What is the current management in advanced endometriosis and infertility?

Engin Oral, M.D.
– President of the Executive Committee of EEL (European Endometriosis League)
– Endometriosis & Adenomyosis Association-Turkey; Founder President

drenginoral@gmail.com
I have no conflict of interest
• Treatment of endometriosis and infertility prompt **complex clinical questions** without **simple answers**.

*I neither know nor think that i know*

*Plato’s Socrates, Apology 21d.*
...EBM does not have all the answers....

‘Evidence does not make decisions, people do’

Hayres RB, ACP Journal Club 2002
“Being diagnosed with endometriosis was a relief, the infertility was the killer, it stole not only my dreams but those of my partner, family and friends. I feel alone, I cannot talk to anyone about this due to the shame of failure and the inability to give answers to hurtful questions”

Gráinne, 38, Multiple failed IVF
How many women with endometriosis have infertility?

Approximately \( \frac{1}{3} \) of women with endometriosis suffer from infertility.

How many women with infertility have endometriosis?

Approximately \( \frac{1}{4} \) of subfertile women have endometriosis.
Natural Fecundity (Per month)

• NO Endometriosis
  • 25-30%

• Endometriosis
  • 2-10%
Advanced Endometriosis

- Stage III-IV Endometriosis
  - Endometrioma
- Deep endometriosis
- Adenomyosis
- Recurrent Endometriosis
Endometriosis and Infertility

- Folllicular environment
- Endometrial environment
- Endometriotic implant

Anatomical distortion

Activated macrophages

- Haptoglobin
- MCP-1
- MMPs
- TIMPs
- VEGF
- Interleukin-1β
- Interleukin-8
- TNF-α
- Interleukin-6
- PGE₂
- NGF

Peritoneal fluid

Endometriotic implants:
- Angiogenesis
- Neurogenesis
- Steroidogenesis
- Proliferation
- Invasion
- Survival

Sensory, sympathetic, and parasympathetic nerves

Progesterone resistance
- ERFF1
- C3 complement
- Gr61
- HoxA10, HoxA11
- αVβ3
- Glutathione peroxidase
- Free radicals
- EBAF
- Glycodelin
- Muscin
How does endometriosis affect fertility?

Pelvic Inflammation.
Adhesions and anatomic distortions.
Tubal damage such as hydrosalpinges due to extrinsic adhesions or hematosalpinges.
Reduced ovarian reserve related to endometrioma surgery.
Endometrial dysfunction and reduced implantation.
Dyspareunia and sexual dysfunction.
Altered oocyte quality.
**Hysterosalpingography in endometriosis: performance and interpretation**

Aoife Kilcoyne¹ · Aileen O’Shea¹ · Debra A. Gervais¹ · Susanna I. Lee¹

Published online: 2 January 2020

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**Table 2  Hysterosalpingography findings in endometriosis**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Imaging finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hydrosalpinx</td>
<td>1. Dilated fallopian tube</td>
</tr>
<tr>
<td>2. Fallopian tube occlusion</td>
<td>2. Partial contrast filling but lack of spill from tube</td>
</tr>
<tr>
<td>3. Peritubal adhesions</td>
<td>3. Loculated contrast spill or pooling collections of spilled contrast</td>
</tr>
<tr>
<td>4. Deep infiltrative endometriosis</td>
<td>4. Pooled contrast in the deep pelvis. Fallopian tube courses posteriorly from the uterus to the midline cul-de-sac</td>
</tr>
<tr>
<td>5. Uterine adenomyosis</td>
<td>5. Abnormal uterine cavity contour with extrusion of contrast into the myometrium</td>
</tr>
<tr>
<td>Associated with endometriosis</td>
<td>Focal—can mimic necrotic fibroid</td>
</tr>
<tr>
<td>Endometrial tissue infiltrates into the myometrium</td>
<td>Diffuse</td>
</tr>
</tbody>
</table>
Treatment of infertility in patients with advanced endometriosis

- Expectant
- Surgery
- ART (IUI/IVF)

Most women with endometriosis will conceive successfully (natural or assisted)
Medical therapy
For the young colleagues

Medical treatment does not help!

Recommendation

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes, et al., 2007).

References

Management of endometriosis associated infertility

- Ovarian reserve +++
- Age
- Infertility (duration)
- Associated infertility factors
- Pain intensity (DIE)
- Previous history of sur surgery for Osis and/or OMA(s)
- Associated Adenomyosis

Desire of the patient

The gold standard is an individualized treatment (Personalized treatment)
CASE

- 29 years old
- Married for 1.5 years
- Main complaints are, painful periods and having difficulty with getting pregnant
- Spermiogram : N
- HSG : N
- 11 cm endometrioma on right ovary
- 4 cm endometrioma on left ovary
- AMH level : 1.9 ng/ml
- D3 FSH: 6.9 mIU/ml
  - LH: 8.4 mIU/ml
- CA125: 276........ROMA index %1.6
• What would you do?
What we did is..

- ICSI
- 12 oocytes have been collected...4 embryos frozen at D5 ----2 months GnRHa –frozen transfer of one embryo
- Singleton pregnancy
- C-section at 38 weeks + cystectomy for endometrioma
What happens to fertility when endometriosis is left untreated?

Population: general infertility

The prognosis for live birth among untreated infertile couples

John A. Collins, M.D.†‡
Elizabeth A. Burrows, M.B.A.†
Andrew R. Willan, Ph.D.§

Endometriosis is a significant factor in the lower conception rate in untreated infertile patients

Table 2  Characteristics of Untreated Infertile Couples That are Associated With the Likelihood of Live Birth*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative hazard†</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary infertility</td>
<td>1.83 (1.24 to 2.69)</td>
<td>0.003</td>
</tr>
<tr>
<td>Duration of infertility ≤ 36 months</td>
<td>1.68 (1.14 to 2.48)</td>
<td>0.007</td>
</tr>
<tr>
<td>Female age ≤30 years</td>
<td>1.50 (1.05 to 2.16)</td>
<td>0.024</td>
</tr>
<tr>
<td>Male defect</td>
<td>0.47 (0.27 to 0.81)</td>
<td>0.003</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0.39 (0.18 to 0.85)</td>
<td>0.006</td>
</tr>
<tr>
<td>Tubal defect</td>
<td>0.50 (0.40 to 0.63)</td>
<td>&lt;0.00005</td>
</tr>
</tbody>
</table>
COH + IUI

SUGGESTED FOR:

• Stage I or II endometriosis

• Surgically diagnosed and absent anatomic distortion

• Not in patients with ‘severe endometriosis’.

IUI for moderate/severe endometriosis

PR/cycle

IUI might be a valuable treatment in moderate-to-severe endometriosis patients and IUI with ovarian stimulation should be offered over IUI with natural/ovarian stimulation. Preceding long-term pituitary down-regulation might positively influence the ongoing pregnancy rate and can be considered. From Van der Houven et al. RBM Online 2014
### 12 months cumulative pregnancy rate

<table>
<thead>
<tr>
<th>Stage</th>
<th>Spontaneous</th>
<th>COH+IUI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I/II</td>
<td>45%</td>
<td>42%</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**COH+IUI does not improve pregnancy rates in any stage of endometriosis**

Stage III/IV → **IVF**

Gandhi AR, JMIG, 2014
Predictive factors for pregnancy after controlled ovarian stimulation and intrauterine insemination: A retrospective analysis of 4146 cycles.


RESULTS: 4146 cycles (1312 couples) included. Mean age was 34.7 +/- 4 years. LBR per couple was 39% for anovulatory infertility compared to (p < 0.05) unexplained infertility (28.6%), mixed (23.4%), male factor (20.1%), unilateral tubal (14.2%), low ovarian reserve (13.2%), and endometriosis (stage I and II) (11.1%). Multivariate analysis showed the following factors were associated with CP: Cycle rank ≤3 (Odds ratio (OR) = 1.5, 95% CI: 1.2-1.9, p < 0.001), age <38 years (OR = 1.5, 95% CI: 1.2-2, p < 0.001), ≥2 preovulatory follicles (OR = 1.4, 95% CI: 1.1-1.8, p = 0.004), TMSC ≥ 5 millions (OR = 1.8, 95% CI: 1.3-2.4, p < 0.001). Endometriosis, low ovarian reserve, unilateral tubal and male factor had a negative impact on CPR (OR = 0.3, 95% CI: 0.1-0.5, p < 0.001; OR = 0.4, 95% CI: 0.3-0.7, p < 0.001; OR = 0.5 95% CI: 0.3-0.9, p = 0.01; OR = 0.6, 95% CI: 0.4-0.8, p = 0.002 respectively) compared to anovulatory infertility.
Bilateral tubo-ovarian abscesses presenting with huge pelvic mass after repeated intrauterine inseminations in a woman with severe endometriosis

Patsama Vichinsartvichai

Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Abstract

A 32-year-old woman consulted for an evaluation of pelvic pain following intrauterine insemination (IUI). Vaginal and abdominal sonography, septic workup were performed and laparoscopic surgery was scheduled after failure to respond to a course of antibiotics. During laparoscopic surgery, bilateral tubo-ovarian abscesses arising on the endometriotic cysts of both ovaries were identified with a vast amount of brownish peritoneal fluid under the adhesion of the greater omentum. Bilateral ovarian cystectomy, right salpingectomy and lysis adhesion were performed. Pathologic organisms were not detected in any of the specimen cultures. Pelvic infection is an uncommon complication following IUI. Endometriosis might be a risk factor predisposing the pelvic organ to be susceptible to such infection. Performing IUI in a patient with endometriosis should be done with great vigilance.

Key words: artificial, endometriosis, homologous, insemination, minimally invasive surgical procedure, tubo-ovarian abscess.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset after IUI (days)</th>
<th>Symptoms</th>
<th>Comobid pelvic pathology</th>
<th>Ultrasound finding</th>
<th>WBC (x10^9/mm³)</th>
<th>Surgery</th>
<th>Operative finding</th>
<th>Gems</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>Septicemia</td>
<td>Adenomyoma</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>E. coli</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Pelvic pain, fever</td>
<td>Mild endometriosis</td>
<td>Unremarkable</td>
<td>7.6</td>
<td>Laparotomy</td>
<td>Ruptured left TOA</td>
<td>NG 4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Pelvic pain, vaginal discharge</td>
<td>Stage I endometriosis</td>
<td>4.5 x 4.4 cm left adnexal mass</td>
<td>11.0</td>
<td>Laparotomy</td>
<td>Dense pelvic adhesion encasing left adnexa, obliterated cul-de-sac</td>
<td>NG 2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Pelvic pain, fever</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>19.7</td>
<td>Laparotomy</td>
<td>Ruptured left TOA</td>
<td>NG 6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>Pelvic pain</td>
<td>Stage IV endometriosis</td>
<td>Huge bilateral ovarian cysts</td>
<td>10.3</td>
<td>Laparoscopy</td>
<td>Greater omentum encasing pelvic collection, bilateral TOA</td>
<td>NG This report</td>
<td></td>
</tr>
</tbody>
</table>

ATB, antibiotics; IUI, intrauterine insemination; NA, not available; NG, no growth; TOA, tubo-ovarian abscess; WBC, white blood cell count.
The efficacy of non-assisted reproductive technology treatment might be limited in infertile patients with advanced endometriosis in their 30s.

Watari Isono, Osamu Wada-Hiraike, Nana Akino, Hiromi Terao, Miyuki Harada, Tetsuya Hirata, Yasushi Hirota, Kaori Koga, Tomoyuki Fujii and Yutaka Osuga

Figure 3 Age-related decrease in cumulative live birth rates (CLBR) in non-assisted reproductive technology (ART) patients with Advanced endometriosis. Age-related declines in the CLBR of the patients with ‘Advanced endometriosis’ were examined. All the patients treated with non-ART were classified according to the aforementioned eight age subgroups and the presence of this infertility factor.

