Chapter 16

Fertility Preservation for Endometriosis

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INTRODUCTION

Endometriosis is a chronic estrogen-dependent disease with high morbidity that affects approximately 10% of women of reproductive age.[1,2] It is strongly associated with infertility, either alone or as an adjunct to other causal factors. This disease generates a chronic systemic inflammatory process and predisposes to anatomical, tubal and ovulatory changes, being present in up to 50% of infertile couples. [3]

Often the patients undergo chronic pain treatments, including long-term hormones administration (GnRH-agonist, hormonal contraceptives based on estradiol and/or progesterone), analgesics and anti-inflammatory drugs, and finally surgical treatment. [2,4] The latter has been less used over time and aims to remove adhesions and eliminate endometriotic focus in the pelvic and abdominal cavities. These treatments also cause infertility, since amenorrhea is an adverse effect commonly presented. [1]

One of the locations most affected by the endometriosis lesions is the ovaries, either by invagination of endometrial tissue by the ovarian cortex in situations of retrograde menstruation or by celomic metaplasia. These lesions called endometriomas generate cysts with a content rich in macrophages and hematic cells, being easily detected on transvaginal ultrasound. Local deleterious effect due to simple "mass effect" or the presence of toxic substances could explain why these patients have less ovarian reserve (OR) and experience infertility more frequently than the healthy population. [4]

Recent published studies also demonstrate impairment of oocyte quality and follicular quantity in this population, stimulating the surgical removal of these lesions in order to reduce the symptoms and restore normal ovarian function when focusing on pregnancy. [5] However, more recently, it is postulated that when performing ovarian surgical procedures to eliminate these lesions, the ovarian reserve could also be compromised, predisposing these women to premature ovarian failure, early menopause and infertility. [1,6] Experts affirm that the surgical approach should be avoided, performing only in exceptional situations, because by drying the lesions and keeping the "free margins" healthy ovarian tissue with its follicular population is also eliminated. [1] This is confirmed by studies that show a sharp drop in Anti-Mullerian Hormone (AMH) and antral follicle count (AFC) of post-surgical patients. [7]

On the other hand, the fertility preservation (FP) is increasingly used, especially in women over 35 years of age, where the decline in reproductive potential is more evident. Situations where the ovarian reserve is diminished, even where biological age is not so advanced, are also often indications of FP. These conditions include patients suffering from endometriosis, where follicular depletion occurs faster.[1]

With the advent of vitrification and high rates of success in thawing (reaching 83%), the freezing of oocytes, embryos and ovarian tissue has been increasingly used. Especially the preservation of oocytes, given the great experience already acquired on the subject and the favourable results published over the years. The freezing of ovarian tissue, despite being described for more than 20 years, is complex, expensive and little used, being an alternative only for emergency situations where it is impracticable to wait for controlled ovarian stimulation (COS) or when there is an indication for oophorectomy. Embryo vitrification is also less used for FP, given the ethical conflicts generated and the need for the partner at the time of oocyte extraction, in addition to controversial situations in the event of the couple separating.[8]

Regardless of the technique used to preserve the fertility of these patients, especially those affected by advanced endometriosis, there is a consensus that the treatment can and should be proposed by the attending physician, since it increases the possibilities of future pregnancy in patients with evolutionary endometriosis or with compromised ovarian reserve in post-surgical conditions.[1,2]

POPULATION CHARACTERISTICS

ENDOMETRIOSIS AND POOR OOCITARY QUALITY

Endometriomas can be present in up to 44% of patients with endometriosis, and their possible impact on oocyte quality has been proposed, especially in patients with advanced disease (deep endometriosis). Many studies point to a direct impact on ovarian activity due to interference with steroidogenesis. [1,9] The reports that ovulation occurs more commonly in the contralateral ovary in the presence of endometriomas also suggests a local deleterious effect on the ovulatory mechanism or even on follicular recruitment.[2,10]

