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MINI-REVIEW

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Endometriosis and Reproduction: What We Have Learned

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Endometriosis, despite only affecting 10-15% of women of fertile age, is still an enigmatic disease. Recent developments in assisted reproductive technology have contributed to a better understanding of where and how endometriosis could compromise fertility. In this mini-review we will show how the main point of damage in endometriosis is quantitative impairment of the ovaries, if the "less is more" mantra should be applied when considering ovarian surgery, and when fertility preservation prior to ovarian surgery could be considered. Endometrial receptivity, however, does not seem to be affected.

INTRODUCTION

Although endometriosis was described in the late 1800s, we still do not fully understand why this progressive disease, characterized by the appearance of endometrial tissue – glands and stroma – outside the endometrial cavity, is present only in some women and not in others. Its huge clinical variability in symptoms and technical difficulty to diagnose precisely in its early stages makes diagnosis only possible when the disease is quite advanced and already producing pelvic pain and/or infertility in patients [1].

Still today, there is a 5- to 10-year delay from the onset of symptoms to the clinical diagnosis of endometriosis [2]. It affects around 10-15% of women of fertile age, so it is not an uncommon disease that may be present in women from menarche to menopause, and even in women beyond menopause, in some exceptional cases [3]. Unfortunately, early stages of the disease will cause very unspecific symptoms, mainly pelvic pain. It represents one of the most common causes of chronic pelvic pain, dysmenorrhea, and infertility [4]. This pain may impair the quality of life of affected women, especially with their partners, their families, and at work. Endometriotic lesions will grow within the peritoneum and ovaries, and the fibrosis induced by this will affect nerve fibers causing pain. These endometriotic lesions are influenced by the menstrual cycle, as they have both endometrial glands and stroma. Thus, in each menstruation the lesions may bleed, causing inflammation and fibrosis in the nearby tissues, such as ovaries, pelvic organs (ureter, bladder, bowel, and intestines), pelvic peritoneum, and/or rec-

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Abbreviations: GnRH, gonadotropin releasing hormone; OC, Oral Contraceptive; ASRM, American Society for Reproductive Medicine; EFI, Endometriosis Fertility Index; ART, assisted reproductive treatment; AFC, antral follicle count; AMH, Anti-Müllerian hormone.

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tovaginal septum [4]. Thus, endometriosis can be divided into three main types: **peritoneal**, **deep infiltrating**, and **ovarian**, and these frequently coexist [5]. But, unless the physician has endometriosis in their differential diagnosis of pelvic pain in young women, the patient will be treated with pain killers, non-steroidal anti-inflammatory drugs (NSAIDs), or even oral contraceptive pills (OCPs), in order to minimize pelvic pain and dysmenorrhea.

Medical therapy is aimed at alleviating the symptoms and reducing the size of the lesions, thus improving the patient's quality of life [6]. Although many drugs and minimally invasive techniques with different side-effects have been tried to date, no agent has been found to be objectively superior to the rest. In fact, given that most interfere with estradiol secretion and ovulation, they may interfere with fertility as well.

A very common practice was to administer a depot of gonadotropin releasing hormone (GnRH) agonist, leading to down-regulation of GnRH receptors and generating a hypogonadotropic hypogonadism state in the body, hence improving the endometriotic lesions due to low estradiol levels [6]. New oral GnRH antagonists, which do not completely suppress estradiol secretion, may be an alternative with less side effects than the agonists [7].

Oral Contraceptive (OC) pills have been shown to have beneficial effects due to their suppressive action [8]. Progestins are also an option in patients with endometriosis due to their anti-proliferative and anti-inflammatory properties [8]. Resveratrol, among other natural remedies, is a natural phytoalexin synthesized by plants in response to ultraviolet radiation and fungal infections which has been proposed as potential treatment for endometriosis due to its anti-inflammatory, anti-oxidative, and anti-angiogenic properties [8].