Figure 4 Age-related decrease in cumulative live birth rates (CLBR) in assisted reproductive technology (ART) patients with advanced endometriosis. Age-related declines in the CLBR following treatment with ART in the patients with ‘Advanced endometriosis’ were examined. All the patients treated with ART were classified according to the aforementioned eight age subgroups and the presence of this infertility factor.
When more is not better: 10 ‘don’ts’ in endometriosis manage position statement

ETIC Endometriosis Treatment Italian Club†

Do not recommend controlled ovarian stimulation and IUI in infertile women with endometriosis at any stage (quality of the evidence, moderate; weak suggestion)

The use of COS–IUI for endometriosis-associated infertility should not be recommended because, according to the available evidence, the procedure is debatable per se, the effect size appears negligible and the procedure may expose women to an increased risk of disease recurrence.
Endometriosis fertility index for predicting non-assisted reproductive technology pregnancy after endometriosis surgery: a systematic review and meta-analysis

Accepted 13 January 2020. Published Online 19 February 2020.

S Vesali, a M Razavi, b M Rezaeinejad, c A Maleki-Hajiagha, d S Maroufizadeh, e M Sepidarkish f g

Background Results of studies that have assessed the accuracy of the endometriosis fertility index (EFI) for predicting non-assisted reproductive technology (ART) pregnancy are inconsistent.

Objective We intended to evaluate the accuracy of EFI for the prediction of non-ART pregnancy.

Search strategy Embase, Medline, Scopus and Web of Science were searched up to 5 October 2019.

Selection criteria We included studies that used EFI to predict non-ART pregnancy in women with surgically documented endometriosis.

Data collection and analysis A total of 5547 studies were identified, from which we included 17 studies on 4598 women in the meta-analysis. Eight studies were classified as good quality, and the rest were considered to be of fair quality. Only five (29.41%) studies used appropriate approaches to account for potential confounders. Pooled effect sizes with corresponding 95% CI were calculated using random-effects model.

Main results The cumulative non-ART pregnancy rate at 36 months was 10% (95% CI: 3, 16%; P < 0.001) for women with an EFI of 0–2, which significantly increased to 69% (95% CI: 58, 79%; P < 0.001) for women with an EFI of 9–10. Compared with women with an EFI of 3–4 (18%, 95% CI: 12, 24%; P < 0.001), the combined cumulative non-ART pregnancy rates were 44% (95% CI: 26, 63%; P < 0.001) for women with an EFT of 5–6 and 55% (95% CI: 47, 64%; P < 0.001) for women with an EFI of 7–8. Paired comparison by the chi-square test showed a significant difference between all categories (P < 0.001). The odds ratio (OR) for EFI was 1.33 (95% CI: 1.17, 1.49, P < 0.001) and the summary area under the curve (AUC) was 72% (95% CI: 65, 80%, P < 0.001).

Conclusion The current findings highlighted the good performance of the EFI score in predicting the non-ART pregnancy rate. However, these findings should be considered with caution because of the substantial heterogeneity between studies.

Keywords Endometriosis Fertility Index, meta-analysis, pregnancy, systematic review.

Tweetable abstract Review findings show the merits of Endometriosis Fertility Index as having a prognostic ability for non-assisted reproductive technology pregnancy.

Linked article This article is commented on by C Tomasetti, p. 810 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16180.
Endometriosis-IVF Indications

- Recurrent endometrioma
- Bilateral endometrioma
- With Adenomyosis
- DOR
- Deep endometriosis?
- Bilateral Tubal Factor
- Male Factor
- rASRM stage III-IV in itself is no indication for ART

(n = 1,589,079).
Compared with male factor (n = 375,557), endometriosis-associated cycles (n = 112,475) yielded fewer oocytes (50.5% vs. 42.5% of cycles with only 0-10 oocytes retrieved), lower risk of hyperstimulation (1.1% vs. 1.3%, adjusted risk ratio [aRR] 0.82, 95% confidence interval [CI] 0.74-0.91), and an increased risk of cancellation (12.9% vs. 10.1%, aRR 1.30, 95% CI 1.25-1.35). Endometriosis was associated with a statistically decreased but likely clinically insignificant difference in the following outcomes: chance of pregnancy per transfer (43.7% vs. 44.8%, aRR 0.96, 95% CI 0.95-0.98) among couples who did not also have tubal factor infertility and live birth per transfer (37.2% vs. 37.6%, aRR 0.96, 95% CI 0.94-0.98).
SART 2015

231,936 ART cycles

Figure 20
Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Live Births, by Type of Infertility Diagnosis, 2015

Diagram showing the percentages of ART cycles by different diagnoses:
- Tubal factor: 24.0%
- Ovulatory dysfunction: 28.8%
- Diminished ovarian reserve: 13.1%
- Endometriosis: 27.6%
- Uterine factor: 17.3%
- Male factor: 27.1%
- Other factor: 18.5%
- Unknown factor: 29.0%
- Female only: 17.3%
- Multiple factors: 22.0%

Diagnosis
A total of 347,185 autologous fresh and frozen assisted reproductive technology cycles from the period 2008–2010. Although cycles of patients with endometriosis constituted 11% of the study sample, the majority (64%) reported a concomitant diagnosis, with male factor (42%), tubal factor (29%), and diminished ovarian reserve (22%) being the most common.

• Endometriosis, when isolated or with concomitant diagnoses, was associated with lower oocyte yield compared with those with unexplained infertility, tubal factor, and all other infertility diagnoses combined.

• Women with isolated endometriosis had similar or higher live birth rates compared with those in other diagnostic groups.

• However, women with endometriosis with concomitant diagnoses had lower implantation rates and live birth rates compared with unexplained infertility, tubal factor, and all other diagnostic groups.
Endometriosis does not affect live birth rates of patients submitted to assisted reproduction techniques: analysis of the Latin American Network Registry database from 1995 to 2011

Mário Murta\textsuperscript{1,2} · Roberto Carlos Machado\textsuperscript{1} · Fernando Zegers-Hochschild\textsuperscript{3,4} · Miguel Angel Checa\textsuperscript{5,6} · Marcos Sampaio\textsuperscript{7} · Selmo Geber\textsuperscript{7,8,9} 

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© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Purpose The purpose of this study is to compare the results of ART treatment in patients with and without endometriosis in a large cohort of patients from different centers over an extended period of time.

Methods This retrospective study is using data from patients undergoing 27,294 cycles of IVF/ICSI treatment between 1995 and 2011 that were registered in the database of the Latin American Registry maintained by the Latin America Network of Assisted Reproduction.

Results The mean number of retrieved oocytes was higher in the control group, but the mean number of metaphase II oocytes was similar. Fertilization rate and transfer rate were higher in the control group. We observed higher pregnancy rates, per cycle initiated and per embryo transfer and higher live birth rate in the endometriosis group. In the group of patients with 25–35 years old, the number of oocytes, fertilization rate, and number of transferred embryos were significantly higher in the control group. However, pregnancy rate and live birth rate were higher in the endometriosis group. In the group of patients with 36–40 years old, the number of transferred embryos was higher in the control group, but the pregnancy rate and live birth rate were higher in the endometriosis group. In the group of patients with 41 to 42 years old, the number of transferred embryos and the transfer rate were higher in the control group, but the pregnancy rate was higher in the endometriosis group.

Conclusion Our results demonstrate that endometriosis does not affect the outcome of patients subjected to IVF/ICSI and although patients with endometriosis present lower number of oocytes and higher cancelation rate, these shortcomings do not reduce pregnancy and live birth rates.
Endometriosis and ART

- **Agonist or antagonist protocol: similar reproductive outcomes**
  - Based on limited data-lack of large RCT with specific patient populations
  - 4 available studies:
    - Pabuccu et al, 2007: RCT divided over 3 groups: similar clinical pregnancy rates
      - Stage I-II (N:58), operated E.oma (N=81), unoperated E.oma (N:67)
    - Bastu et al, 2014: retrospective study, after endometrioma resection
      - N+86 (44 vs 42)
      - Similar ongoing pregnancy rate (with agonist, more oocytes)
    - Rodrigues-Purata et al, 2013: retrospective cohort study, any stage endometriosis
      - N=1180 (of which 263 antagonist)
      - After matching: similar pregnancy rate
    - Drakopoulos et al, 2018: retrospective study, any stage endometriosis, subgroup analysis
      - Antagonist vs agonist
        - Stage I-II (42 vs 75): similar clinical pregnancy and live birth rate
        - Stage III-IV (143 vs 126): similar clinical pregnancy and live birth rate

Courtesy by Carla Tomasetti
# Pregnancy outcomes after controlled ovarian hyperstimulation in women with endometriosis-associated infertility: GnRH-agonist versus GnRH-antagonist

K. Kolanska a,b,c, J. Cohen a,b,c, S. Bendifallah a,c, L. Selleret a,c, J.-M. Antoine a,c, N. Chabbert-Buffet a,b,c, E. Darai a,b,c, E.-M. d’Argent a,c

## Table 2

Results of IVF/ICSI in women with endometriosis treated with a GnRH-agonist or GnRH-antagonist protocol.

<table>
<thead>
<tr>
<th></th>
<th>Agonist (n = 165)</th>
<th>Antagonist (n = 119)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COH characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of FSH (UI)</td>
<td>2425 (30–6600)</td>
<td>2500 (14–5850)</td>
<td>0.4</td>
</tr>
<tr>
<td>Stimulation duration (days)</td>
<td>11 (6–92)</td>
<td>11 (6–18)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cancellation rate</td>
<td>5 (3)</td>
<td>7 (6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Number of embryos transferred in freeze-thaw</td>
<td>0 (0–5)</td>
<td>0 (0–3)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Analysis per started cycle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh embryo transfer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR per started cycle [n (%)]</td>
<td>41 (25)</td>
<td>15 (13)</td>
<td>0.017</td>
</tr>
<tr>
<td>Live-birth rate per started cycle [n (%)]</td>
<td>31 (18)</td>
<td>9 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Miscarriage &lt; 12 GW [n (%)]</td>
<td>9 (6)</td>
<td>3 (3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Freeze-thaw embryo transfer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR per started cycle [n (%)]</td>
<td>8 (5)</td>
<td>8 (7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Live-birth rate per started cycle [n (%)]</td>
<td>3 (2)</td>
<td>8 (7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Miscarriage &lt; 12 GW [n (%)]</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Fresh + frozen embryos transfers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR per started cycle [n (%)]</td>
<td>48 (29)</td>
<td>22 (18)</td>
<td>0.06</td>
</tr>
<tr>
<td>Live-birth rate per started cycle [n (%)]</td>
<td>34 (21)</td>
<td>17 (14)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Analysis per cycle with embryo transfer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh embryo transfer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR per cycle with transfer [n (%)]</td>
<td>41 (29)</td>
<td>15 (17)</td>
<td>0.053</td>
</tr>
<tr>
<td>Live-birth rate per transfer [n (%)]</td>
<td>31 (22)</td>
<td>9 (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Miscarriage per transfer [n (%)]</td>
<td>9 (7)</td>
<td>3 (4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Freeze-thaw embryo transfer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR per transfer [n (%)]</td>
<td>8 (16)</td>
<td>8 (22)</td>
<td>0.7</td>
</tr>
<tr>
<td>Live-birth rate per transfer [n (%)]</td>
<td>3 (6)</td>
<td>8 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Miscarriage per transfer [n (%)]</td>
<td>3 (3)</td>
<td>7 (7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Fresh + frozen embryos transfers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR per transfer [n (%)]</td>
<td>48 (29)</td>
<td>22 (18)</td>
<td>0.1</td>
</tr>
<tr>
<td>Live-birth rate per transfer [n (%)]</td>
<td>34 (24)</td>
<td>17 (18)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
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

Main results

We included eight parallel-design RCTs, involving a total of 640 participants. We did not assess any of the studies as being at low risk of bias across all domains, with the main limitation being lack of blinding. Using GRADE methodology, the quality of the evidence ranged from very low to low quality.