On the other hand, the chronic systemic inflammatory process presented can also impact the quality/quantity of the follicles by increasing oxidative stress. [2] Nakahara et al. showed a greater apoptotic activity of granulosa cells and cumulus oophorus in patients with ovarian endometriomas, which may explain the poorer quality of the oocytes obtained and embryos generated after the COS of these patients.[11]

It is evident that in order to freeze eggs or embryos for fertility preservation we need good quality gametes, which have good rates of survival to thawing and satisfactory competence to perform the implantation and originate a live birth. A review published in 2017 reveals the scarcity of literature available on oocyte quality in patients with endometriosis. The authors cite reports of decreased expression of P450 aromatase by these oocytes, with decreased Estradiol (E2) concentrations and considerable intra-follicular imbalance, resulting in increased local oxidative stress. These gametes also

seem to show worse rates of in-vitro maturation, propensity to altered morphology and decreased mitochondrial cytoplasmic content.[2,9]

This increase in reactive oxygen species could promote oocyte meiotic and chromosomal abnormalities. This could explain the lower percentages of mature oocytes found after follicular aspiration in patients with endometriosis.[9]

A retrospective study published in 2019 comparing infertile patients due to endometriosis vs tubal factor demonstrated an increase in the amount of cytoplasmic granules and vacuoles in the oocytes of patients with the disease. A considerably larger amount of immature oocytes was also obtained in this group ($p < 0.005$). The oocyte quality suffered a greater impact, especially when the endometriomas were more than 3 cm in diameter, suggesting a size/toxicity relationship.[12]

Histologically analyzing samples from 13 ovarian cortex of young patients with and without endometriomas, Kitajima et al. showed a significant increase in the amount of atretic follicles in the ovaries affected by endometriotic cysts. The primordial follicles and oocytes diameter were also smaller, probably due to the ovarian inflammatory process generated by the cystic content. Using immunohistochemistry for apoptosis analysis, increased apoptotic activity in the follicles of patients with the disease was confirmed.[13]

Studies in mice have also shown changes in the oocyte meiotic spindle when exposed to endometriotic content, suggesting possible interference in oocyte quality also through the oxidative stress generated. However, studies carried out subsequently did not find concise evidence of these theories, since oocytes and embryos of women with endometriosis showed the same rates of blasturation and aneuploidies as healthy patients. The same controversial theories are valid for reports of lower production of ATP and mitochondrial activity of its oocytes, which still need confirmation by the scientific community.[2,14]

The impact of endometriosis on the quality of gametes was also analysed in studies with women participating in oocyte donation programs. Oocytes generated by patients with this disease showed worse clinical results when transferred to healthy patients, indicating the possible qualitative impairment[15]

Following the same reasoning, another French retrospective study published in 2020 attempted to prove this impact on embryonic quality by analyzing patients with and without endometriosis, and found no significant differences in obtaining high-quality embryos between groups. The smaller number of oocytes and mature oocytes in the group with the pathology directly influenced the cumulative live births rates, however the pregnancy rates per cycle did not differ. The results confirmed that in this sample the quality was equivalent between gamentes obtained from patients with and without the disease.[16]

In the country where this study was carried out, egg freezing in patients with advanced endometriosis has been funded by the government since 2018, demonstrating the

concern of public health systems about the negative impact on the reproductive capacity of patients with the disease, which can reach high levels of up to 40%. [5]

Therefore, the potential impairment of oocyte quality in patients with endometriosis is not completely clear so far. The studies published show contradictory results, and new well-designed studies with this purpose, especially in patients who underwent fertility preservation, could elucidate the capacity of these oocytes to generate a live birth.