Finally, minimally invasive surgery is usually the best option for women with extensive endometriosis and excruciating pain [3,9]. Careful laparoscopic excision of the endometriotic lesions and scar tissue, avoiding damage to the surrounding tissues, will in most cases, reduce pain and improve quality of life. Special care should be taken when removing lesions from the ovaries in order to avoid reducing the ovarian reserve in young women. In fact, spontaneous pregnancy after surgery in a population of women with severe endometriosis may be up to 73% [3], but this may not be exactly the same in infertile women with endometriosis.

BUT HOW DOES THIS DISEASE AFFECT FERTILITY?

It is important to note that not all women with endometriosis suffer from infertility. However, the prevalence of the disease is much higher in infertile women (around 30-40%) than in the fertile population (10-15%) [10]. This does not mean that all women with endometriosis will have difficulty having children, and vice versa, not all infertile women have endometriosis. In fact, young women with endometriotic ovarian cysts showed a similar ovulation rate in the healthy ovary than in the affected ovary (49.7 vs 50.3%, p=ns), and a spontaneous pregnancy rate of 43% in 4 years [11]. The problem, most of the time, is that women/couples do not want to wait so long to get pregnant, or that due to their advanced age, this may not be advisable.

This spontaneously reduced fertility in women with endometriosis may be due to different pathomechanisms [12]. If there are major mechanical distortions of the pelvis with extensive disease and pelvic adhesions that may even embed the ovaries, mechanical occlusion of the fallopian tubes may be the main reason. However, alternative mechanisms should be considered in the absence of major pelvic disease. Possible causes for reduced fertility in these women might be minor adhesions, chronic intraperitoneal inflammation – a characteristic feature of endometriosis, disturbed folliculogenesis, luteal phase defects, the interesting theory of progesterone resistance due to a reduced expression of progesterone receptors in the endometrium, dysfunctional uterotubal motility, and differences in immunological changes. Changes including anti-endometrial antibodies and increased concentrations of interleukin 1β, 6, 8 and 10, and TNF-α, which may contribute to sperm DNA damage, interfere in sperm-oocyte interactions and embryo development, and compromise implantation [12].

According to the American Society for Reproductive Medicine (ASRM) classification, which created a score system based on extension of the disease, endometriosis is classified in four stages: minimal, mild, moderate, or severe [13]. Despite this being the most accepted classification for endometriosis, it unfortunately does not show a good correlation with fertility: some patients with mild disease have difficulties having children whereas women in stage IV (severe disease) may still be fertile. So, in 2010, Adamson *et al*. [14] created the Endometriosis Fertility Index (EFI), a much more precise and robust staging system to estimate fertility in women with endometriosis. It does require laparoscopy – as the ASRM classification does – but also takes into consideration the ASRM stage plus the function of the fallopian tubes, fimbria, and ovaries, the age of the patient the duration of infertility, and if the patient has had prior pregnancies. An EFI score of 10 suggests a 75% pregnancy rate after 36 months, but only 5-10% if their EFI score was 1. This index is helpful for developing treatment plans in infertile patients with endometriosis. With the EFI score and the prognosis regarding spontaneous pregnancy in the coming years that it provides, the doctor can discuss with their patients the plan for the next coming months: how long it would be