Paucity and very low quality

Long-term GnRH agonist therapy versus no pretreatment

We are uncertain whether long-term GnRH agonist therapy affects the live birth rate (RR 0.48, 95% CI 0.26 to 0.87; 1 RCT, n = 147; I² not calculable; very low quality evidence) or the overall complication rate (Peto OR 1.23, 95% CI 0.37 to 4.14; 3 RCTs, n = 318; I² = 73%; very low quality evidence) or this intervention affects the clinical pregnancy multiple pregnancy rate (Peto OR 0.14, 95% CI 0.03 to 0.45, 95% CI 0.10 to 2.00; 2 RCTs, n = 208; I² = 0%; very low-quality evidence) or low-quality evidence).

Outcome: clinical pregnancy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>GnRH agonist Events</th>
<th>Standard IVF/ICSI Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deleer 2016</td>
<td>24</td>
<td>61</td>
<td>85</td>
<td>25.7%</td>
<td>1.01 (0.65, 1.58)</td>
<td></td>
</tr>
<tr>
<td>Dicker 1992</td>
<td>12</td>
<td>35</td>
<td>47</td>
<td>23.8%</td>
<td>3.22 (1.33, 7.65)</td>
<td></td>
</tr>
<tr>
<td>NCT01269125</td>
<td>15</td>
<td>60</td>
<td>75</td>
<td>15.4%</td>
<td>1.07 (0.57, 2.02)</td>
<td></td>
</tr>
<tr>
<td>NCT01581359</td>
<td>15</td>
<td>71</td>
<td>86</td>
<td>29.7%</td>
<td>1.29 (0.47, 3.83)</td>
<td></td>
</tr>
<tr>
<td>Rickes 2002</td>
<td>21</td>
<td>28</td>
<td>49</td>
<td>11.8%</td>
<td>1.58 (0.94, 2.66)</td>
<td></td>
</tr>
<tr>
<td>Surrey 2002</td>
<td>20</td>
<td>25</td>
<td>45</td>
<td>15.1%</td>
<td>1.49 (0.99, 2.23)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>280</td>
<td></td>
<td>272</td>
<td>100.0%</td>
<td>1.13 (0.91, 1.44)</td>
<td></td>
</tr>
</tbody>
</table>

Favours standard IVF/ICSI Favours GnRH agonist

<table>
<thead>
<tr>
<th>Risk Ratio</th>
<th>0.05</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed, 95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUTHTORS' CONCLUSIONS

This review raises important questions regarding the merit of long-term GnRH agonist therapy compared to no pretreatment prior to standard IVF/ICSI in women with endometriosis. 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. Further, we are uncertain whether this intervention impacts on the clinical pregnancy rate, multiple pregnancy rate, miscarriage rate, mean number of oocytes and mean number of embryos. 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, not only compared to no pretreatment, but also compared to other proposed alternatives to endometriosis management.
Use of oral contraceptives in women with endometriosis before assisted reproduction treatment improves outcomes

- In women with endometriosis, including those with endometriomas, 6 to 8 weeks of continuous use of oral contraception (OC) before assisted reproduction treatment (ART) maintains ART outcomes comparable with the outcomes of age-matched controls without endometriosis.
- In contrast, ART outcomes are markedly compromised in endometriosis patients who are not pretreated with OC.
- Ovarian responsiveness to stimulation was not altered by 6 to 8 weeks’ use of pre-ART OC (0.03 mg of ethinyl E2 (EE) and 0.125 mg of levonorgestrel), including in poor responders with endometriomas.
- The GnRH-agonist long protocol was the standard protocol used in the majority (>75%) of endometriosis and control patients.

Dominique de Ziegler, 2010
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


Design: Dutch multicenter RCT, non-inferiority
Patients: Surgically proven endometriosis stage 3-4
Randomization: 3 months OCP prior to IVF (N=165)
3 months GnRH agonist prior to IVF (N=165)
Outcome: Live birth rate
Materials and methods: A prospective cohort study of 144 infertile women planning IVF after laparoscopic surgery of ovarian endometriomas was conducted at our department in 2012–2015. Patients were divided into three groups: group I (N38) with dienogest course, group II (N70) with a-GnRH group III (N70) without any hormonal therapy within 6 months preceding IVF.

Results: The study groups did not differ by removed endometriomas size and ovarian reserve indicators. The gonadotropin dose per Cycle was higher, while the number of retrieved oocytes was lower in group III patients (p<.001).

In women with dienogest pretreatment, clinical pregnancy rate was 2.5 times (44.7% versus 16.7%, p¼.012) and delivery rate – three times higher (36.8% versus 11.1%, p¼.013) as compared with those from group III.
The clinical outcome of Dienogest treatment followed by in vitro fertilization and embryo transfer in infertile women with endometriosis

Hiroshi Tamura1*, Hiroaki Yoshida2, Hiroyuki Kikuchi3, Mai Josaki1, Yumiko Mihara1, Yuichiro Shirafuta1, Masahiro Shinagawa1, Isao Tamura1, Toshiaki Taketani1, Akihisa Takasaki3 and Norihiro Sugino1

Abstract

Background: Endometriosis is considered to be the most intractable cause of female infertility. Administering any type of treatment for endometriosis before in vitro fertilization and embryo transfer (IVF-ET) is an important strategy for improving the IVF-ET outcomes for infertile women with endometriosis. In fact, treatment with a gonadotropin-releasing hormone (GnRH) agonist just before IVF-ET has been reported to improve the clinical outcome in endometriosis patients. However, the benefit of Dienogest (DNG), a synthetic progestin, treatment just before IVF-ET remains unclear.

Methods: Sixty-eight infertile women with Stage III or IV endometriosis (ovarian endometrial cyst < 4 cm) were recruited for this study. The subjects were divided into 2 groups: a DNG group (n = 33) and a control group (n = 35). DNG was administered orally every day for 12 weeks prior to the conventional IVF-ET cycle in the DNG group. Standard controlled ovarian hyperstimulation with the GnRH agonist long protocol was performed in the control group. The numbers of mature follicles and retrieved oocytes, fertilization rates, implantation rates, and clinical pregnancy rate were compared between the two groups. In addition, the concentrations of inflammatory cytokines, oxidative stress markers, and antioxidants in follicular fluids were also measured.

Results: The numbers of growing follicles, retrieved oocytes, fertilized oocytes, and blastocysts were significantly lower in the DNG group than in the control group. The fertilization and blastocyst rates were also lower in the DNG group than in the control group. Although there was no significant difference in the implantation rate between the groups, the cumulative pregnancy rate and live birth rate were lower in the DNG group than in the control group. There was no significant difference in the abortion rate. Our results failed to show that DNG reduces the inflammatory cytokine levels and oxidative stress in follicular fluids.

Conclusions: Administering DNG treatment just before IVF-ET did not provide any benefits to improve the clinical outcomes for infertile women with endometriosis.
ENDOMETRIOSIS

The effects of letrozole on women with endometriosis undergoing ovarian stimulation for in vitro fertilization

Se Jeong Kim\textsuperscript{a,b,*}, Chang Woo Choo\textsuperscript{c,*}, Seul Ki Kim\textsuperscript{a,b}, Jung Ryeol Lee\textsuperscript{a,b}, Byung Chul Jee\textsuperscript{a,b}, Chang Suk Suh\textsuperscript{b}, Won Don Lee\textsuperscript{c} and Seok Hyun Kim\textsuperscript{b}

\textsuperscript{a}Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Korea; \textsuperscript{b}Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea; \textsuperscript{c}Seoul Maria Fertility Hospital, Seoul, Korea

Table 3. Comparison of IVF outcomes of the study subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose (IU)</td>
<td>316 ± 108</td>
<td>286 ± 77</td>
<td>.393</td>
</tr>
<tr>
<td>Total gonadotropin (IU)</td>
<td>3141 ± 1198</td>
<td>2772 ± 950</td>
<td>.303</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>9.7 ± 1.4</td>
<td>9.5 ± 1.7</td>
<td>.938</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>0.85 ± 0.69</td>
<td>0.91 ± 0.61</td>
<td>.561</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>722 ± 1076</td>
<td>2168 ± 1521</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>EOR</td>
<td>82.4 ± 95.5</td>
<td>333.8 ± 182.0</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>EMOR</td>
<td>125.3 ± 117.3</td>
<td>487.9 ± 401.3</td>
<td>&lt;.001**</td>
</tr>
<tr>
<td>No. of total oocytes retrieved (n)</td>
<td>8.0 [5.0, 12.0]</td>
<td>6.5 [4.0, 10.0]</td>
<td>.230</td>
</tr>
<tr>
<td>No. of mature oocytes retrieved (n)</td>
<td>6.0 [2.0, 10.0]</td>
<td>5.0 [2.0, 8.0]</td>
<td>.505</td>
</tr>
<tr>
<td>Percentage of mature oocytes (%)</td>
<td>69.9 ± 23.7</td>
<td>80.2 ± 21.0</td>
<td>.029*</td>
</tr>
<tr>
<td>No. of 2PN (n)</td>
<td>5.0 [3.0, 9.0]</td>
<td>4.0 [2.0, 7.0]</td>
<td>.394</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>63.2 ± 17.0</td>
<td>68.1 ± 23.8</td>
<td>.207</td>
</tr>
<tr>
<td>No. of usable embryo (n)</td>
<td>3.5 [2.0, 4.0]</td>
<td>3.0 [2.0, 3.0]</td>
<td>.282</td>
</tr>
<tr>
<td>Embryo transfer canceled cycle (n)</td>
<td>4</td>
<td>3</td>
<td>1.000</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>10.5 ± 1.3</td>
<td>11.8 ± 1.4</td>
<td>.003*</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>20.6 (7/34)</td>
<td>30.4 (7/23)</td>
<td>.397</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (interquartile range). EOR: estradiol oocyte ratio; EMOR: estradiol mature oocyte ratio; 2PN: two pronuclei.

\*\(p < .05\); \**\(p < .001\).

This is the first study evaluating the effects of a protocol with letrozole and gonadotropin for the treatment of IVF in infertile women with endometriosis. In summary, letrozole may be an excellent treatment for patients diagnosed with endometriosis undergoing IVF treatments with low estrogen levels. Our research team is currently working on a prospective study to better analyze these conclusions.
The deferred embryo transfer strategy improves cumulative pregnancy rates in endometriosis-related infertility: A retrospective matched cohort study

Mathilde Bourdon¹,², Pietro Santulli¹,²,³ *, Chloé Maignien¹, Vanessa Gayet¹, Khaled Pocate-Cheriet⁴, Louis Marcellin¹,²,³, Charles Chapron¹,²,³

Table 2. IVF/ICSI-characteristics and outcomes in matched fresh and deferred frozen embryo transfer groups.

