Chapter

The Impact of Endometriosis on Controlled Ovarian Stimulation Outcome

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Abstract

Endometriosis, a frequent condition in reproductive age women, is also associated with infertility by mechanisms incompletely clarified. The effectiveness of endometriosis treatment for infertility is debated, being possible that in vitro fertilization (IVF) offers a better alternative. The response to controlled ovarian stimulation (COS) is an important predictor of live birth, but it might be affected in endometriosis possibly through a decrease of ovarian reserve. Moreover, the predictive value of anti-mullerian hormone (AMH) for the response to COS could be altered by factors disrupting the AMH production in endometriosis. Therefore, we aim to review the literature regarding the response to COS and the AMH production and their predictive value for COS response in patients with endometriosis.

Keywords: endometriosis, controlled ovarian stimulation, in vitro fertilization, oocytes number

1. Introduction

Endometriosis is a frequent disease in reproductive-age women [1], consisting of the presence of endometrial tissue outside the uterine cavity. Endometriosis is frequently associated with infertility, being present in 25–50% of infertile patients [2]. On the other hand, 30–50% of endometriosis patients report difficulties to become pregnant [2]. In a large cohort study, women with endometriosis younger than 35 years old had a two-fold higher risk of infertility in comparison with women without endometriosis [3]. The mechanisms underlying the association between endometriosis and infertility are incompletely clarified, with both anatomical and microenvironmental disturbances being suggested [4]. While in infertile patients with advanced-stage endometriosis anatomical changes might be involved (peritubal and periovarian adhesions), the presence of infertility in milder forms of endometriosis suggests other mechanisms. Thus, decreased ovarian reserve, altered folliculogenesis, oocyte quality and endometrial receptivity were reported as possible contributors to infertility [4].

The extent and severity of endometriosis lesions are variable, ranging from few implants on the pelvic peritoneum to surrounding organs infiltration or extension outside the pelvis. Several grading systems for endometriosis have been created, but their predictive value for fertility is unclear. One of these classification systems, the Endometriosis Fertility Index (EFI) which is based on the scores from the American

Society for Reproductive Medicine (ASRM) system [5] combined with anamnestic and information from surgery, gives a score from 0 to 10 points [6]. It was shown that a score between 0 and 3 is associated with a 10% probability of obtaining pregnancy after 3 years with non-IVF treatments, while a score of 9–10 points is associated with a 75% chance of pregnancy [6, 7]. The predictive value of the EFI score for pregnancy was also confirmed for IVF treatments [8].

The impact of variate treatments for endometriosis on chances to obtain pregnancy and the efficacy of infertility treatments is still a matter of discussion. Thus, whether surgery contributes to the improvement of fertility in endometriosis or is preferable to perform infertility treatments needs further clarification.

In minimal or mild endometriosis without anatomical disruption, it was shown that laparoscopic removal of endometriosis implants improves fertility with an increase of risk ratio of 1.44 [9] and an odds ratio of 1.94 [10]. In a large Canadian multicenter study, the monthly fecundity rate and the 36-week cumulative probability of pregnancy increased from 2.4 to 17.7% for a diagnostic laparoscopy to 4.7 and 30.7% for laparoscopic surgery [11]. However, these rates of pregnancy should be discussed with the patients in the light of similar success rates of 30% after only one cycle of IVF taking into account the age, ovarian reserve or the cost of the treatment [12].

In patients with moderate and severe endometriosis surgery aims to remove large endometriomas and to restore the pelvic anatomy. Data regarding the effect of surgery on fertility in this category of patients are lacking. Excision of endometrioma is controversial in infertile patients taking into account the risk to decrease the ovarian reserve and lack of evidence of benefits on IVF outcome [13].

IVF could be a treatment option for infertility in patients with endometriosis. Therefore, the performance of patients with endometriosis at IVF and their predictors should be clarified to elaborate strategies for ovarian stimulation and to improve IVF outcomes. Oocyte yield at IVF is an important predictor of live birth in the general population of patients performing IVF, but it might be affected by the microenvironmental changes associated with endometriosis. Moreover, the AMH production could be disturbed in endometriosis, possibly interfering with its relationship with the ovarian reserve.

Therefore, the present paper aims to review the literature regarding the association of endometriosis with oocytes number and serum AMH level in infertile patients performing IVF, and the predictive value of AMH for the response to controlled ovarian stimulation.