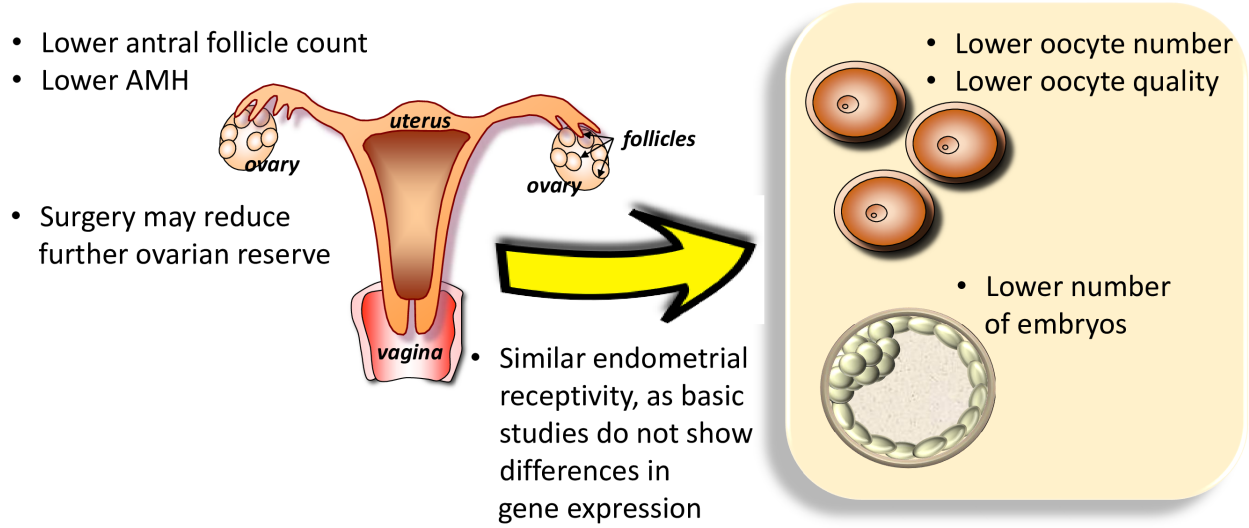

Figure 1. Different areas whereas endometriosis may impact human reproduction.

reasonable to wait prior to initiating fertility treatments, if pregnancy does not happen, when to start and how (ovarian stimulation, timed intercourse, intrauterine insemination…), what to expect for these treatments and success rates, and when, if needed, would be reasonable to move to IVF.

Many infertile women with endometriosis require assisted reproductive treatment (ART) to get pregnant, and this has been a great learning tool to understand how endometriosis affects fertility.

This disease may affect the reproductive process in almost all aspects (Figure 1), but we will focus on those where the evidence is convincing enough to prove a causal relationship.

LOWER OVARIAN RESERVE

One of the main prognostic factors regarding fertility is the woman's age. In fact, this is the only qualitative marker. Generally speaking, women under 35 years old have fairly good fertility, from 35 to 40 years of age, fertility starts to decline rapidly, and after 40 it is extremely difficult to have a child [15]. Maternal age is probably the best qualitative marker of oocyte quality and fertility. With the recent trend to postpone maternity and start families at a later age, it becomes crucial to have a quantitative marker as well. Today, the best quantitative markers of ovarian reserve are antral follicle count (AFC), done by transvaginal ultrasound and Anti-Müllerian hormone (AMH), evaluated in serum [16].

Endometriosis mainly affects the ovaries, reducing the healthy tissue as it grows into the ovaries, even though it is a benign but progressive disease. This will reduce the ovarian reserve of the patient. There is plenty of data showing that women with endometriosis have a lower ovarian reserve, lower AFC and lower AMH concentrations, especially in advanced disease (*i.e.* when bilateral ovarian cysts – endometriosis – are present) [17,18].

IMPACT OF OVARIAN SURGERY ON FERTILITY AND OVARIAN RESERVE

The old paradigm "when in doubt, cut it out" does not work in endometriosis. Classically, if an ovarian endometriotic cyst was visible in ultrasound, and the patient had infertility, surgery was the first approach [19]. The cyst was removed, but also a safety margin around the cyst, reducing even more the healthy tissue available, and consequently, reducing the ovarian response to ovarian stimulation. Using women who had unilateral endometriotic cyst removed by laparoscopy as a model, several studies have shown operated ovaries having a lower AFC, lower number of developing follicles, and a significantly higher risk of no response to the ovarian stimulation when compared to the contralateral healthy ovary [20-22]. In a pioneering work combining data from Yale University and our group IVI in Spain, we demonstrated that surgery prior to ART did not improve the chances

of pregnancy, increased the costs, increased the time to pregnancy, reduced the ovarian reserve even more, and exposed the patient to surgical risks [23]. Surgery should only be considered if the patient is symptomatic (pain), the cyst has suspicious malignant characteristics in the ultrasound (rapid growth, vascularization, etc.), or she is very young and has at least one year to consider spontaneous pregnancy [24]. In addition, if the patient has already had ovarian surgery due to endometriosis and needs another surgery (recurrence of cysts, pelvic pain refractory to medical treatment, etc.), the ovarian reserve will be affected even further [25]. In fact, today, the European guidelines suggest advising women who undergo ovarian surgery for endometriosis about the impact on the ovarian reserve before performing the surgery [26]. Therefore, when discussing surgery in women with endometriosis, we could summarize with the saying "less is more".