<table>
<thead>
<tr>
<th></th>
<th>Fresh-ET group (n = 135)</th>
<th>Def-ET group (n = 135)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of oocytes retrieved (mean ± SD)</td>
<td>7.4 ± 4.3</td>
<td>9.9 ± 7.0</td>
<td>0.001³⁶</td>
</tr>
<tr>
<td>Total number of embryos transferred</td>
<td>278</td>
<td>224</td>
<td>NA</td>
</tr>
<tr>
<td>Mean No. of embryos transferred (mean ± SD)</td>
<td>2.1 ± 0.9</td>
<td>1.7 ± 0.9</td>
<td>&lt;0.001³⁶</td>
</tr>
<tr>
<td>Total number of embryo transfers</td>
<td>155</td>
<td>170</td>
<td>NA</td>
</tr>
<tr>
<td>Mean No. of transfers (mean ± SD)</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.7</td>
<td>0.132³⁶</td>
</tr>
<tr>
<td>Cumulative clinical pregnancy rate—(n,%)</td>
<td>40 (29.6)</td>
<td>58 (43.0)</td>
<td>0.047⁵⁴</td>
</tr>
<tr>
<td>Miscarriage—(n,%)</td>
<td>16/40 (40.0)</td>
<td>11/58 (19.0)</td>
<td>0.022¹⁰</td>
</tr>
<tr>
<td>Multiple pregnancy—(n,%)</td>
<td>7/40 (17.5)</td>
<td>5/58 (8.6)</td>
<td>0.220¹⁰</td>
</tr>
<tr>
<td>Cumulative ongoing pregnancy—(n,%)</td>
<td>24 (17.8)</td>
<td>47 (34.8)</td>
<td>0.005⁵⁴</td>
</tr>
<tr>
<td>Cumulative live birth rate—a—(n,%)</td>
<td>21 (15.6)</td>
<td>41 (29.6)</td>
<td>0.012⁵⁴</td>
</tr>
</tbody>
</table>

IVF/ICSI, in vitro fertilization / intra cytoplasmic sperm injection; Fresh-ET, Fresh embryo transfer; Def-ET, Deferred frozen- thawed embryo transfer; NA, non applicable

³⁶, Paired t-test;
⁵⁴, McNemar test;
¹⁰, Pearson’s chi-square test.

¹² and 5 women were lost to follow up in Fresh and Def-ET group respectively
Assessment of 382 babies showed no statistically significant difference in the mode of delivery, sex of live-born, gestational age, unadjusted median birth weight, and z-score between two study groups.

**Conclusion:** Freeze-all strategy is an attractive option to improve the outcomes of ART for women with advanced endometriosis.
Conclusion: Based on the review of the current literature, endometriosis seems to negatively affect oocyte quality, in terms of several relevant clinical and biological outcomes.

Single-cell RNA Sequencing of Oocytes From Ovarian Endometriosis Patients Reveals a Differential Transcriptomic Profile Associated With Lower Quality

Hortensia Ferrero, Ana Corachán, Alejandra Aguilar, Alicia Quiñonero, María Cristina Carbajo-García, Pilar Alámâ, Alberto Tejera, Esther Taboas, Elkin Muñoz, Antonio Pellicer, Francisco Domínguez

1-4 oocytes/patient
Oocytes (n=32)

Vitrification
NGS analysis

Differential Expressed Genes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of samples</th>
<th>Significant DEG</th>
<th>Up-regulated genes</th>
<th>Down-regulated genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Donors vs. Ovarian endometriosis</td>
<td>32 (16 vs 16)</td>
<td>520</td>
<td>394</td>
<td>126</td>
</tr>
<tr>
<td>Healthy Donors vs. Affected Ovary</td>
<td>24 (8 vs 16)</td>
<td><strong>103</strong></td>
<td>97</td>
<td>6</td>
</tr>
<tr>
<td>Healthy Donors vs. Unaffected Ovary</td>
<td>24 (8 vs 16)</td>
<td>71</td>
<td>62</td>
<td>9</td>
</tr>
<tr>
<td>Affected vs. Unaffected Ovary</td>
<td>16 (8 vs 8)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The most prominent incidence of DEG was found between oocytes from ovarian endometriosis compared to oocytes from healthy donors.

Endometriosis has a global effect in oocyte quality, independently if the endometrioma is present or not in the ovary.
Is there an impact of endometriosis on endometrial function and embryo implantation?

Most clinical studies show impaired implantation in endometriosis patients undergoing IVF/ICSI.
What do clinical studies show us?

Table 4 The Effect of Endometriosis on Pregnancy Rate and Implantation After IVF: Review of Literature

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. of cycles per no. of patients</th>
<th>Pregnancy rate per transfer</th>
<th>Implantation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endometrosis</td>
<td>Control</td>
<td>Endometrosis</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Jones et al. (1984) (10)</td>
<td>20/11</td>
<td>454/249*</td>
<td>40</td>
</tr>
<tr>
<td>Chillik et al. (1985) (18)</td>
<td>24/18</td>
<td>15/8†</td>
<td>33%</td>
</tr>
<tr>
<td>Yovich et al. (1988) (23)</td>
<td>57/30‡</td>
<td>40/28*</td>
<td>1.9§</td>
</tr>
<tr>
<td>Oehninger et al. (1988) (11)</td>
<td>226/113</td>
<td>54/23†</td>
<td>26.7</td>
</tr>
<tr>
<td>Mills et al. (1992) (4)</td>
<td>67/67</td>
<td>122/122*</td>
<td>27</td>
</tr>
<tr>
<td>Inoue et al. (1992) (19)</td>
<td>476/309</td>
<td>701/372*</td>
<td>30.9</td>
</tr>
<tr>
<td>Simon et al. (1994) (20)</td>
<td>96/59</td>
<td>78/96*</td>
<td>15.1§</td>
</tr>
<tr>
<td>Arici et al. (1995)</td>
<td>89/35</td>
<td>247/167*</td>
<td>14.8</td>
</tr>
</tbody>
</table>

* Control group is women with tubal factor infertility.
† Control group is women with previous history of but treated endometriosis.
‡ Only stage IV endometriosis.
§ Statistically significant difference.
∥ Control group is women with all other indications of IVF.
The aim of this study was to assess the endometrial receptivity gene signature in patients with different stages of endometriosis by investigating transcriptomic modifications of their endometrium using the endometrial receptivity array (ERA) test.

Gene expression microarray was used to diagnose the receptivity status by quantifying the expression of 238 specific genes directly related to human endometrial Receptivity.

None of the 238 genes present in the ERA array were significantly over- or under- expressed in any of different stages of the disease compared with controls.

Endometrial receptivity gene signature during the implantation window does not vary significantly among patients with endometriosis even considering different stages compared with healthy women.
Endometrial receptivity in the eutopic endometrium of women with endometriosis: it is affected, and let me show you why

Bruce A. Lessey, M.D., Ph.D. and J. Julie Kim, Ph.D.

Timeline for Endometriosis and Endometrial Receptivity Defects

Timeline for major discoveries in endometriosis and related defects in endometrial receptivity. Pivotal research on endometriosis commenced with the work of Sampson, and changes in endometrium have been noted by representative investigators up to the present day. There are many other important contributions that are not indicated here (140–163).
Endometrial receptivity in eutopic endometrium in patients with endometriosis: it is not affected, and let me show you why

Jose Miravet-Valenciano, Ph.D., a María Ruiz-Alonso, Ph.D., a Eva Gómez, Ph.D., a and Juan A. García-Velasco, M.D. b

TABLE 1

<table>
<thead>
<tr>
<th>Donors' cause of infertility</th>
<th>Cycles, n</th>
<th>Pregnancy rate/transfer (%)</th>
<th>Implantation rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertile</td>
<td>34</td>
<td>44</td>
<td>16.2</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>58</td>
<td>60.3</td>
<td>23.6</td>
</tr>
<tr>
<td>Idiopathic infertility</td>
<td>20</td>
<td>45</td>
<td>11.2</td>
</tr>
<tr>
<td>Tubal infertility</td>
<td>27</td>
<td>55.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Male infertility</td>
<td>28</td>
<td>60.7</td>
<td>19.1</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>11</td>
<td>27.3</td>
<td>7.0 a</td>
</tr>
</tbody>
</table>

Note: Adapted from Simon et al. (2). a P< .05.

Impact of endometriosis in the egg recipient.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Stage III/IV endometriosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation rate (%)</td>
<td>16</td>
<td>14.8</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>45.5</td>
<td>40</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>26</td>
<td>30</td>
</tr>
</tbody>
</table>

Note: All values are percentages. Differences are not significant. Adapted from Díaz et al. (5).
Design: a case-control study

Objective: to investigate endometrial transcriptome (mRNA and miRNA) by next generation sequencing (NGS)

Patients: endometrial samples (six END, six IC, five FC) were collected during the Window of Implantation

Conclusion: no differentially expressed genes were found in endometriosis patients vs controls
Patients with endometriosis undergoing IVF have aneuploidy rates equivalent to their age-matched peers in the in vitro fertilization population.

In women undergoing in vitro fertilization, the rate of aneuploidy in the embryos of endometriosis patients did not differ from that of women without endometriosis.
Summary

• **Oocyte quality**----evidence for lower oocyte quality in both basic and clinical studies
• **Embryo quality**------controversial data, but similar aneuploidy rate
• **Endometrium**----controversial data, ERA test did not detect any single alteration
RESULTS: Among the cohort, we identified 1006 women with endometriosis as study group and 2012 unaffected women matched in a 1:2 ratios as control group. The miscarriage rate between women with and without endometriosis was similar (22.4 and 20.1%, P = 0.085). The odds ratio after adjusting for the risk factors for miscarriage was 1.14 (95% confidence interval 0.95-1.37). In the study group, the women with and without endometrioma did not show a significant risk of miscarriage, (19.8 and 23.8%, P = 0.152, OR 0.79, 95% CI 0.58-1.09). The miscarriage rate in women with endometrioma ≥30 mm (37.3 ± 7.1 mm) and < 30 mm (19.3 ± 5.5 mm) was not significantly different, (24.7 and 18.5%, P = 0.229, OR 1.44, 95% CI 0.79-2.63). After adjustment for risk factors for miscarriage, the presence of endometrioma and the size of endometrioma, regression model confirmed no significant increase for the risk of miscarriage in the subgroup analyses.

CONCLUSIONS: The risk of miscarriage did not statistically increase in women with endometriosis who achieved pregnancy through IVF fresh cycles.
Factors related to early spontaneous miscarriage during IVF/ICSI treatment: an analysis of 21,485 clinical pregnancies

<table>
<thead>
<tr>
<th></th>
<th>&lt;35</th>
<th>P-value</th>
<th>≥35</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage rate (%)</td>
<td>Miscarriage rate (%)</td>
<td></td>
<td>Miscarriage rate (%)</td>
<td></td>
</tr>
<tr>
<td>Uterus malformation</td>
<td>14.44 (26/180)</td>
<td>0.027</td>
<td>25.64 (10/39)</td>
<td>0.223</td>
</tr>
<tr>
<td>Male factor</td>
<td>9.47 (413/4363)</td>
<td></td>
<td>17.79 (87/489)</td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>11.43 (491/4296)</td>
<td>0.003</td>
<td>17.63 (70/397)</td>
<td>0.951</td>
</tr>
<tr>
<td>Male factor</td>
<td>9.47 (413/4363)</td>
<td></td>
<td>17.79 (87/489)</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>10.18 (87/855)</td>
<td>0.519</td>
<td>21.74 (50/230)</td>
<td>0.209</td>
</tr>
<tr>
<td>Male factor</td>
<td>9.47 (413/4363)</td>
<td></td>
<td>17.79 (87/489)</td>
<td></td>
</tr>
</tbody>
</table>

PCOS = polycystic ovary syndrome.
Damage Mechanism due to Endometrioma

The presence of a **cyst ‘per se’** distorts and exerts a **toxic effect** on healthy ovarian parenchyma.