2. The serum level of AMH in infertile patients with endometriosis

The relationship between endometriosis and serum AMH level is largely debated and data available in infertile women undergoing IVF are scarce. Only a limited number of studies with small study groups evaluated the impact of endometriosis on circulating AMH levels in patients with a wider range of endometriosis lesions [14, 15], most of the studies included only patients with endometrioma. The surgery for endometrioma probably affects the serum AMH level as suggested by two systematic reviews [16, 17] and represents a possible confounder of the relationship between endometrioma and AMH. It was shown that the decrease of serum AMH level after surgery was significant and persistent at 12 months in patients with endometrioma over 7 cm, with bilateral cysts and with endometriosis stage IV [18]. In turn, patients with smaller and unilateral ovarian endometrioma and stage III endometriosis had higher chances to have an only transient decline in circulating AMH [18]. However, a recent meta-analysis showed that the mere presence of

endometrioma, without previous surgery, is associated with lower AMH levels in patients without clearly defined fertility status [19]. In this study the serum AMH level was decreased in patients with endometrioma both versus patients with non-endometriotic cysts and with healthy ovaries, suggesting a specific effect of endometriosis independent of mass effect. The dimension of the endometriotic cyst could be an important contributor to the decrease of AMH level, although the available data are limited. In the meta-analysis of Muzii et al. most of the studies included patients with mean endometrioma dimension over 6 cm, being therefore impossible to conclude smaller cysts [19]. A small study found that even endometrioma bigger than 2 cm had lower serum AMH levels in comparison with controls [20]. On the other hand, Yoon et al. failed to find any relationship of ovarian endometrioma size with serum AMH level [21]. A small study with less than 60 patients per study group showed that patients with bilateral endometrioma had lower serum AMH levels in comparison with both unilateral endometrioma and no cysts [22]. Moreover, a negative linear relationship was found between endometrioma size and serum AMH level [22]. A prospective study with 40 women per study group reported that patients with endometrioma have a progressive decline in serum AMH level at an accelerated rate in comparison with patients without endometrioma [23].

Data regarding the impact of a wider range of endometriosis lesions on serum AMH levels are limited. A cross-sectional study that evaluated women surgically explored for a benign gynecological condition irrespective of their fertility status reported a similar serum AMH level in endometriosis patients and controls [24]. Patients in this study presented with various types of endometriosis: endometrioma, deep infiltrating endometriosis and superficial lesions [24]. However, in this study, infertile patients with decreased ovarian reserve might be underrepresented since these patients are more probably referred for reproductive treatments rather than for surgery.

Several studies evaluated the relationship between endometriosis and serum AMH levels in patients with infertility. Thus, Yoo et al. found that infertile patients with endometriosis performing IVF had lower AMH in comparison with male factor infertility patients [14]. In this study, the type of the endometriosis lesions was not specified and the number of patients in the two groups was reduced (43 versus 48). Moreover, patients with and without previous surgery for endometriosis were included, without a significant difference in terms of circulating AMH in these two categories of patients. Ashrafi et al. reported that serum AMH level is decreased in patients with deep infiltrating endometriosis with or without endometrioma and infertility [25]. Another small study showed that infertile patients with endometriosis stage I and II have lower circulating AMH levels in comparison with patients with tubal infertility undergoing IVF [15]. Inal et al. found no difference in serum AMH level in infertile patients with and without endometrioma performing IVF [26]. Shebl et al. studied the serum AMH level in patients undergoing IVF and found a decreased AMH only in patients with endometriosis stage III-IV in comparison with male factor infertility, but not in patients with stage I-II endometriosis [27].

3. The association between endometriosis and oocyte yield in infertile patients performing IVF

The relationship between endometriosis and oocytes yields in infertile patients performing IVF was previously studied, but the results are divergent. Senapati et al. found that patients with endometriosis obtain fewer oocytes in comparison with patients with other causes of infertility undergoing IVF in a big database of