OOCYTE AND EMBRYO QUALITY

There is plenty of evidence from animal models that clearly show a lower oocyte quality in women with endometriosis. When mice oocytes are exposed to peritoneal fluid from women with endometriosis, chromosome misalignment and spindle aberrations were observed with confocal microscopy, having a higher impact as the stage of the disease advanced [27]. Similarly, when endometriosis is induced in mice models, these mice showed a lower proportion of normal oocytes (61 vs 83%, $p<0.001$), with a higher percentage of spindle abnormalities, and incomplete extrusion of 1st polar body. They also showed a lower number of zygotes per mouse (21 vs 35.5, $p=0.02$), but similar embryo quality, suggesting a lower oocyte quality and, thus, a lower embryo number [28].

When looking into the follicular milieu of these patients, women with endometriosis showed a pro-oxidative shift in their oxidative stress system, and a pro-inflammatory status [29]. Electron microscopy showed abnormal mitochondria structures, decreased mitochondrial mass, and a lower mitochondrial DNA copy number [30]. Similarly, cumulus cells from women with endometriosis produced a significantly lower amount of ATP per total DNA. This suggests that reduced energy production has a role in the decrease of oocyte quality [31].

A recent contribution to this debate about the questionable oocyte quality in women with endometriosis showed that oocytes from women with endometriosis display a different transcriptome behavior, with differentially expressed genes when they were compared with women without endometriosis [32]. Pathways involved included key biological processes and molecular functions related to steroid metabolism, response to oxidative stress and cell growth regulation, which might explain this reduced oocyte quality.

All this basic information provides a rationale to consider that women with endometriosis have a lower oocyte quality. However, this does not seem to have a clear clinical impact based on two relevant pieces of information. First, when considering large registries of assisted reproductive treatment from the ASRM, after reviewing around 350,000 cycles, it was shown that women with endometriosis do have a lower oocyte yield (lower response to medication), but not a lower success rate, suggesting a quantitative rather than qualitative damage of the disease on the ovaries [33]. On the other hand, we are all aware that embryo aneuploidy is the major cause for failed IVF cycles: our group recently demonstrated that women with endometriosis do not have a higher incidence of aneuploidy when compared with healthy women across all age strata, again suggesting a quantitative impact only [34].

ENDOMETRIAL QUALITY

One of the reasons why endometriosis affects fertility could be by generating endometrial changes that can hamper embryo implantation, as it is a steroid based disease. Early basic studies identified molecular differences in the endometrium of these women: differences in transcriptomic signature revealed an upregulation of genes related with DNA synthesis and cellular mitosis, which would fit it in a chronic, progressive disease; and downregulation of genes related with progesterone response, which would make sense within the context of the "progesterone resistance" theory [35].

But then again, clinical data suggested otherwise. On one hand, the oocyte donation model showed that patients with severe endometriosis who receive donated oocytes from a healthy donor had comparable success rates as recipients without endometriosis, confirming that it is the oocyte but not the endometrium that may be affected in endometriosis [36]. On the other hand, a transcriptomic analysis of the endometrium in women with endometriosis, focusing on the days of peak receptivity, and analyzing 238 genes directly implicated in embryo implantation, did not show any difference between women with or without endometriosis [37].