ENDOMETRIOSIS AND REDUCTION OF OVARIAN RESERVE

The impact of endometriosis on oocytes quality is a controversial topic and still needs scientific proof, but the impairment of the ovarian reserve of patients with the disease is a widespread concept. This impact on the pool of antral follicle is basically justified by two situations: the disease evolution itself and iatrogenic surgical acts. Studies comparing HAM and CFA levels show considerably lower figures in this population, even in the absence of post-surgical states. [17,18]

Bearing in mind that these markers are currently the most accepted ways to measure OR, a study carried out in Brazil using infertile patients undergoing laparoscopy to confirm endometriosis compared the dosages of this hormone in patients with mild endometriosis and women without the disease, adjusting the respective confounding factors. The results showed a lower serum dosage of HAM in the group with endometriosis (1.26 vs 2.02 ng/ml), as well as greater heterogeneity and asynchrony in the size of antral follicles. [18]

Another research group carried out a prospective study to compare women with unilateral, bilateral endometriomas and patients without the pathology in order to determine the impact of endometriomas on the ovarian reserve of non-surgical patients. [17]

There were statistically significant differences in the concentrations of HAM in patients with bilateral ovarian involvement vs free of pathology. These data demonstrate the deleterious effect of endometriotic cysts at the ovarian level and their impact on OR, which can be justified by the effect of cytokines and the free radicals produced by them, which stimulate tissue fibrosis with vascular impairment and consequently interference with local perfusion. In addition, reports of proliferation of disorganized smooth muscle

parallel to cysts replacing functional ovarian tissue would also justify the decrease in the concentration of HAM presented by these patients. [17]

One of the mechanisms proposed by the local toxicity induced by endometriotic cysts is also the high concentrations of free iron in its interior. This free metal can stimulate the production of free radicals, which cause damage at the cellular and vascular level. [19]

The presence of iron in high concentrations alters ovarian gene expression, inducing the production and recruitment of local pro-inflammatory substances (tumor necrosis factor alpha, a proinflammatory cytokine, interleukin IL-6 and IL-8), which in the absence of homeostasis, have deleterious effects on the ovary. [19,20]

These same free radicals present within the cyst can alter the muscular layers of the vessels that carry out the ovarian blood supply, altering their relaxation and compliance. [19]

Other studies have shown that patients with endometriosis commonly have fewer aspirated oocytes and mature oocytes when compared to patients without the pathology undergoing COS. These data confirmed also in non-surgical patients, can be explained by the "mass effect " exerted by endometriomas. [4,7]

Therefore, based on the currently available literature, we conclude that the presence of endometriosis, especially at the ovarian level and by different mechanisms, has a deleterious effect on the follicular population. This impact can compromise the ovarian reserve of these patients, therefore being a plausible justification for proposing the fertility preservation of this population.

CLINICAL REPERCUSES OF SURGICAL REMOVAL OF ENDOMETRIOMES

One of the most controversial issues involving endometriosis is undoubtedly the indication of surgical intervention. In the past, much more interventionist and active behaviors were tried in the treatment of these patients, with gynecologists even "divided" into two opinion groups, those in favor and those against early surgical management. For years, early surgical intervention was justified by the ease of removal of small lesions and by decreasing the ovarian vascular involvement during the procedure, in addition to facilitating the diagnosis of lesions not seen in imaging exams. In this way, interference with ovarian functionality would be minimal, and may even increase the chances of spontaneous post-surgical pregnancy, also delaying the evolution of the disease. [8,21]

One of the first studies with this purpose was published in 1997, analyzing 341 women who underwent laparoscopy due to endometriosis. The authors found significant differences in pregnancy rates in patients who had the removal of endometriotic tissue during the procedure, compared to patients who had a conservative management after diagnosis (30.7% vs 17.7%). These results stimulated surgical performance at the time.[22]

Studies even suggested a possible capacity for ovarian self-repair after the procedure, reversing the damage caused by the surgery. These studies were based on the partial restoration of HAM in the late postoperative period, even if lower than the baseline. [7]

Years later, surgical excision of ovarian endometriomas pre-COS was also advocated for preventing a possible evolution of the cyst volume during treatment. This increase was not found in other studies carried out later. [23] The greater ease of ultrasound monitoring of follicular growth during the administration of gonadotropins also justified the procedure. The overall rates of spontaneous pregnancy reported in patients undergoing endometriosis are high, at approximately 73%. In addition, during oocyte extraction, the ovaries would be more accessible, and would reduce possible post-puncture complications, such as haemorrhage and formation of ovarian abscesses. [2,24,25,26]

