symptoms, progression, or recurrences of endometriosis.
3. Leakage of endometrioma leading to peritonism
4. Rarely rupture of endometrioma.

Endo-metriosis-related infertility: assisted reproductive technology has no adverse impact on pain or quality-of-life scores. *Santulli P, et al. Fertil Steril 2016;105:978-87.e4.*

IVF and endometriosis-related symptom progression: insights from a prospective study. *Benaglia L, et al. Hum Reprod 2016*

Good outcomes with ART are not affected by the endometriosis phenotype,

3 subtypes :

- superficial peritoneal endometriosis (SUP),
- ovarian endometrioma (OMA),
- Deep infiltrating endometriosis (DIE)

Maignien C, et al.Prognostic factors for assisted reproductive technology in women with endometriosis-related infertility. Am J Obstet Gynecol 2017;216:280.e1-9.

Endometriosis

Guideline of European Society of Human Reproduction and Embryology

2022
ESHRE Endometriosis Guideline Development Group

55	Clinicians are not recommended to routinely perform surgery prior to ART to improve live birth rates in women with rASRM stage I/II endometriosis, as the potential benefits are unclear.	⊕⊕◯◯	Strong recommendation
56	Clinicians are not recommended to routinely perform surgery for ovarian endometrioma prior to ART to improve live birth rates, as the current evidence shows no benefit and surgery is likely to have a negative impact on ovarian reserve.	⊕⊕◯◯	Strong recommendation
57	Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.		GPP
58	The decision to offer surgical excision of deep endometriosis lesions prior to ART should be guided mainly by pain symptoms and patient preference as its effectiveness on reproductive outcome is uncertain due to lack of randomised studies.	⊕◯◯◯	Strong recommendation

- COS for IVF in women with endometriosis is similar to those without endometriosis and dose of gonadotropin and protocol depends on the age, ovarian reserve and previous response to stimulation.
- Attention is now focusing on pre-treatment in women with high stage endometriosis to reduce the proinflammatory detrimental effect of the disease on oocyte, embryo and endometrium.
- The first drug used for this purpose was prolong GnRh agonist.
- However, a plethora of newer cost effective and easy to administer drugs are being tried with the same aim of reducing proliferation, vascularization, and inflammation by endometriotic implants thus its adverse effect on IVF outcome.

Take home message:

Greetings from SGRH IVF