QUALITY OF LIFE DURING FERTILITY TREATMENT

As this disease is estrogen dependent, it may seem reasonable to think that ovarian stimulation for fertility treatment may induce disease progression, cyst growth, and consequently, a deterioration of the quality of life of patients. Nonetheless, data is reassuring regarding patient safety. Indeed, it has been shown that ovarian endometriotic cysts do grow during the ovarian stimulation cycle; however, such a short duration of hormonal stimulation

(7 to 10 days) induces a minimal growth (22.2ml at the beginning of the cycle vs 24.9 at the time of the trigger), so differences are clinically irrelevant [38]. Even more convincing is the work done in Belgium by D'Hooghe *et al*. [39] doing a laparoscopy at the beginning of the fertility treatments and another laparoscopy when treatments were finalized. No deleterious impact of ovarian stimulation for IVF using the ASRM classification of the disease was found in this study.

Finally, Benaglia *et al*. [40] did a quality of life assessment in women with endometriosis undergoing fertility treatment. They assessed whether ovarian stimulation had an impact on the symptoms' progression, such as pelvic pain, dyspareunia, dysmenorrhea, etc. They demonstrated that symptoms are not aggravated by the ovarian stimulation, as probably duration is too short to have any impact.

An interesting concept is how this disease may affect pregnancy itself. There has been a long discussion regarding the risk of miscarriage in these patients, and today it seems that this risk is similar to the general population. However, there is slightly increased obstetrical risk in women with endometriosis [41]. For instance, during pregnancy decidualization of bowel lesions may happen creating bowel obstruction. But these severe complications are rare and unpredictable.

FUTURE PERSPECTIVE

Endometriosis is a progressive disease, although progression varies among individuals [11]. As we are currently unable to predict which patients will have a very aggressive growth of their disease, there is a tendency to treat young women diagnosed with endometriosis with either progestins or oral contraceptive pill in a continuous protocol – without placebo – in order to avoid the monthly bleeding, and hypothetically, contributing to the control of the disease. However, recurrence of the disease may happen even under these hormonal treatments [42].

Fertility preservation is an attractive alternative which gives women the option of having a child with their own gametes when they are at risk of premature depletion of their ovarian reserve. The first indication for this were oncological patients, especially those receiving alkylating agents causing high risk of premature ovarian failure as a secondary effect [43].

Today, fertility preservation is discussed prior to their oncological treatment and those who opt to freeing their oocytes, in case they enter premature menopause after the chemotherapy, can have their own children without considering oocyte donation [43]. Still, the return rate – women who froze their oocytes and after failing to conceive at home spontaneously, came back to use their oocyte in an IVF cycle – is low: 6 to 12%. Some women do get pregnant spontaneously, some do not survive the disease, for others it may still be too early for them to use their frozen oocytes, and some will never come back to use them [43].

Another indication are women who decide to postpone maternity for many different reasons [44]. Here also the return rate is still low. Our group recently published the first study on fertility preservation in women with endometriosis. Being a progressive disease, women with endometriosis are at risk of premature reduced ovarian reserve, so oocyte vitrification is a valid alternative to increase their reproductive chances. We recently analyzed data from 485 women who underwent fertility preservation for endometriosis at our institution [45]. Mean age was 35.7 years, and those patients who underwent surgery prior to oocyte freezing had a younger age (33.4 vs 36.7 years, $p < 0.05$). The number of oocytes obtained, as well as the cumulative live birth rate, was significantly higher in women who vitrified their oocytes before surgery, and not after surgery. In this group of patients, we observed a higher return rate than in oncological patients or social freezers, which could suggest that, in these patients, the vitrification of oocytes was performed as an adjuvant option within the treatment of endometriosis-related infertility. Thus, the advantage of fertility preservation in young women with endometriosis is that they can obtain a good number of mature oocytes, and especially if the procedure is done prior to surgery.

CONCLUSIONS

Endometriosis has been described for many decades, and it has been often linked to infertility. The impact of endometriosis on fertility is mainly quantitative damage to the female reproductive tract, reducing ovarian reserve, oocyte and embryo quality, and quality of life, thus interfering with fertility. Even though there is a biological rationale for a lower oocyte quality as shown in basic research, this does not seem to translate when clinical data is analyzed. Treatments should be tailored carefully, as surgery does not improve the results of ART. It should be carefully performed when the patient is symptomatic, as it may further reduce their ovarian reserve. Today, fertility preservation could be discussed with the patient prior to their surgery so they could vitrify their oocytes and have a valid alternative to have children in case surgery and/or disease progression compromises their ovarian reserve.