- **Ovarian Reserve**
- **Ovulation Rate**
- **Pregnancy Rate**
- **Ovarian Response to Stimulation**

Widely reported in the literature the possible relationship between surgery mediated damage and healthy ovarian parenchyma.
Rethinking mechanisms, diagnosis and management of endometriosis

Charles Chapron¹,²,³ *, Louis Marcellin¹,²,³, Bruno Borghese¹,²,³ and Piet Cools²

Table 2 | The decision-making process for choosing between surgery and ART

<table>
<thead>
<tr>
<th>Factor</th>
<th>In favour of surgery</th>
<th>In favour of ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian reserve³</td>
<td>Satisfactory</td>
<td>Decreased</td>
</tr>
<tr>
<td>Patient's intentions and priorities</td>
<td>Patient choiceᵇ</td>
<td>Patient choiceᵇ</td>
</tr>
<tr>
<td>Age</td>
<td>Young</td>
<td>Old</td>
</tr>
<tr>
<td>Infertility duration</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Associated infertility factors (male infertility or tubal blockage)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous surgery for endometriosis (specifically OMA)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pelvic pain intensity</td>
<td>Intense</td>
<td>Low</td>
</tr>
<tr>
<td>Ovarian endometrioma (specifically whether bilateral)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Associated adenomyosis</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ART, assisted reproductive technologies; OMA, ovarian endometriomas.ᵃHormonal levels and antral follicle count at day 2 or 3 of the menstrual cycleᵇInfluenced by culture, religion, educational level and the health-care system
Endometrioma is associated with a progressive **decline in ovarian reserve** and a progressive reduction in AMH serum levels, faster than in healthy controls.

Endometrioma-related reduction in ovarian reserve (ERROR): a prospective longitudinal study

Kasapoglu et al 2018

(2018)
Ovarian reserve evaluated with AMH is reduced in patients with ovarian endometriomas compared both to patients with other benign ovarian cysts, and to patients with healthy ovaries.
The effect of endometriosis on the ant Müllerian hormone level in the infertile population

Phillip A. Romanski¹ • Paula C. Brady¹ • Leslie V. Farland² • Ann M. Thomas¹ • Mark D. Hornstein¹

Methods A retrospective cohort study included three groups of women who presented for IVF treatment at our tertiary care center from 04/27/2015 to 05/31/2017: women with endometriosis and prior ovarian surgery (EnSx), women with endometriosis without prior ovarian surgery (En), and women with a primary diagnosis of male factor infertility (MF; reference group).

Results There were 671 patients that met inclusion criteria (78 EnSx, 60 En, and 533 MF). Compared to the MF group (3.6 ± 3.0), a lower mean AMH level (ng/mL) was observed in the EnSx group (2.5 ± 2.5; αβ – 1.21; 95% CI [−1.79, −0.62]) and in the En group (2.5 ± 2.2; αβ – 1.11; 95% CI [−1.68, −0.54]). Both endometriosis groups had a statistically significantly higher proportion of patients with an AMH < 1 (EnSx, 24.4%; OR, 2.39 [95% CI, 1.31, 4.36]; En, 28.3%; OR, 2.67 [95% CI, 1.41, 5.08]) compared to the MF group (13.9%). The mean baseline FSH level (IU/L) was statistically significantly higher in both endometriosis groups (EnSx, 8.6 ± 4.3; β, 1.37 [95% CI, 0.39, 2.34]; En, 8.4 ± 3.7; β, 0.96 [95% CI, 0.04, 1.87]) compared to the MF group (7.3 ± 2.2).

In summary, this study demonstrates that infertile women with endometriosis, both with and without a history of prior ovarian surgery, have worse ovarian reserve markers (lower AMH, higher FSH) when compared to women with male factor infertility. Both endometriosis groups also had a higher proportion of women with decreased ovarian reserve at the time of presentation to the infertility clinic. These findings may suggest that there is a pathologic process related to endometriosis which alters ovarian reserve, independent of any surgical injury which may occur in women who undergo ovarian surgery. Future studies could further investigate the relationship between endometriosis and rate of ovarian reserve decline over time and whether the age of menopause onset is altered in both infertility and non-infertility populations.
AMH levels temporarily decreased after laparoscopic cystectomy for ovarian endometriomas, with complete recovery of preoperative AMH values at 12 months postoperatively.

Six months after surgery, anti-Müllerian hormone values continued to be depressed from baseline but were no longer significantly different.
Surgical diminished ovarian reserve after endometrioma cystectomy versus idiopathic DOR: comparison of in vitro fertilization outcome

Table I  Clinical and biological characteristics of patients with DOR diagnosed after cystectomy(s) for endometrioma(s) (group A) and patients with idiopathic DOR (group B).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>51</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>No. of patients ‘poor responder’</td>
<td>39</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>(Bologna criteria)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table IV  IVF outcomes in women with DOR diagnosed after cystectomy(s) for endometrioma(s) (group A) and patients with idiopathic DOR (group B).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (125 cycles)</th>
<th>Group B (243 cycles)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation rate (%)</td>
<td>13/181 (7.2%)</td>
<td>49/364 (13.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Clinical pregnancy rate per cycle (%)</td>
<td>14/125 (11.2%)</td>
<td>50/243 (20.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per cycle</td>
<td>9/125 (7.2%)</td>
<td>41/243 (16.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Per transfer</td>
<td>9/104 (8.7%)</td>
<td>41/216 (18.8%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Spontaneous abortion rate (%) (before or after 12 weeks of gestation)</td>
<td>4/13 (30.8%)</td>
<td>8/49 (16.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ectopic pregnancy rate (%)</td>
<td>1/14 (7.1%)</td>
<td>1/50 (2.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple pregnancy rate (%)</td>
<td>2/13 (15.4%)</td>
<td>6/49 (12.2%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. NS, not significant.
The effect of surgical management of endometrioma on the IVF/ICSI outcomes when compared with no treatment? A systematic review and meta-analysis

M. Nickkho-Amiry\textsuperscript{1,2} - R. Savant\textsuperscript{2} - K. Majumder\textsuperscript{2} - E. Edi-Osagie\textsuperscript{2} - M. Akhtar\textsuperscript{2}

**A. Surgical treatment vs No treatment (10 studies)**

1. **Live birth rate / cycle**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treated Endometrioma</th>
<th>Non Treated Endometrioma</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bengoauren 2011</td>
<td>29</td>
<td>112</td>
<td>46</td>
</tr>
<tr>
<td>Dong 2014</td>
<td>58</td>
<td>143</td>
<td>26</td>
</tr>
<tr>
<td>Lee 2014</td>
<td>12</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Tinnesen 2000</td>
<td>11</td>
<td>55</td>
<td>12</td>
</tr>
</tbody>
</table>

   Total (55% CI): 356

   Total events: 310

   Heterogeneity: Tau^2 = 3.00, Chi^2 = 12.65, df = 3 (P = 0.005); P = 0%

   Test for overall effect: Z = 1.81 (P = 0.01)

2. **Clinical Pregnancy / cycle**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treated Endometrioma</th>
<th>Non Treated Endometrioma</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Damroo 2005</td>
<td>17</td>
<td>86</td>
<td>18</td>
</tr>
<tr>
<td>Dong 2014</td>
<td>66</td>
<td>145</td>
<td>35</td>
</tr>
<tr>
<td>Garcia-Vallejo 2004</td>
<td>37</td>
<td>147</td>
<td>14</td>
</tr>
<tr>
<td>Lee 2014</td>
<td>11</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>Pabuccu 2004</td>
<td>11</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td>Pabuccu 2007</td>
<td>27</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>Virog 2004</td>
<td>17</td>
<td>36</td>
<td>13</td>
</tr>
</tbody>
</table>

   Total (55% CI): 546

   Total events: 118

   Heterogeneity: Tau^2 = 0.63, Chi^2 = 5.17, df = 6 (P = 0.52); P = 0%

   Test for overall effect: Z = 0.63 (P = 0.22)

3. **Pregnancy / cycle**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treated Endometrioma</th>
<th>Non Treated Endometrioma</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Bengoauren 2011</td>
<td>41</td>
<td>112</td>
<td>60</td>
</tr>
<tr>
<td>Garcia-Vallejo 2004</td>
<td>44</td>
<td>147</td>
<td>10</td>
</tr>
<tr>
<td>Saganu 2002</td>
<td>10</td>
<td>62</td>
<td>11</td>
</tr>
<tr>
<td>Tinnesen 2000</td>
<td>12</td>
<td>55</td>
<td>17</td>
</tr>
<tr>
<td>Virog 2004</td>
<td>18</td>
<td>39</td>
<td>13</td>
</tr>
</tbody>
</table>

   Total (55% CI): 111

   Total events: 133

   Heterogeneity: Tau^2 = 0.34, Chi^2 = 5.46, df = 4 (P = 0.29); P = 26%

   Test for overall effect: Z = 0.64 (P = 0.51)
Controversy exists regarding surgical management of endometriomas in infertile women before in vitro fertilization (IVF) because growing evidence indicates that surgery may impair the ovarian response. The objective of the present systematic review and meta-analysis was to compare surgical and expectant management of endometriomas regarding IVF outcomes. Prospective and retrospective controlled studies were found via the Cochrane Library, Embase, and MEDLINE databases. Thirteen studies (1 randomized controlled trial and 12 observational studies, N = 2878) were pooled, and similar live birth rates were observed in the surgically and expectantly managed groups (odds ratio = 0.83; 95% confidence interval [CI], 0.56-1.22; p = .98). The clinical pregnancy rates (odds ratio = 0.83; 95% CI, 0.66-1.05; p = .86), the number of mature oocytes retrieved, and the miscarriage rates were not statistically different between study groups. However, the total number of oocytes retrieved was lower in the surgery group (mean difference = -1.51; 95% CI, -2.60 to -0.43; p = .02). Findings suggest that surgical management of endometriomas before IVF therapy yields similar live birth rates as expectant management. However, future properly designed randomized controlled trials are warranted.
Assisted reproduction in endometriosis.

**Fig. 4.** Infertility associated with endometriosis: Choice between surgery vs. ART as a function of age and ovarian reserve.
Fertility outcome of laparoscopic treatment in patients with severe endometriosis and repeated in vitro fertilization failures

David Soriano, M.D., a,b,e Iris Adler, M.D., e Jerome Bouaziz, M.D., a,b,e Matti Zoliti, M.D., a,b,e Vered H. Eisenberg, M.D., a,b,e Mordechai Goldenberg, M.D., a,e Daniel S. Seidman, M.D., a,c,d,e and Shai E. Elizur, M.D. a,c,d,e

Main Outcome Measure(s): Delivery rate after surgery.

Result(s): Seventy-eight women were included in the present study. All women were diagnosed with severe endometriosis during surgery (AFS 3–4) and all women had experienced failed IVF treatments before surgery. All women were symptomatic before their surgery. After surgical treatment 33 women (42.3%) delivered. Three women (9%) conceived spontaneously and all other women conceived after IVF treatment. Women who delivered were younger (32.5 [±4.1] years vs. 35.5 [±3.8] years), were less often diagnosed with diminished ovarian reserve before surgery (6% vs. 28.8%), and were more often diagnosed with normal uterine anatomy (by preoperative transvaginal ultrasound and during operation). In addition, performing salpingectomy during surgery was associated with a trend of improvement in delivery rates after surgery (70% in women who delivered vs. 51% in women who failed to deliver).