However, despite the positive points mentioned, many studies demonstrate a considerable decrease in the ovarian reserve in patients undergoing ovarian surgery, and it can have a considerable impact on the ability of these women to conceive, even after assisted reproduction treatments. Studies show that after surgery, considerable falls in the ovarian reserve markers are presented. Corroborating with these data, after the surgery a smaller amount of oocytes and embryos are generated, thus decreasing the chances of reaching embryo transfer in cycles of assisted reproduction. [5,16]

Authors cite that after undergoing surgery to remove endometriotic foci, women undergoing OCD obtain up to 1.4 oocytes less per stimulation than patients that are not operated. This could have a direct impact on the amount of stimulations needed to be able to vitrify a reasonable number of oocytes in cases of preservation of fertility.[21]

Since the infertility commonly presented by these women is due to depletion of the ovarian reserve as consequence of the disease evolution or iatrogenic surgical procedures, the need to perform highly complex reproductive treatments has grown exponentially, currently corresponding to up to 25% of IVF indications. [4] These data encourage the oocyte vitrification of these patients. The study by Cobo et al. in 2020 showed a significant return of patients to the clinics where they performed the vitrified oocytes to use them in search of conception, about 46.5%. This reflects the low rates of spontaneous pregnancy in patients with endometriosis who suffer from infertility, even after said surgical intervention. [1]

When it comes to the surgical techniques for the elimination of endometriomas, there are laparoscopic surgical excision, electrocalterization, vaporization and puncture of endometriotic cysts. Some of these procedures have high recurrence rates, reaching up to 66.6%. [4,21] Regardless of the technique employed, the need for a well-trained and experienced professional team can minimize the deleterious effects of the procedure itself, as well as avoid the use of electrocautery. [5,21] Interestingly, in 2017 a Chinese study found no differences in the obtainment of oocytes and mature oocytes between patients who had undergone ovarian surgery to remove endometriomas when compared to patients who underwent endometriotic cyst puncture and those who underwent expectant conduct before the COS. [27]

These data should be interpreted with caution, given the mechanical action exerted by surgical procedures, which in addition to removing healthy ovarian tissue, also stimulates fibrosis at the site, which occupies the space previously intended for follicular development. As described by Garcia-Velasco et al. in a study carried out in different countries clinics, the performance of ovarian surgery to remove endometriotic cysts considerably increased the time until pregnancy, decreased the ovarian reserve (<CFA) and decreased the patient's response to COS.[2]

Another study published in 2020 also reports that performing ovarian surgery before COS has a negative influence on the amount of oocytes aspirated, unlike the presence of endometriomas during the process, which has not been shown to significantly interfere with the cycle. [3]

Therefore, performing oocyte vitrification to fertility preservation before surgery seems to be the most accepted strategy today, since if the surgical procedure performed subsequently does not result in spontaneous pregnancy, the frozen oocytes will again bring the opportunity to gestate these women who now post surgery may have your ovarian reserve compromised. [3]

The retrospective study led by Cobo et al. published in 2020 was very important for our better understanding of this topic. He aimed to evaluate the clinical results of patients with endometriosis who underwent oocyte vitrification, as well as the impact of ovarian surgery on COS. In the 485 women who participated in the study, the number of vitrified oocytes and the rates of ongoing pregnancy per cycle were higher in patients who did not undergo surgery (6.2-5.8). In patients under 35 years of age, having surgery had a considerable impact on the ovarian response to COS. The cumulative rate of live births in this population was 70% in conservative treatment versus 50% in operated patients.[1]

This study contradicts the logical reasoning that younger women would be the best candidates for surgical intervention for endometriosis because they have better ovarian reserve. This is reasonable to think, but this population was the one that suffered the most with the negative impact of the surgery. Despite having a larger pool of antral follicles, the removal of healthy ovarian tissue together with endometriomas had a negative impact on their treatment, so the recommendation is to perform the surgical procedure (when necessary) after the capture of oocytes. [1]