REFERENCES

1. Sampson JA. Perforating hemorrhagic (chocolate) cysts of ovary. Their importance and especially their relation to pelvic adenomas of endometriotic type ("adenomyoma" of the uterus, rectovaginal septum etc.). Arch Surg. 1921;3:245–61.

2. van der Zanden M, Arens MW, Braat DD, Nelen WL, Nap AW. Gynaecologists' view on diagnosis delay and care performance in endometriosis in the Netherlands. Reprod Biomed Online. 2018;37:761–8.
3. Nesbitt-Hawes EM, Campbell N, Maely PE, et al. The surgical treatment of severe endometriosis positively affects the chance of natural or assisted pregnancy postoperatively. BioMed Res Int. 2015;2015:438790.
4. De Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. Lancet. 2010;376:730–8.
5. Zondervan K, Becker C, Missmer S. Endometriosis. N Engl J Med. 2020;382:1244–56.
6. Giudice L, Kao LC. Endometriosis. Lancet. 2004;364:1789–99.
7. Taylor HS, Giudice L, Lessey B, Abrao M, Kotanski J, Archer D, et al. Treatment of endometriosis-associated pain with Elagolix, and oral GnRH antagonist. N Engl J Med. 2017;377:28–40.
8. Schwartz K, Llarena N, Rehmer J. Richards, Falcone T. The role of pharmacotherapy in the treatment of endometriosis across the lifespan. Expert Opin Pharmacother. 2020;21:893–903.
9. Abbot J. Surgical treatment is an excellent option for women with endometriosis and infertility. Aust N Z J Obstet Gynaecol. 2017;57:679–81.
10. Ceccino GN, Garcia-Velasco JA. Endometrioma, fertility, and assisted reproductive treatments: connecting the dots. Curr Opin Obstet Gynecol. 2018;30:223–8.
11. Leone Roberti Maggiore U, Scala C, Venturini P, et al. Endometriotic ovarian cysts do not negatively affect the rate of spontaneous ovulation. Hum Reprod. 2015;30:299–307.
12. Chapron C, Marcellini L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. Nat Rev Endocrinol. 2019;15:666–82.
13. American Fertility Society. Revised American Fertility Society classification of endometriosis. Fertil Steril. 1985;43:351–2.
14. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010;94:1609–15.
15. Richardson MC, Guo M, Fauser BC, Macklon NS. Environmental and developmental origins of ovarian reserve. Hum Reprod Update. 2014;20:353–69.
16. Iliodromiti S, Nelson SM. Ovarian response biomarkers: physiology and performance. Curr Opin Obstet Gynecol. 2015;27:182–6.
17. Nieweglowska D, Hajdyla-Banas I, Pitynski K, et al. Age-related trends in anti-Mullerian hormone serum level in women with unilateral and bilateral ovarian endometriomas prior to surgery. Reprod Biol Endocrinol. 2015;13:128.
18. Nezhat C, Silfen S, Nezhat F, Martin D. Surgery for endometriosis. Curr Opin Obstet Gynecol. 1991;3:385–93.
19. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:3146–54.
20. Almog B, Shehata F, Sheizaf B, et al. Effect of different types of ovarian cyst on antral follicle count. Fertil Steril. 2010;94:2338–9.
21. Ragni G, Somigliana E, Benedetti F, et al. Damage to ovarian reserve associated with laparoscopic excision of endometriomas: a quantitative rather than a qualitative injury. Am J Obstet Gynecol. 2005;193:1908–14.
22. Somigliana E, Infantino M, Benedetti F, et al. The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins. Fertil Steril. 2006;86:192–6.
23. Garcia-Velasco JA, Mahutte N, Corona J, et al. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case–control study. Fertil Steril. 2004;81:1194–7.
24. Garcia-Velasco JA, Somigliana E. Endometrioma and IVF: to touch or not to touch. Hum Reprod. 2009;24:496–501.
25. Ferrero S, Scala C, Racca A, et al. Second surgery for recurrent unilateral endometriomas and impact on ovarian reserve: a case-control study. Fertil Steril. 2015;103:1236–43.
26. Dunselman G, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29:400–12.
27. Mansour G, Sharma RK, Agarwal A, Falcone T. Endometriosis-induced alterations in mouse metaphase II oocyte microtubules and chromosomal alignment: a possible cause of infertility. Fertil Steril. 2010;94:1894–9.
28. Cohen J, Ziyyat A, Naoura I, Chabbert-Buffet N, Aractingi S, Darai E, et al. J Assist Reprod Genet. 2015;32:263–70.
29. Prieto L, Quesada JF, Cambero O, Pacheco A, Pellicer A, Codoceo R, et al. Fertil Steril. 2012;98:126–30.
30. Xu B, Guo N, Zhang M, Shi W, Tong XH, Iabal F, et al. Oocyte quality is decreased in women with minimal or mild endometriosis. Sci Rep. 2015;5:10779.
31. Hsu AL, Townsend PM, Oehninger S, Castora FJ. Endometriosis may be associated with mitochondrial dysfunction in cumulus cells from subjects undergoing in vitro fertilization-intracytoplasmic sperm injection, as reflected by decreased adenosine triphosphate production. Fertil Steril. 2015;103:347–52.
32. Ferrero H, Corachan A, Aguilar A, Quiñonero A, Carbajo-Garcia MC, Alama P, et al. Single-cell RNA sequencing of oocytes from ovarian endometriosis patients reveals a differential transcriptomic profile associated with lower quality. Hum Reprod. 2019.
33. Senapati S, Sammel M, Morse C, Barnhart KT. Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society of Assisted Reproductive Technologies Database. Fertil Steril. 2016;106:164–71.
34. Juneau C, Kraus E, Werner M, Franasiak J, Morin S, Patounakis G, et al. Patients with endometriosis have aneuploidy rates equivalent to their age-matched peers in the in vitro fertilization population. Fertil Steril. 2017;108:284–8.
35. Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology. 2007;148:3814–26.
36. Miravet-Valenciano J, Ruiz-Alonso M, Gomez E, Garcia-Velasco JA. Endometrial receptivity in eutopic endometrium in patients with endometriosis: it is not affected,