Conclusion(s): Symptomatic women with severe endometriosis and repeated IVF implantation failures may benefit from extensive laparoscopic surgery when performed by an experienced multidisciplinary surgical team to improve IVF outcome. (Fertil Steril® 2016;106:1264–9. ©2016 by American Society for Reproductive Medicine.)
Risks of ART in patients with Endometriomas

1. Risk of infectious complications and tubo-ovarian abscess.

2. Risk of progression of the disease or change in size of endometriomas.
Risks of tubo-ovarian abscess in cases of endometrioma and assisted reproductive technologies are both under- and overreported

Claire Villette, M.D., Antoine Bourret, M.D., Pietro Santulli, M.D., Ph.D., Vanessa Gayet, M.D., Charles Chapron, M.D., and Dominique de Ziegler, M.D.
Oocyte retrieval difficulties in women with ovarian endometriomas

Laura Benaglia a,b,*, Andrea Busnelli a,c, Rossella Biancardi a,c, Walter Vegetti a, Marco Reschini a, Paolo Vercellini a,c, Edgardo Somigliana a,c

Research question: What are the frequency, characteristics and consequences of technical difficulties encountered by physicians when carrying out oocyte retrieval in women with ovarian endometriomas?

Design: We prospectively recruited women undergoing IVF and compared technical difficulties between women with (n = 56) and without (n = 227) endometriomas.

Results: In exposed women, the cyst had to be transfixed in eight cases (14%, 95% CI 7 to 25%) and accidental contamination of the follicular fluid with the endometrioma content was recorded in nine women (16%, 95% CI 8 to 27%). Moreover, follicular aspiration was more frequently incomplete (OR 3.6, 95% CI 1.4 to 9.6). In contrast, the retrievals were not deemed to be more technically difficult by the physicians and the rate of oocytes retrieved per developed follicle did not differ. No pelvic infections or cyst ruptures were recorded (0%, 95% CI 0 to 5%).

Conclusions: Oocyte retrieval in women with ovarian endometriomas is more problematic but the magnitude of these increased difficulties is modest.
• **Results:** In total 52 women with endometriosis undergoing ART, 50 not undergoing ART, and 52 without endometriosis undergoing ART completed two questionnaires each.

• Both groups with endometriosis experienced a small increase in their quality of life, while women without endometriosis experienced a decrease.

• Pelvic pain worsened among women undergoing ART, but no greater worsening was detected among women with endometriosis compared with women without.

• **Conclusions:** This study showed no worsening in quality of life and a slight worsening in pelvic pain during ART regardless of endometriosis status.
Overall, five conclusions can be drawn: (i) IVF does not worsen endometriosis-related pain symptoms (moderate quality evidence); (ii) IVF does not increase the risk of endometriosis recurrence (moderate quality evidence); (iii) the impact of IVF on ovarian endometriomas, if present at all, is mild (low quality evidence); (iv) IUI may increase the risk of endometriosis recurrence (low quality evidence); (v) deep invasive endometriosis might progress with ovarian stimulation (very low quality evidence).
If no surgery
just IVF   -----Be careful

– AVOID puncturing the cyst during egg aspiration
  • If you do: switch to clean needle, consider longer AB
– Always under antibiotics
– Inform patients on infection risks
  • Ovarian abscess!
– Inform patients on not aspirating unaccessible follicles
– Inform patients on possible evolution of the cyst in pregnancy
Assisted reproduction in endometriosis.

**Infertility workup**

- Age
- Ovarian reserve
- Tubal factor
- Sperm

**Surgery**

- No OS-IUI
- Proceed to ART after 12-18Mo of natural conception attempt

**ART**

- No surgery before ART
- Segmented ART with deferred ET

**Fig. 5.** Therapeutic choice between surgery and ART in women whose infertility is associated with endometriosis.
Management of Endometrioma

Prior Surgery
- Good ovarian reserve
- Under age 35
- No additional infertility cause
- Unilateral endometrioma

Prior IVF
- Diminished ovarian reserve
- Advanced maternal age (37)
- Prolonged infertility history
- Male factor
- Tubal factor

SURGERY BEFORE IVF
- No response to medical treatment
- Suspicion of ovarian cancer

Oocyte cryopreservation
- Before the first surgical management
- Prior to recurrent surgery

Prof Dr Engin Oral
My recommendation

• If IVF is necessary in case of endometriosis, I recommend using an antagonist protocol with GnRH trigger and (pre GnRHa 2 months) deferred embryo transfer, which limits the risk of disease flaring and optimizes results.
DEEP ENDOMETRIOSIS (DIE)
CASE

- 36 years old
- Has 1 spontaneous pregnancy (6 years ago) complicated with HELLP syndrome
- Blood in the urine which has started almost 3 years ago
- Has painful periods
- No dyspareunia
- Doesn’t complain about bowel symptoms
- Desire for getting pregnant
- 1cm sized bluish lesion on the previous C section scar.
- A mass inside the bladder on TVUSG
- A 4 cm endometrioma on left ovary...1-2 follicles on left and 4-5 follicles on right ovary
- Grade 2 hydronephrosis on left kidney
- No palpable bowel mass on rectal examination
- Spermogram:N
- AMH:1.1
- HSG:N
Urinary ultrasonography

- A mass lesion sized 13x12x10mm, in the bladder at a distance of 4-5 cm to the ureter entrance, with a wide base and arteriovenous signals at the base
- Grade 2 hydronephrosis on left kidney
- Compensatory hypertrophy of right kidney
• What would you do?
What we did is...

• 1\textsuperscript{st} Operation
  Excision of scar endometriosis
  Left ovarian cyst aspiration
  Ureter dissection, excision of the lesion from the bladder, ureteroneocystostomy
  Pathology: All specimens were compatible with endometriosis

• 2\textsuperscript{nd} IVF
  Antagonist protocol
  14 oocytes...3 embryos
  D5 fresh transfer of 2 embryos

Result: Twin pregnancy
Endometriotic lesion excision from the inguinal canal during C-section
Postnatally on daily dienogest, and in remission without any complaints
NO HIGH QUALITY EVIDENCE IN CASES OF INFERTILITY ASSOCIATED TO DIE
in case of deeply infiltrating endometriosis associated infertility, what is the best therapeutic strategy? Which one is True?

- First-line surgery and then in vitro fertilization (IVF) in case of persistent infertility or
- first-line IVF, without surgery?

- Do surgical interventions for colorectal endometriosis improve pregnancy rates, pregnancy and neonatal outcomes?
Colorectal Surgery versus IVF

Favor IVF
- Nodule less than 2 cm
- Easy access to follicles
- Advanced age
- Reduce ovarian reserve
- Additional male factor
- Additional tubal factor
- DIE recurrence (previous surgery)
- Few symptoms
- Mild severity

Favor Surgery
- Associated Pain
- Bowel, ureter stenosis
- Difficult access to follicles
- Nodules larger than 2-3 cm
- Younger age
- Normal ovarian reserve
- Fast growing cyst
- Non-reassuring US
- No previous surgeries
- Previous failed IVF

Patient desire
Factors favoring surgery

- Relieve the pain returne of normal sexuel life
- Increase the fertility after surgery and offers couples the possibility for a spontaneous conception with reported PR between 40-60%
- To avoid risk of infection and abces at the time of oocyt pick-up during IVF.
- The risk of disease progression with bowel obstruction with COH prior to IVF
• 76 patientes with bowel endometriosis who were treated conservatively and underwent IVF 9 (11.8%) severe worsening of bowel symptoms (2 with colon ileus, 1 subocclusion) than IVF was stopped.

• 88% of women completed fertility without need for surgery.

Seyer-Hansen M et al Acta Obst Gynec Scand 2018
No randomized controlled studies were found, and we also failed to identify studies with control groups for assessment of the potential effects of DIE surgery on SPR.
Colorectal endometriosis-associated infertility: should surgery precede ART?

![Graphs showing cumulative live birth rate and pregnancy rate](image)

1\(^{st}\) group: 32.7%  58.9%  70.6%
2\(^{nd}\) group: 13%  24.8%  54.9%
Objectives. – The population of Reunion Island has a high prevalence of endometriosis impacting fertility. The aim of this series is to assess the fertility of women undergoing surgical approach of deep infiltrating endometriosis and to study the characteristics of the pregnancy outcomes.

Material and methods. – This is a retrospective 2 centers study, including all women wanting to be pregnant and operated for deep endometriosis in any of the 2 hospitals of the CHU of Reunion Island between January 2012 and May 2013.

Results. – Sixty-three women were included. Twenty-four (38%) had more than one operation and 16 (25.4%) experienced one or more complications. Fifty-eight (92%) had complete resection of the endometriosis. Twenty-seven (42.9%) women became pregnant at least once, spontaneously in 44.4%. Average delay for first pregnancy was 14.2 months. Twenty-two (34.9%) women became pregnant before 24 months. Among the 34 pregnancies, 20 ended with a live newborn. Premature delivery rate was 35%, cesarean section rate 10% and average birth weight was at 45th percentile.

Conclusion. – Fertility remains good after surgery for deep infiltrating endometriosis but the delay between operation and pregnancy is increased when a surgical complication occurs. Premature delivery rate is high. No pregnancy occurred in case of incomplete resection or after age of 36.
A lower CPR was found for women who experienced anastomotic leakage (with or without rectovaginal fistula) ($P = 0.02$) or deep pelvic abscess (with or without anastomotic leakage) ($P = 0.04$).
Effect of Anterior Compartment Endometriosis Excision on Infertility

Gabriele Centini, MD, PhD, Karolina Afors, MD, Joao Alves, MD, István Máté Argay, MD, Philippe R. Koninckx, MD, PhD, Lucia Lazzeri, MD, PhD, Giorgia Monti, MD, Errico Zupi, MD, Arnaud Wattiez, MD, PhD

Methods: This multicentre, retrospective study included a group of 55 patients presenting with otherwise-unexplained infertility who had undergone laparoscopic excision of anterior compartment endometriosis with histological confirmation. Patient medical records and operative reports were reviewed. Telephone interviews were conducted for long-term followup of fertility outcomes.

Results: The pregnancy rate following surgical excision of endometriotic lesions was 44% (n = 11) among those with anterior compartment involvement alone and 50% (n = 15) in case of posterior lesions association without

Figure 4. Kaplan-Meier estimates the time elapsed from surgery to conception.
Noteworthy, deep invasive peritoneal lesions (ie nodules infiltrating the peritoneum by >5 mm) were highly common in these published cases, being present in at least 9 out of 13 affected women.
Study design: Women with endometriosis who underwent IVF and who had a second evaluation after 3–6 months from a failed cycle were retrospectively reviewed. The main inclusion criteria were the presence of deep invasive endometriosis and/or a history of surgery for this form of the disease. The primary aim of the study was to determine the frequency of endometriosis-related complications in the interval between the two evaluations. Secondary aims were pain symptoms and lesion size modifications.

Results: Eighty-four women were ultimately selected: baseline ultrasound documented deep invasive lesions in 60 of them. One case of possible endometriosis-related complication was recorded, corresponding to a rate of 1.2% (95%: 0.05%–5.5%) for the whole cohort and 1.7% (95%CI: 0.08–7.6%) for the subgroup of women with ultrasound detected lesions. This rate appears similar to the reported frequency of endometriosis progression in women not receiving IVF. No significant modifications in pain symptoms or lesions size occurred.

Conclusions: Women with deep invasive endometriosis who underwent IVF do not seem to be exposed to a substantially increased risk of recurrence/disease progression. Larger evidence from independent groups is however required for a definitive conclusion.
Pregnancy Rates After Surgical Treatment of Deep Infiltrating Endometriosis in Infertile Patients With at Least 2 Previous In Vitro Fertilization or Intracytoplasmic Sperm Injection Failures

Pauline Breteau, MD, Isabella Chanavaz-Lacheray, MD, Chrystele Rubod, MD, PhD, Mélusine Turck, MD, Sophie Sanguin, MD, Ionut Pop, MD, Benoit Resch, MD, and Horace Roman, MD, PhD

ABSTRACT

Study Objective: To assess the postoperative probabilities of pregnancy in patients with deep infiltrating endometriosis (DIE) and ≥2 previous in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) failures.