Another retrospective cohort study published in 2016 analyzed more than 400 thousand cycles of in vitro fertilization and showed that patients with endometriosis corresponded to 11% of those who underwent infertility treatment, and 22% of them had an association with low ovarian reserve. The vast majority of these women also had other diagnoses that can cause infertility, with only 4% of them having the exclusive diagnosis of endometriosis. [20]

A curious finding of this publication is that patients with exclusive diagnosis of endometriosis had an equal or even higher rate of live births compared to patients with other diagnoses, despite a smaller number of acquired oocytes. Patients with endometriosis associated with another pathology causing infertility had lower

pregnancy and live birth rates than patients free from the disease. These results were in line with a Norwegian study that lasted twenty years and also found cumulative rates of live births in patients undergoing IVF equal between patients with endometriosis (regardless of degree) and patients with other causes of infertility. [20]

Some authors have found significantly greater impacts on the ovarian reserve of patients with bilateral lesions compared to patients without endometriosis, but HAM levels do not seem to differ between patients with uni vs bilateral lesions. A 2020 study showed fewer mature oocytes rescued from patients with bilateral lesions compared to unilateral (5.1 x 3.3) after COS to preserve fertility. The COS was performed before the surgical excision of the lesions. [23] These populations should, therefore, be advised on the freezing of eggs and their unfavorable prognosis, with the purpose of making them also participate in the decisions about their treatment, freezing their eggs before the surgical intervention. [5]

Therefore, from a practical point of view, the current evidence suggests that the surgical procedure for the removal of ovarian endometriotic lesions should be performed only after the extraction of oocytes to preserve fertility, given the possible impairment of the ovarian reserve imposed by the surgery and the high rate of return of these patients to assistive reproduction clinics to use their previously vitrified oocytes.

STRATEGIES FOR COS OF PATIENTS WITH ENDOMETRIOSIS

One of the issues that undoubtedly deserves special attention is the choice of the controlled ovarian stimulation protocol implemented to preserve the fertility of patients with endometriosis. The quest to optimize the results of these women, who often have low ovarian reserve, is a major challenge for contemporary reproductive medicine. Increased obtainment of oocytes and mature oocytes for vitrification is directly related to the likelihood of future pregnancy. [28]

One of the pioneering works on this topic was published by Bastu et al, where COS protocols with GnRH agonist and antagonist were compared with each other in infertile patients who underwent ovarian endometrioma exeresis. Patients who used the agonist protocol obtained higher amounts of mature oocytes and good quality embryos, but the pregnancy rates and live birth rates did not differ between groups. This study was limited by its small sample size, however, when it comes to oocyte vitrification for preservation of fertility, the use of protocols with GnRH agonists should be considered.[30]

Another more recently published study compared 3 protocols of COS (long, short agonist and GnRh antagonist) in patients with compromised ovarian reserve after cystectomy due to ovarian endometriomas. Among the 342 participating women, no significant differences were found in the number of oocytes obtained and in the fertilization rates between the groups, with an average number of 4 oocytes aspirated per patient, the three protocols proved to be equally effective[31].

Taking into account the pathophysiology of endometriosis and its estrogen-dependent character, a Canadian retrospective study sought to compare the clinical results of patients who underwent COS cycles with 2 months of previous preparation with a GnRh agonist and patients who underwent this same treatment and associated Letrozole 5mg orally daily. [32]

This study showed that the combined therapy group had a higher CFA (10.3 x 6.4), mature oocytes (9.1 x 4.0) and a considerable decrease in the size of ovarian endometriomas (1.8 cm x 3.2 cm). The good results of this combination therapy were attributed to a significant decrease in the ovarian and pelvic inflammatory process, which was now strongly blocked by both medications. [32]

The results were even more expressive if we compare this same population with the IVF cycle previously performed without any prior preparation. Where the mean CFA was 6.2 per patient, mature oocytes obtained 3.2 and endometrioma size 3.5 cm. [32]

Taking into account the published work on therapy with GnRh agonists prior to COS of patients with endometriosis, an Italian study published in 2020 proved that the use of Dienogest for 3 months prior to the COS of women with previous failure in IVF cycles also brought benefits in pregnancy and live birth rates. Among the 63 patients who used the therapy, an important increase in the amount of oocytes obtained and embryos generated was evidenced.[20]