347,185 assisted reproductive technic cycles [28]. In this study, the presence of endometriosis was associated with a lower number of oocytes in patients with isolated endometriosis or association with other causes of infertility, including diminished ovarian reserve [28]. The negative association between endometriosis and oocytes yield was also studied by a meta-analysis that included 20,167 patients with endometriosis and 121,931 without endometriosis [29]. Subgroups with 1703 women with stage III/IV endometriosis were compared with 2227 women with stage I/II endometriosis. Although, a small difference in oocytes yield was observed in favor of non-endometriosis patients, the authors concluded that the quality of the evidence is very low, not allowing meaningful conclusions to be drawn [29]. No significant difference in patients with variate stages of endometriosis was reported [29]. Moreover, in both studies patients with and without previous surgery for endometriosis were included, generating a possible bias [28, 29]. Thus, Dong et al. analyzed only patients with previous surgery for endometriosis and found that patients with stage III/IV endometriosis obtained lower oocytes number in comparison with controls [30], suggesting that surgery for severe endometriosis might negatively affect COS response. Several other studies confirmed the negative association between surgery for endometriosis and oocytes yield in women with advanced-stage endometriosis [31]. In patients operated for endometrioma, laparoscopic cystectomy is associated with decreased oocytes number, with an additional effect of bilateral versus unilateral cystectomy [32]. Similarly, bilateral surgery for endometrioma was shown to decrease the oocytes number in comparison with unoperated patients [33].

Regarding the association of variate types of endometriosis with COS response, a recent meta-analysis found that unoperated endometriomas are associated with reduced oocytes number in IVF cycles [34]. Papaleo et al. found that profound infiltrative endometriosis has an additional negative effect on oocytes yield in comparison with patients with isolated ovarian endometrioma, supporting the hypothesis that variate types of endometriosis lesions can differently impact the ovarian response [35]. In turn, a small study that included only patients with stage I and II endometriosis found similar oocytes number with patients performing IVF for tubal infertility [15].

4. The predictive value of AMH for oocyte yield in endometriosis

Although, circulating AMH levels are considered, in general, a valuable tool for the prediction of the ovarian response to COS, in endometriosis its predictive value might be affected. This hypothesis is supported by studies that demonstrated that AMH production could be influenced independently of the ovarian reserve. However, its predictive value in endometriosis is largely unknown.

Yoo et al. showed that serum AMH level is a significant predictor of oocytes yield in endometriosis patients performing IVF [14], while Wahd et al. found no predictive value of AMH in patients with advanced endometriosis [36]. The lack of the predictive ability of AMH was confirmed in another study that analyzed only patients with endometrioma [26]. The design of the studies and differences in study populations might explain the divergent results of the studies, being possible that more severe endometriosis and endometrioma, especially bigger ones to significantly disrupt the relationship between AMH and ovarian reserve.

Despite the negative relationship between endometriosis and circulating AMH reported by several studies, two reports found an increasing serum AMH level with endometrioma size [37, 38]. If this finding will be confirmed by future studies, a possible explanation is a different impact of endometrioma on AMH production

from the other endometriosis lesions. The authors hypothesized that the increasing AMH level could be due to higher discharge in the systemic circulation by increased ovarian blood flow as a consequence of the inflammation and neoangiogenesis found in endometriosis. In support of this hypothesis are the studies that reported increased levels of vascular endothelial growth factor (VEGF) in serum and peritoneal fluid of patients with endometriosis [39]. These increased levels are correlated with microvessels density in the endometriotic tissue [40]. Thus, increased vascularization might contribute to disproportionately higher serum AMH levels in comparison with ovarian reserve, therefore affecting its value as a predictor of COS response in endometriosis. However, this mechanism could be particular to endometrioma as suggested by a study that showed that the gene expression of VEGF is increased only in patients with endometrioma and not in those with deep infiltrating endometriosis [41].

5. The mechanisms explaining the decreased ovarian response and decreased serum AMH level in infertile patients with endometriosis

Besides the mass effect of the endometrioma, other mechanisms might be also involved in the occurrence of reduced oocytes yield since similar oocytes number was found in the contralateral ovary of women with unilateral endometriomas [42]. Moreover, more severe endometriosis seems to have an additional negative impact on oocytes number [35].

Histological studies found that the cortex of ovaries with endometrioma presents decreased follicular density, increased fibrosis, loss of cortex-specific stroma [43] and high density of atretic follicles [44]. Moreover, activated follicular recruitment was observed in ovaries with endometrioma [44], suggesting follicle 'burnout' as a possible cause of decreased follicle number. It was suggested that the structural changes are the consequence of the cytokines produced in the endometriotic tissue which might affect the surrounding ovarian tissue by diffusion [44]. It was also showed that the addition of human endometriotic fluid to mouse preantral follicles decreases the follicles survival rates proportional with the endometriotic fluid supernatant concentration [45]. These data support the hypothesis that endometriotic fluid components can influence the ovarian response to COS through long-term destructive effects of ovarian tissue and, therefore, decreased ovarian reserve, but also by directly influencing the follicles survival [45]. It is also possible that the diffusion of the endometriotic fluid components from the peritoneum or the endometrioma to be able to influence the unaffected ovary function and structure [46].