Design: Retrospective study using data prospectively recorded in the North-West Inter Regional Female Cohort for Patients with Endometriosis (CIRENDO) database.

Setting: University tertiary referral center.

Patients: Infertile patients under the age of 43 years, having undergone ≥2 previous IVF or ICSI failures, who were surgically managed for DIE.

Interventions: Complete excision of DIE.

Measurements and Main Results: The pregnancy rate after surgery was assessed. One hundred and four infertile patients had surgery in 7 different centers participating in the database. Seventy-seven women intended to get pregnant postoperatively. Four patients who got pregnant by oocyte donation were excluded, resulting in a sample of 73 women. The mean patient age was 31.9 years (standard deviation [SD], 4.1), and the mean length of history of infertility was 48.4 months (SD, 26.5). Stage III and IV endometriosis were recorded in 83.6% of patients. The mean postoperative follow-up was 46.6 months (SD, 20.5). The postoperative pregnancy rate was 43.8% with a mean time from surgery to pregnancy of 11.1 months. 21.8% of pregnancies were spontaneous, 31.2% were obtained by IVF, 21.8% by frozen embryo transfer, 18.7% by IVF-ICSI, and 3.1% by intrauterine insemination. Multivariate analysis revealed that ovarian surgery, age ≥35 years old, and stage II endometriosis was associated with the probability of conception.

Conclusion: Infertile women with ≥2 IVF-ICSI failures may be referred for surgery as it appears related to reasonable postoperative pregnancy rates, particularly when endometriomas surgery is either not required or not performed. Surgery for DIE does not routinely delay conception, as it usually occurs during the year following surgery. Journal of Minimally Invasive Gynecology (2019) 00, 1–10. © 2019 AAGL. All rights reserved.
Deep Infiltrating Endometriosis: A Previous History of Surgery for Endometriosis May Negatively Affect Assisted Reproductive Technology Outcomes

Chloé Maignien 1 2, Pietro Santulli 3 4, Mathilde Bourdon 1 2, Diane Korb 1, Louis Marcellin 1 2, Marie-Charlotte Lamau 1, Charles Chapron 1 2 5

Abstract

For patients with endometriosis-related infertility, the impact of previous surgery for endometriosis before assisted reproductive technology (ART) remains controversial, particularly in cases of deep infiltrating endometriosis (DE). To study the impact of previous surgery for endometriosis on ART cumulative live-birth rates in DE patients, a retrospective cohort study included 222 DE patients who underwent ART. DE diagnosis was based on strict imaging criteria and histological confirmation of the disease for women with a previous history of surgery for endometriosis. ART outcomes were compared for patients with and without a previous history of surgery for endometriosis. The main outcome measures were cumulative live-birth rates (CLBR). Prognostic factors were identified by comparing women who became pregnant and those who did not, using an adjusted multiple logistic regression model. Two hundred twenty-two DE patients underwent a total of 440 ART cycles (including fresh and associated frozen-thawed embryo transfers). One hundred fifty-five women (69.8%) had a prior history of surgery for endometriosis. The CLBR was 26% after four ART cycles in the "previous history of surgery for endometriosis" group, while it reached 51.3% after four cycles (p < 0.001) in patients who had not previously undergone surgery for endometriosis. After multivariate analysis, a previous history of surgery for endometriosis (p = 0.001) and a past surgery for endometrioma (p = 0.005) were established as independent factors associated with lower pregnancy rates. Our preliminary results suggest that for DE patients, a previous history of surgery for endometriosis may be associated with negative ART outcomes.
Fig. 3. Clinical algorithm in women with deep endometriosis. IVF: in vitro fertilization; VAS: visual analog scale for pain symptoms; AMH: anti-Müllerian hormone.
DE-Infertility-Guidelines

• For infertile women with DE, ASRM, ACOG, ESHRE, and FEBRASGO guidelines suggest that the results of surgical resection of DE are controversial and do not recommend routinely performing surgical excision of DE.
• Spontaneous fertility of infertile patients with deeply infiltrating endometriosis found 10%. Treatment should be considered in infertile women with deeply infiltrating endometriosis when they wish to conceive.
• First-line IVF is a good option in case of no operated deeply infiltrating endometriosis associated infertility.
• The use of IVF in the indication "deep infiltrating endometriosis" allows satisfactory pregnancy rates without significant risk, regarding disease progression or oocyte retrieval procedure morbidity.
Nine cohort studies and one case–control study including 2896 women were included in this meta-analysis.

The risk of EP increased in women with endometriosis compared with those without endometriosis (the pooled RR, 2.81; 95 % CI, 2.48–3.18).
Recurrent Surgery

**Advantages**
- Spontaneous Pregnancy
- No increase in multiple pregnancy
- Decrease in pain
- Histologic diagnosis

**Disadvantages**
- Cost effectivity
- Morbidity (ovarian reserve)
- Increased time for pregnancy
- Need for qualified surgeon

ANY ROLE OF SURGERY IN RECURRENT ENDOMETRIOSIS? 
NO
If re-operation of recurrent ovarian endometriomas

- Only 25% of women conceive (half of the primary surgery) after repeated surgery

  Berlanda et al Curr Opin Obst Gyn 2010
  Del Forno et al J.Endometrios 2013

- Ovarian reserve (AMH,AFC)
- It has to be done in an expert center with an experienced surgeon
- All risks have to be explained to the patients
- In some cases, embryos or eggs frozen before the operation.

- When there is no risk of malignancy and no pain IVF should be preferred over surgery in these patients
What is the role of fertility preservation within endometriosis care?

• In cases of ovarian endometriosis (surely if recurrent), fertility preservation options should be at least proposed:
  • oocytes vitrification and/or ovarian tissue freezing
Fertility Preservation in Women With Endometriosis

Natalia C Llarena, Tommaso Falcone and Rebecca L Flyckt
Cleveland Clinic, Cleveland, OH, USA.

Figure 1. Practical approach to fertility preservation in presurgical endometriosis patients.
Endometriosis  Fertility Preservation  
Conclusion  

• Oocyte vitrification  
  ▪ YOUNG WOMEN  
  ▪ NO İMMEĐİATE PREGNANCY DESİRE  
• Bilateral endometrioma  
• Recurrent endometrioma  
• Altered ovarain reserve (AMH,AFC)  
• Infertile women after splitting with her partner  
• Routine ??
Eight studies were eligible. Ovarian endometriosis is associated with high recurrence rates after one ultrasonography-guided aspiration (28.9%–91.5%), but involves less ovarian manipulation.

The results of aspiration followed by sclerotherapy (95% ethanol, methotrexate, tetracycline and recombinant interleukin-2) are not uniform, but overall the addition of a sclerosing agent does not seem to significantly reduce the likelihood of recurrence (13.3%–75.0%).

Repeated aspiration of the cysts can reduce the recurrence rate to 5.4% by the sixth aspiration.
Eighteen studies were included in our review. The overall recurrence rates of endometrioma after sclerotherapy ranged from 0 to 62.5%. The risk of recurrence was significantly higher in women who were treated by means of ethanol washing than by means of ethanol retention.

The number of oocytes retrieved was higher after endometrioma sclerotherapy compared with laparoscopic cystectomy, but clinical pregnancy rates were similar.

There was no difference in the number of oocytes retrieved and the clinical pregnancy rates between the sclerotherapy-treated group with and the untreated group.

Conclusion(s): Sclerotherapy for ovarian endometrioma may be considered in symptomatic women who plan to conceive
ADENOMYOSIS
Adenomyosis may adversely impact fertility by its impact on myometrial contractility and/or via altered molecular expressions in the endometrium. Local hyperestrogenism is thought to be related to increased and dysfunctional peristalsis of the inner myometrium, leading to disruption of the integrity of the endometrial–myometrial interface, thereby facilitating growth of endometrium into the myometrium. This process is self-propagating as the mechanism of repair itself results in increased local levels of E₂. Adenomyosis may also reduce endometrial receptivity when it is associated with abnormal molecular expressionism, such as reduced levels of HOXA-10, -11 and increases or decreases in other factors thought or known to be important for implantation and early embryo development.

• Medline, Cochrane Central Register of Controlled Trials, and Google Scholar, identifying all related articles up to November 2016.

• We included 11 comparative studies that evaluated the clinical outcomes of IVF treatments in women with (519 patients) and without (1,535 patients) adenomyosis diagnosed with the use of magnetic resonance imaging or transvaginal ultrasound.
A) Clinical pregnancy rate per cycle in women without and with adenomyosis. (B) Ongoing pregnancy rate per cycle in women without and with adenomyosis. (C) Live birth rate per cycle in women without and with adenomyosis. (D) Miscarriage rate in women without and with adenomyosis.
**ADENOMYOSIS AND IVF**

**Miscarriage rate**

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benaglia et al</td>
<td>0.42 (0.07, 2.59)</td>
</tr>
<tr>
<td>Chiang et al</td>
<td>7.50 (0.84, 91.48)</td>
</tr>
<tr>
<td>Costello et al</td>
<td>0.40 (0.04, 2.18)</td>
</tr>
<tr>
<td>Martinez et al</td>
<td>2.50 (1.37, 4.64)</td>
</tr>
<tr>
<td>Mijatovic et al</td>
<td>0.65 (0.12, 3.28)</td>
</tr>
<tr>
<td>Salim et al</td>
<td>35.00 (1.74, 576.62)</td>
</tr>
<tr>
<td>Thakuri et al</td>
<td>2.89 (0.05, 40.04)</td>
</tr>
<tr>
<td>Yan et al</td>
<td>2.24 (0.71, 7.21)</td>
</tr>
<tr>
<td>Youm et al</td>
<td>7.34 (2.66, 20.04)</td>
</tr>
<tr>
<td><strong>Combined [fixed]</strong></td>
<td><strong>2.20 (1.53, 3.15)</strong></td>
</tr>
</tbody>
</table>

**OR=2.20 (95% CI: 1.53-3.15)**
The impact of adenomyosis on the outcome of IVF–embryo transfer

Dimitrios Mavrelos a,*, Tom K Holland b, Oliver O’Donovan a, Mohamed Khalil b, George Ploumidis c, Davor Jurkovic a, Yakoub Khalaf b

a Reproductive Medicine Unit, University College London Hospitals, London, UK
b Guy’s St Thomas’ Hospital, London, UK
c Institute of Education, University College London, UK

Table 2 – Logistic regression results with each level of adenomyosis score as independent variable and clinical pregnancy as dependent variable. Reference category is no adenomyosis features and all variables are entered in the model.

<table>
<thead>
<tr>
<th>Number of ultrasonic adenomyosis features [score] (n)</th>
<th>Odds ratio of clinical pregnancy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single adenomyosis feature [1] (10)</td>
<td>0.85 (0.23–3.20)</td>
</tr>
<tr>
<td>Two features [2] (15)</td>
<td>0.95 (0.31–2.80)</td>
</tr>
<tr>
<td>Three features [3] (8)</td>
<td>1.00 (0.23–4.60)</td>
</tr>
<tr>
<td>Four features [4] (8)</td>
<td>0.22 (0.26–1.80)</td>
</tr>
<tr>
<td>Five features [5] (17)</td>
<td>0.39 (0.12–1.30)</td>
</tr>
<tr>
<td>Six features [6] (11)</td>
<td>0.30 (0.07–1.60)</td>
</tr>
<tr>
<td>Seven features [7] (3)</td>
<td>0.24 (0.09–6.40)</td>
</tr>
</tbody>
</table>

Table 3 – Calculated probability of clinical pregnancy at each level of adenomyosis score based on a logistic regression model with clinical pregnancy as dependent variable and adenomyosis score as a continuous independent variable (odds ratio 0.80 [95% confidence interval 0.70–0.91]).