Trying to elucidate this issue, another study this year also evaluated the use of progesterone in COS cycles by comparing it with cycles with an antagonist for patients with endometriosis. Fifty-four women were included in each group, with similar characteristics and an average age of 30 years of age. The number of oocytes obtained (8.1) and vitrified oocytes (6.4) after cos were the same between groups. The use of progesterone (P4) to suppress the LH peak proved to be effective, cheap and more comfortable than cycles with antagonists, since many of these patients already used P4 to treat endometriosis prior to stimulation, and only maintained its use. [3]

Similar results had been published in 2017, when patients with endometriomas undergoing progesterone COS had a higher amount of mature oocytes and good quality morulae per stimulation cycle when compared to the group that used GnRh analogues. No peak of premature of LH was reported in the 147 cases analyzed and the implantation, pregnancy, fertilization and cycle cancellation rates did not differ between the protocols. This study confirmed the viability of COS with progesterone for endometriotic patients and suggests a possible pelvic inflammatory decrease during its use, which may justify the good results presented by this protocol. [27]

When analyzing the chronic inflammatory process of patients with endometriomas and their possible impacts on fertility already mentioned throughout this chapter, the administration of GnRh, progesterone or letrozole agonists during or prior to EOC can be considered, since it produced equivalent results or even better than the protocols usually implemented. These findings can be justified by the anti-inflammatory properties presented by these drugs. Therefore, it is recommended to personalize and

individualize each case, as well as analyze the drug and financial tolerability of each patient.

CONCLUSION

Endometriosis patients should be instructed on the possibility of freezing oocytes to preserve fertility. When these women have ovarian endometriomas, worse responses to controlled ovarian stimulation are observed, with lower rates of oocytes and mature oocytes obtained. The impact of endometriosis on oocyte quality is not fully understood, and similar rates of aneuploidy among patients with and without the pathology suggest similar quality. Surgical performance to remove endometriotic foci, especially ovarian (endometriomas), compromises the ovarian reserve and justifies the freezing of eggs prior to surgery.

BIBLIOGRAPHIC REFERENCES

1 - Ana Cobo, Ph.D.,a Juan Giles, M.D.,a Stefania Paolelli, M.D.,a Antonio Pellicer, M.D.,a Jos_e Remohí, M.D.,and Juan Antonio García-Velasco, M.D.b Oocyte vitrification for fertility preservation in women with endometriosis: an observational study. Fertility and Sterility® Vol. 113, No. 4, April 2020 0015-0282/$36.00.

2 - Jaime Garcia-Fernandez and Juan A. García- Velasco, Endometriosis and Reproduction: What We Have Learned YALE JOURNAL OF BIOLOGY AND MEDICINE 93 (2020), pp.571-577.

3 - Emmanuelle Mathieu d'Argent, Clément Ferrier , Chrysoula Zacharopoulou, Naouel Ahdad-Yata, Anne-Sophie Boudy, Adèle Cantalloube, Rachel Levy, Jean-Marie Antoine, Emile Daraï and Sofiane Bendifallah. Outcomes of fertility preservation in women with endometriosis: comparison of progestin-primed ovarian stimulation versus antagonist protocols Mathieu d'Argent et al. Journal of Ovarian Research (2020) 13:18.

4 - Sajal Gupta, Ashok Agarwal, Rishi Agarwal, J Ricardo Loret de Mola. Impact of ovarian endometrioma on assisted reproduction outcomes RBMOnline - Vol 13 No 3. 2006 349–360 Reproductive BioMedicine Online.

5 - Natalia C Llarena, Tommaso Falcone and Rebecca L Flyckt Fertility Preservation in Women With Endometriosis Clinical Medicine Insights: Reproductive Health Volume 13: 1–8.

6 - BusaccaM, Riparini J, Somigliana E, Oggioni G, Izzo S, Vignali M, Candiani M. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. Am J Obstet Gynecol 2006;195:421–425.