The decreased serum AMH level in patients with endometriosis might be the consequence of reduced ovarian reserve due to structural ovarian changes. However, it was shown that the endometriotic fluid components can directly induce the dysfunction of the granulosa cells [47]. Tumor necrosis factor (TNF) alpha, one of the cytokines overproduced in endometriosis, was found to be negatively associated with serum AMH level [15], suggesting its involvement in decreased circulating AMH. Indeed, an experimental study showed that TNF alpha administration decreases the expression of AMH in bovine ovarian granulosa cells [48]. In mice, TNF alpha was demonstrated to inhibit the AMH production in testis [49]. Thus, TNF alpha might be the mediator of functional decrease of AMH production in endometriosis.

Another mechanism that can contribute to low oocytes yield is a decreased response to gonadotropin stimulation in endometriosis. Thus, interleukin 1 (IL1) was found to be increased in the peritoneal fluid of patients with endometriosis [50–52]. Il1 is also a regulator of ovarian function, being able to decrease the ovary

receptors of FSH and LH [53], thus inducing a reduced sensitivity to gonadotropin stimulation. Moreover, women with endometriosis seem to have a decreased expression of the soluble decoy receptor IL1-RII which can generate an augmentation of IL1 alpha and IL1 beta effects [51, 54].

6. Conclusions

The data available in the literature support a negative association between the presence of an endometrioma and serum AMH level. Moreover, previous surgery for endometrioma is associated with decreased serum AMH level, the risk of the persistence of low AMH being higher in patients with bilateral endometrioma, bigger than 7 cm and with stage IV endometriosis. However, in patients with a wider range of endometriosis without clearly defined fertility status the serum AMH level does not seem to be decreased. In infertile patients with endometriosis available studies suggest lower serum AMH levels, although further research is necessary to clarify this aspect. Moreover, endometriosis seems to negatively impact the oocyte yield, especially in patients with previous surgery for severe endometriosis and endometrioma. The impact of variate types of endometriosis on the oocytes yield is incompletely clarified, the available evidence supporting that endometrioma has a deleterious effect on the ovarian response, with a possible additional negative effect of deep infiltrating endometriosis.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertility and Sterility. 2012;**98**(3): 511-519

[2] ASRM. Practice Committee of the American Society for reproductive Medicine Endometriosis and infertility: A committee opinion. Fertility and Sterility. 2012;**98**:591-598

[3] Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Human Reproduction. 2016;**31**:1475-1482

[4] Da Broi MG, Ferriani RA, Navarro PA. Ethiopathogenic mechanisms of endometriosis-related infertility. JBRA Assisted Reproduction. 2019;**23**(3):273-280

[5] American Society for Reproductive Medicine. Revised American society for reproductive medicine revised classification of endometriosis. Fertility and Sterility. 1997;**67**:817-821

[6] Adamson GD, Pasta DJ. Endometriosis fertility index: The new, validated endometriosis staging system. Fertility and Sterility. 2010; **94**:1609-1615

[7] Tomassetti C, Geysenbergh B, Meuleman C, Timmerman D, Fieuws S, D'Hooghe T. External validation of the endometriosis fertility index (EFI) staging system for predicting non-ART pregnancy after endometriosis surgery. Human Reproduction. 2013; **28**:1280-1288

[8] Boujenah J, Bonneau C, Hugues JN, Sifer C, Poncelet C. External validation of the endometriosis fertility index in a French population. Fertility and Sterility. 2015;**104**:119-123

[9] Jin X, Ruiz BJ. Laparoscopic surgery for subfertility related to endometriosis: A meta-analysis. Taiwanese Journal of Obstetrics & Gynecology. 2014; **53**:303-308

[10] Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R, et al. Laparoscopic surgery for endometriosis. Cochrane Database of Systematic Reviews. 2014;**4**:CD011031

[11] Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. The New England Journal of Medicine. 1997;**337**:217-222

[12] Tanbo T, Fedorcsak P. Endometriosis-associated infertility: Aspects of pathophysiological mechanisms and treatment options. Acta Obstetricia et Gynecologica Scandinavica. 2017;**96**:659-667

[13] Benschop L, Farquhar C, van der Poel N, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. Cochrane Database of Systematic Reviews. 2010;**11**:CD008571

[14] Yoo JH, Cha SH, Park CW, Kim JY, Yang KM, Song IO, et al. Serum anti-Müllerian hormone is a better predictor of ovarian response than FSH and age in IVF patients with endometriosis. Clinical and Experimental Reproductive Medicine. 2011;**38**(4):222-227. DOI: 10.5653/cerm.2011.38.4.222