and let me show you why. Fertil Steril. 2017;108:28–31.
37. Garcia-Velasco J, Fassbender A, Ruiz-Alonso M, et al. Is endometrial receptivity transcriptomics affected in women with endometriosis? A pilot study. Reprod Biomed Online. 2015;31:647–54.
38. Seyhan A, Urman B, Turkgeldi E, et al. Do endometriomas grow during ovarian stimulation for assisted reproduction? A three-dimensional volume analysis before and after ovarian stimulation. Reprod Biomed Online. 2018;36:239–44.
39. D'Hooghe T, Denys B, Spiessens C, Meuleman C, Debrock S. Is the endometriosis recurrence rate increased after ovarian hyperstimulation? Fertil Steril. 2006;86:283–90.
40. Benaglia L, Somigliana E, Santi G, Scarduelli C, Ragni G, Fedele L. IVF and endometriosis-related symptom progression: insights from a prospective study. Hum Reprod. 2011;26:2368–72.
41. Leone Roberti Maggiore U, Ferrero S, Mangili G, et al. A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes. Hum Reprod Update. 2016;22:70–103.
42. Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril. 2016;106:1552–7.
43. Domingo J, Garcia-Velasco JA. Oocyte cryopreservation for fertility preservation in women with cancer. Curr Opin Endocrinol Diabetes Obes. 2016:23.
44. Cobo A, Garcia-Velasco JA, Domingo J, Remohi J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril. 2013;99:1485–95.
45. Cobo A, Giles J, Paolelli S, Pellicer A, Remohi J, Garcia-Velasco JA. Oocyte vitrification for fertility preservation in women with endometriosis: an observational study. Fertil Steril. 2020;113:836–44.