7 - Johnny S. Younis, Nora Shapso, Richard Fleming, Izhar Ben-Shlomo and Ido Izhaki. Impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve: a systematic review and meta-analysis Human Reproduction Update, pp. 1–17, 2019.

8 - Gloria Calagnaa, Luigi Della Corteb, Pierluigi Giampaolinoc, Marianna Marantoa, Antonino Perinoa Endometriosis and strategies of fertility preservation: a systematic review of the literature European Journal of Obstetrics & Gynecology and Reproductive Biology 254 (2020) 218–225.

9 - Ana Maria Sanchez, Valeria Stella Vanni, Ludovica Bartiromo, Enrico Papaleo, Eran Zilberberg, Massimo Candiani, Raoul Orvieto and Paola Viganò. Is the oocyte quality affected by endometriosis? A review of the literature Sanchez et al. Journal of Ovarian Research (2017) 10:43.

10 - Benaglia L, Somigliana E, Vercellini P, Abbiati A, Ragni G, Fedele L. Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation. Hum Reprod 2009;24:2183–2186.

11 - Kenji Nakahara, M.D., Hidekazu Saito, M.D., Takakazu Saito, M.D., Mariko Ito, M.D., Nobuhiko Ohta, M.D., Toshifumi Takahashi, M.D., and Masahiko Hiroi, M.D. Ovarian fecundity in patients with endometriosis can be estimated by the incidence of apoptotic bodies FERTILITY AND STERILITYt VOL. 69, NO. 5, MAY 1998.

12 - Mekan Rakhimberdievich Orazov, Victor Yevseyevich Radzinsky, Igor Isaakovich Ivanov, Marina Borisovna Khamoshina & Victoriya Borisovna Shustova Oocyte quality in women with infertility associated endometriosis Gynecological Endocrinology, 35:sup1, 24-26.

13 - Michio Kitajima, Marie-Madeleine Dolmans, Olivier Donnez, Hideaki Masuzaki, Michelle Soares and Jacques Donnez. Enhanced folicular recruitment and atresia in cortex derived from ovaries with endometriomas Fertility and Sterility® Vol. 101, No. 4, April 2014 0015-0282/$36.00.

14 - Hsu, A.L.; Townsend, P.M.; Oehninger, S.; Castora, F.J. 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, 347–352.

15 - Garcia-Velasco JA, Arici A. Is the endometrium or oocyte/embryo affected in endometriosis? Hum Reprod. 1999; 14:77-89. doi:10.1093/humrep/14.suppl_2.77.

16 - Lisa Boucret, Pierre-Emmanuel Bouet, Jérémie Riou, Guillaume Legendre, Léa Delbos, Hady El Hachem, Philippe Descamps, Pascal Reynier, and Pascale May-Panloup. Endometriosis Lowers the Cumulative Live Birth Rates in IVF by Decreasing the Number of Embryos but Not Their Quality J. Clin. Med. 2020, 9, 2478; doi:10.3390/jcm9082478.

17 - Dorota Nieweglowska, Iwona Hajdyla-Banas, Kazimierz Pitynski, Tomasz Banas, Oliwia Grabowska, Grzegorz Juszczyk, Artur Ludwin and Robert Jach. Age-related trends in anti-Mullerian hormone serum level in women with unilateral and bilateral ovarian endometriomas prior to surgery Nieweglowska et al. Reproductive Biology and Endocrinology (2015) 13:128.

18 - Nadiane Albuquerque Lemos, Elisangela Arbo, Renata Scalco,Eduardo Weiler, Virginia Rosa, João Sabino Cunha-Filho. Decreased anti-Mullerian hormone and altered ovarian follicular cohort in infertile patients with mild/minimal endometriosis Fertility and Sterility_ Vol. 89, No. 5, May 2008.

19 - A.M. Sanchez, P. Vigano, E. Somigliana, P. Panina-Bordignon, P. Vercellini, and M. Candiani. The distinguishing cellular and molecular features of the endometriotic ovarian cyst: from pathophysiology to the potential endometrioma-mediated damage to the ovary Human Reproduction Update, Vol.20, No.2 pp. 217–230, 2014.