[15] Falconer H, Sundqvist J, Gemzell-Danielsson K, von Schoultz B, D'Hooghe TM, Fried G. IVF outcome in women with endometriosis in relation to tumour necrosis factor and anti-Müllerian hormone. Reproductive BioMedicine Online. 2009;**18**(4):582-588

[16] Raffi F, Metwally M, Amer S. The impact of excision of ovarian

endometrioma on ovarian reserve: A systematic review and meta-analysis. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**:3146-3154

[17] Somigliana E, Berlanda N, Benaglia L, Viganò P, Vercellini P, Fedele L. Surgical excision of endometriomas and ovarian reserve: A systematic review on serum antimüllerian hormone level modifications. Fertility and Sterility. 2012;**98**:1531-1538

[18] Wang Y, Ruan X, Lu D, Sheng J, Mueck AO. Effect of laparoscopic endometrioma cystectomy on anti-Müllerian hormone (AMH) levels. Gynecological Endocrinology. 2019;**35**(6):494-497

[19] Muzii L, Di Tucci C, Di Feliciantonio M, Galati G, Di Donato V, Musella A, et al. Antimüllerian hormone is reduced in the presence of ovarian endometriomas: A systematic review and meta-analysis. Fertility and Sterility. 2018;**110**(5):932-940.e1. DOI: 10.1016/j.fertnstert.2018.06.025

[20] Uncu G, Kasapoglu I, Ozerkan K, Seyhan A, Yilmaztepe AO, Ata B. Prospective assessment of the impact of endometriomas and their removal on ovarian reserve and determinants of the rate of decline in ovarian reserve. Human Reproduction. 2013;**28**(8):2140-2145. DOI: 10.1093/humrep/det123

[21] Yoon H, Lee H, Kim S, Joo J. The relationship of ovarian endometrioma and its size to the preoperative serum anti-Mullerian hormone level. Ginekologia Polska. 2020;**91**(6):313-319

[22] Karadağ C, Yoldemir T, Karadağ SD, Turgut A. The effects of endometrioma size and bilaterality on ovarian reserve. Journal of Obstetrics and Gynaecology. 2020;**40**(4):531-536. DOI: 10.1080/01443615.2019.1633518

[23] Kasapoglu I, Ata B, Uyaniklar O, Seyhan A, Orhan A, Yildiz Oguz S, et al. Endometrioma-related reduction in ovarian reserve (ERROR): A prospective longitudinal study. Fertility and Sterility. 2018;**110**(1):122-127. DOI: 10.1016/j.fertnstert.2018.03.015

[24] Streuli I, de Ziegler D, Gayet V, Santulli P, Bijaoui G, de Mouzon J, et al. In women with endometriosis anti-Mullerian hormone levels are decreased only in those with previous endometrioma surgery. Human Reproduction. 2012;**27**(11):3294-3303. DOI: 10.1093/humrep/des274

[25] Ashrafi M, Arabipoor A, Hemat M, Salman-Yazdi R. The impact of the localization of endometriosis lesions on ovarian reserve and assisted reproduction techniques outcome. Journal of Obstetrics and Gynaecology. 2019;**39**(1):91-97. DOI: 10.1080/01443615.2018.1465898

[26] Inal ZO, Ustun YE, Yilmaz N, Aktulay A, Bardakci Y, Gulerman C. Does the anti-Müllerian hormone truly reflect ovarian response in women with endometrioma? Journal of Obstetrics and Gynaecology. 2019;**39**(4):516-521

[27] Shebl O, Ebner T, Sommergruber SA, Tews G. Anti muellerian hormone serum levels in women with endometriosis: A case-control study. Gynecological Endocrinology. 2009;**25**(11):713-716. DOI: 10.3109/09513590903159615

[28] Senapati S, Sammel MD, Morse C, Barnhart KT. Impact of endometriosis on in vitro fertilization outcomes: An evaluation of the Society for assisted reproductive technologies database. Fertility and Sterility. 2016;**106**(1):164-171.e1. DOI: 10.1016/j.fertnstert.2016.03.037

[29] MAP B, Teixeira DM, Navarro PAAS, Ferriani RA, Nastri CO, Martins WP. Impact of endometriosis and its staging on assisted reproduction outcome: Systematic review and

meta-analysis. Ultrasound in Obstetrics & Gynecology. 2014;**44**(3):261-278. DOI: 10.1002/uog.13366