<table>
<thead>
<tr>
<th>Adenomyosis score</th>
<th>Clinical pregnancy rate (% n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>42.7 (37.1–48.3)</td>
</tr>
<tr>
<td>One</td>
<td>37.2 (32.0–42.5)</td>
</tr>
<tr>
<td>Two</td>
<td>32.4 (26.0–38.6)</td>
</tr>
<tr>
<td>Three</td>
<td>27.3 (19.1–35.5)</td>
</tr>
<tr>
<td>Four</td>
<td>22.9 (13.4–32.6)</td>
</tr>
<tr>
<td>Five</td>
<td>19.2 (8.6–29.7)</td>
</tr>
<tr>
<td>Six</td>
<td>15.9 (4.9–26.8)</td>
</tr>
<tr>
<td>Seven</td>
<td>13.0 (2.2–23.9)</td>
</tr>
</tbody>
</table>
Presence of adenomyosis seems to have adverse effects on IVF outcomes in clinical pregnancy rate, live birth rate and miscarriage rate.
The rate of euploid miscarriage is increased in the setting of adenomyosis

V. Stanekova 1,*, R.J. Woodman 2, and K. Tremellen 1,3

1College of Medicine and Public Health, Flinders University, Sturt Road, Bedford Park, South Australia 5042, Australia 2Flinders Centre for Epidemiology and Biostatistics, Sturt Road, Bedford Park, South Australia 5042, Australia 3Repromed, 180 Fullarton Road, Dulwich, South Australia 5065, Australia

STUDY DESIGN, SIZE, DURATION: A retrospective cohort study was undertaken in a private infertility (IVF) clinic examining the outcome for women (n = 345) undergoing the transfer of a genetically screened frozen–thawed embryo between 2012 and 2015.

PARTICIPANTS/MATERIALS, SETTING AND METHOD: A total of 171 women who successfully conceived (positive serum βhCG) following the transfer of a single euploid good morphology frozen–thawed embryo were included in analysis after meeting the inclusion criteria. Only the first conception cycle for each patient was included in the study. Patients with known pre-existing medical risk factors for miscarriage (e.g. thrombophilia, poorly controlled diabetes, coeliac disease, SLE, uterine septum, chromosomal abnormalities) and those women undergoing treatment using donated oocytes and surrogacy were excluded. Patients were then classified as having adenomyosis or not based on a high-quality pelvic ultrasound or MRI. The direct and indirect effects of adenomyosis and BMI on overall miscarriage rate by 12 weeks gestation was then assessed using multivariate logistic regression and mediation analysis. Furthermore, the data were also analysed to elucidate the influence of GnRH ultra-long down-regulation therapy on miscarriage rates.

MAIN RESULTS AND ROLE OF CHANCE: Overall, the adjusted rate of miscarriage was higher in those patients with adenomyosis compared to those without (44.1 vs 15.3%, P < 0.0001), with most of these miscarriages occurring at the early biochemical stage. The rate of miscarriage was especially high in adenomyosis patients not receiving GnRH agonist pre-treatment (82.4%), compared to those patients who did receive GnRH pre-treatment (35.7%, P = 0.0089).
GnRH-a use in adenomyosis

- First reported in 1991
- Biopsy proven adenomyosis, 6 months
  Leuprolide acetate 1mg/d
- Decreased the uterine size by 67%

(Grow DR, Filer RB, ObstetGynecol 1991)

- Not only cause shrinkage but also increase endometrial receptivity

(Hirata JD, FertilSteril 1993)
The Impact of Adenomyosis on Women’s Fertility

Tasuku Harada, MD, PhD, DMSci,*, Yin Mon Khine, MB, BS,† Apostolos Kaponis, MD, PhD,‡ Theocharis Nikellis, MD,§ George Decavalas, MD, PhD,|| and Fuminori Taniguchi, MD, PhD||

### TABLE 1
Successful Pregnancies After GnRH-a in Women With Adenomyosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Treatment Period With GnRH-a</th>
<th>Pregnancy Outcome</th>
<th>Duration of Infertility</th>
<th>Interval Between Spontaneous Pregnancy and Completed Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson and Corson²⁴</td>
<td>1</td>
<td>Over 3-year period</td>
<td>Viable first-trimester pregnancy</td>
<td>No infertility</td>
<td>1 month</td>
</tr>
<tr>
<td>Silva et al.²⁵</td>
<td>1</td>
<td>5 months</td>
<td>Cesarean section at term</td>
<td>10 years</td>
<td>5 months</td>
</tr>
<tr>
<td>Huang et al.²⁶</td>
<td>2</td>
<td>3 months</td>
<td>Term, healthy infant, vaginal and cesarean section</td>
<td>2 years and 4 years</td>
<td>4 to 6 months</td>
</tr>
<tr>
<td>Wang et al.²⁷</td>
<td>37</td>
<td>6 months</td>
<td>Cumulative 3-year pregnancy rate, 10.8% (4/37); cumulative 3-year successful delivery rate, 8.1% (3/37)</td>
<td>&gt;3 years</td>
<td>&lt;12 months</td>
</tr>
<tr>
<td>Al Jama et al.²⁸</td>
<td>22</td>
<td>6 months</td>
<td>Spontaneous abortion, 1; ectopic, 1; vaginal; term, 1</td>
<td>6–15 years</td>
<td>5–18 months</td>
</tr>
</tbody>
</table>

N, number of women who intended pregnancy.
GnRH agonist improves pregnancy outcome in mice with induced adenomyosis by restoring endometrial receptivity

Materials and methods: Adenomyosis was induced in 12 female ICR mice, neonatally treated with tamoxifen, while another six female mice (control group) received solvent only. At 75 days, the induced adenomyosis group was randomly divided into two groups: an untreated group and a group treated with GnRH agonist (n = 6 each). Sixty days later, the mice were mated and pregnancy outcomes were observed and compared among the three groups (n = 6 each). In a parallel experiment using the same treatment regimes, uterus samples were collected on day 4 of pregnancy for immunohistochemistry, gene (quantitative polymerase chain reaction) and protein expression (Western blot), and scanning electron microscopy analyses.

Results: We found that the average live litter size was reduced in the adenomyosis compared with control group (8 ± 0.56 versus 13 ± 0.71; P = 0.03). However, the litter size was significantly increased in the treated with GnRH agonist group compared with the untreated group (12 ± 0.35 versus 8 ± 0.56; P = 0.04). The uterine expression levels of Hoxa10, Hoxa11, Lif and integrin b3 mRNA and protein were decreased in the adenomyosis group, and were significantly increased after GnRH agonist treatment. Additionally, pinopodes were reduced in number and poorly developed in mice with induced adenomyosis. However, pinopodes were abundant and well-developed in the GnRH agonist treatment group.

Conclusion: Adenomyosis may have an adverse impact on endometrial receptivity and reduce pregnancy outcomes in mice. However, GnRH agonist may improve the pregnancy outcome by partially restoring endometrial receptivity.
Six studies evaluated surgical treatments of adenomyosis. When considering only spontaneous pregnancies, the overall clinical pregnancy rate was very low (18.2%). However, when using GnRH analogues for 24 weeks after surgery, the pooled spontaneous pregnancy rate was higher (40.7% vs 15.0%; P ¼ .002).
Effect of pretreatment with a levonorgestrel-releasing intrauterine system on IVF and vitrified–warmed embryo transfer outcomes in women with adenomyosis

LEVONORGESTREL-IUD

- Retrospective cohort study
- Adenomyosis by US and MRI
- 1° Frozen embryo transfer

![Graph showing pregnancy and live birth rates with comparison between LNG-IUD and controls.](graph.png)

LNG-IUD 3 months then ET (n=134)

ET straight (n=224)

Liang et al., RBMO, 2019

Zhou Liang, Mingru Yin, Meng Ma, Yun Wang*, Yanping Kuang*

Zhou Liang, Mingru Yin, Meng Ma, Yun Wang* and Yanping Kuang*

Department of Assisted Reproduction, Shanghai Ninth People’s Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

**Methods:** Data collected on 22,865 women undergoing IVF using a freeze-all strategy from 2007 to 2017 were analyzed to estimate the rate of congenital malformations. We used an adjusted OR to compare the fertility outcomes of women with advanced endometriosis to the control group.

**Results:** We studied 1,495 infants born from women with advanced endometriosis and 27,105 infants born from endometriosis-free women. There was a 1.557-fold risk that the infants with advanced maternal endometriosis would develop a congenital malformation (adjusted OR: 1.557, 95% CI: 1.03–2.35). Compared with singletons, twins were 1.957 times more likely to experience an adverse outcome (OR: 1.957, 95% CI: 1.561–2.455). When analyzing specific categories of birth defects, the proportion of circulatory system defects was higher than the other categories of birth defects in total (0.56%), followed by musculoskeletal system defects (0.15%).

**Conclusions:** Maternal advanced endometriosis might increase the risk of congenital malformations for infants born after IVF-ET. The organ system most frequently affected by congenital malformations was the cardiovascular system, followed by the musculoskeletal system.
## Complications of a Pre-Existing Endometriosis During Pregnancy

<table>
<thead>
<tr>
<th>System</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI System</td>
<td>Appendicitis, Intestinal Perforation</td>
</tr>
<tr>
<td>Vascular</td>
<td>Spontaneous Hemoperitoneum</td>
</tr>
<tr>
<td>Urinary System</td>
<td>Uroperitoneum</td>
</tr>
<tr>
<td>Adnexal</td>
<td>Infected Endometrioma, Enlarged endometrioma, Rupture of endometrioma</td>
</tr>
<tr>
<td>Uterine</td>
<td>Uterine rupture</td>
</tr>
</tbody>
</table>
Endometriosis and Risk of Adverse Pregnancy Outcomes


Nurses Health Study II Data (187, 867 Controls vs 8875 Endometriosis)

Endometriosis was associated with a **greater risk of**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pregnancy loss:</td>
<td>1.40, 95% CI 1.31–1.49</td>
</tr>
<tr>
<td>Ectopic pregnancy:</td>
<td>1.46, 95% CI 1.19–1.80</td>
</tr>
<tr>
<td>Greater risk of GDM:</td>
<td>1.35, 95% CI 1.11–1.63</td>
</tr>
<tr>
<td>Hypertensive disorders of pregnancy:</td>
<td>1.30, 95% CI 1.16–1.45</td>
</tr>
</tbody>
</table>
A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes

Umberto Leone Rosati Maggiore, Simone Ferrero, Giorgia Mangili, Alice Bergamin, Annalisa Inversetti, Veronica Giorgioni, Paola Viganò, and Massimo Candiani

"There is no evidence that prophylactic surgery would prevent the negative impact of endometriosis itself on pregnancy outcome"
For the young colleagues

‘It does not matter how slowly you go, as long as you don’t stop’

Confucius, 551-479 BC
ESHRE campus workshop
Istanbul, 11-13 March, 2021

Adenomyosis: What we know, and what we don’t know

11-13 March 2021 | Istanbul, Turkey

Course description
State-of-the-art view on pathogenic mechanism and clinical management of patients with adenomyosis

Read more

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Controversies in endometriosis and adenomyosis
SIG Endometriosis / Endometrium in association with the Turkish Society of Endometriosis and Adenomyosis
Istanbul, Turkey
26-28 February 2016