20 - Fabio Barra, Antonio Simone Laganà, Carolina Scala, Simone Garzon, Fabio Ghezzi, Simone Ferrero. Pretreatment with dienogest in women with endometriosis undergoing IVF after a previous failed cycle RBMO VOLUME 41 ISSUE 5 2020.

21 - Nicola Pluchino, Horace Roman. Oocyte vitrification offers more space for a tailored surgical management of endometriosis RBMO COMMENTARY 2020.

22 - Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. N Engl J Med. 1997;337:217-222. doi:10.1056/ NEJM199707243370401.

23 - Se Jeong Kim, Seul Ki Kim, Jung Ryeol Lee, Chang Suk Suh, Seok Hyun Kim. Oocyte cryopreservation for fertility preservation in women with ovarian endometriosis 827 RBMO VOLUME 40 ISSUE 6 2020.

24 - Laura Benaglia, Andrea Busnelli, Rossella Biancardi, Walter Vegetti, Marco Reschini, Paolo Vercellini, Edgardo Somigliana. Oocyte retrieval difficulties in women with ovarian Endometriomas RBMO VOLUME 37, ISSUE 1, P77-84, JULY 01, 2018.

25 - Bárbara Romero, Laura Aibar, Luis Martínez Navarro, Juan Fontes, Maria-Angeles Calderón, Juan Mozas. Pelvic abscess after oocyte retrieval in women with endometriosis: A case series Iran J Reprod Med Vol. 11. No. 8. pp: 677-680, August 2013.

26 - Johnny S. Younis, Yossi Ezra, Neri Laufer, And Gonen Ohel. Late Manifestation Of Pelvic Abscess Following Oocyte Retrieval, For In Vitro Fertilization, In Patients With Severe Endometriosis And Ovarian Endometriomata Journal Of Assisted Reproduction And Genetics, Vol. 14. No. 6, 1997.

27 - Haiyan Guo, Yun Wang, Qiuju Chen, Weiran Chai, Lihua Sun, Ai Ai, Yonglun Fu, Qifeng Lyu & Yanping Kuang. Use of medroxyprogesterone acetate in women with ovarian endometriosis undergoing controlled ovarian hyperstimulation for in vitro fertilization ScieNtific REPOrTS | 7: 11927 | DOI:10.1038/s41598-017-12151-7.

28 - Panagiotis Drakopoulos, Christophe Blockeel, Dominic Stoop, Michel Camus, Michel de Vos, Herman Tournaye, and Nikolaos P. Polyzos. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? Human Reproduction, Vol. , No. pp. 1 –7, 2016.

29 - Suneeta Senapati, M.D., M.S.C.E.,a Mary D. Sammel, Sc.D.,b Christopher Morse, M.D.,c and Kurt T. Barnhart, M.D., M.S.C.E.a,b Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database Fertility and Sterility® Vol. -, No. -, - 2016 0015-0282/$36.00.

30 – Ercan Bastu, Cenk Yasa, Ozlem Dural, Mehmet Firat Mutlu, Cem Celik, Funda Gungor Ugurlucan, Faruk Buyru. Comparison of Ovulation Induction Protocols After Endometrioma Resection July–Sept 2014 Volume 18 Issue 3 e2014.00128.

31 - Feiyan Zhao, Yonglian Lan, Tong Chen, Zhimin Xin, Yu Liang, Ying Li, Shuyu Wang, Jun Zhang and Xiaokui Yang. Live birth rate comparison of three controlled ovarian stimulation protocols for in vitro fertilization-embryo transfer in patients with diminished ovarian reserve after endometrioma cystectomy: a retrospective study Zhao et al. Journal of Ovarian Research (2020) 13:23.

32 - Arielle Cantor, Samer Tannus, Weon-Young Son, Seang Lin Tan, Michael H Dahan. A comparison of two months pretreatment with GnRH agonists with or without an aromatase inhibitor in women with ultrasound-diagnosed ovarian endometriomas undergoing IVF 520 RBMO VOLUME 38 ISSUE 4 2019.