[30] Dong X, Liao X, Wang R, Zhang H. The impact of endometriosis on IVF/ICSI outcomes. International Journal of Clinical and Experimental Pathology. 2013;**6**(9):1911-1918

[31] Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. Fertility and Sterility. 2007;**88**(6):1568-1572. DOI: 10.1016/j.fertnstert.2007.01.037

[32] Esinler I, Bozdag G, Aybar F, Bayar U, Yarali H. Outcome of in vitro fertilization/intracytoplasmic sperm injection after laparoscopic cystectomy for endometriomas. Fertility and Sterility. 2006;**85**:1730-1735

[33] Somigliana E, Arnoldi M, Benaglia L, Iemmello R, Nicolosi AE, Ragni G. IVF-ICSI outcome in women operated on for bilateral endometriomas. Human Reproduction; **208**(23):1526-1530

[34] Alshehre SM, Narice BF, Fenwick MA, Metwally M. The impact of endometrioma on in vitro fertilisation/intra-cytoplasmic injection IVF/ICSI reproductive outcomes: A systematic review and meta-analysis. Archives of Gynecology and Obstetrics. 2021;**303**(1):3-16. DOI: 10.1007/s00404-020-05796-9

[35] Papaleo E, Ottolina J, Viganò P, Brigante C, Marsiglio E, De Michele F, et al. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. Acta Obstetricia et Gynecologica Scandinavica. 2011;**90**(8):878-884. DOI: 10.1111/j.1600-0412.2011.01161.x

[36] Wahd SA, Alalaf SK, Al-Shawaf T, Al-Tawil NG. Ovarian reserve markers and assisted reproductive technique (ART) outcomes in women with advanced endometriosis. Reproductive Biology and Endocrinology. 2014;**12**:120

[37] Marcellin L, Santulli P, Bourdon M, Comte C, Maignien C, Just PA, et al. Serum antimüllerian hormone concentration increases with ovarian endometrioma size. Fertility and Sterility. 2019;**111**(5):5944-5952

[38] Roman H, Chanavaz-Lacheray I, Mircea O, Berby B, Dehan L, Braund S, et al. Large ovarian endometriomas associated with high preoperative anti-Mullerian Hormone levels. RBMOnline. 2021;**42**(1):158-164. DOI: 10.1016/j.rbmo.2020.09.008

[39] McLaren J, Prentice A, Charnock-Jones DS, Smith SK. Vascular endothelial growth factor (VEGF) concentrations are elevated in peritoneal fluid of women with endometriosis. Human Reproduction. 1996;**11**:220-223

[40] Bourlev V, Volkov N, Pavlovitch S, Lets N, Larsson A, Olovsson M. The relationship between microvessel density, proliferative activity and expression of vascular endothelial growth factor-A and its receptors in eutopic endometrium and endometriotic lesions. Reproduction. 2006;**132**:501-509

[41] Filippi I, Carrarelli P, Luisi S, Batteux F, Chapron C, Naldini A, et al. Different expression of hypoxic and angiogenic factors in human endometriotic lesions. Reproductive Sciences. 2016;**23**(4):492-497. DOI: 10.1177/1933719115607978

[42] Yang C, Geng Y, Li Y, Chen C, Gao Y. Impact of ovarian endometrioma on ovarian responsiveness and IVF:

A systematic review and meta-analysis. Reproductive Biomedicine Online. 2015;**31**(1):9-19. DOI: 10.1016/j.rbmo.2015.03.005

[43] Kitajima M, Defrere S, Dolmans MM, Colette S, Squifflet J, Van Langendonckt A, et al. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertility and Sterility. 2011;**96**(3):685-691. DOI: 10.1016/j.fertnstert.2011.06.064

[44] Kitajima M, Dolmans MM, Donnez O, Masuzaki H, Soares M, Donnez J. Enhanced follicular recruitment and atresia in cortex derived from ovaries with endometriomas. Fertility and Sterility. 2014;**101**(4):1031-1037. DOI: 10.1016/j.fertnstert.2013.12.049

[45] Kim SK, Jee BC, Kim SH. Effects of supplementation of human endometriotic fluids on in vitro mouse preantral follicle culture. Reproductive Sciences. 2018;**25**(5):683-689. DOI: 10.1177/1933719116678687

[46] Sanchez AM, Somigliana E, Vercellini P, Pagliardini L, Candiani M, Vigano P. Endometriosis as a detrimental condition for granulosa cell steroidogenesis and development: From molecular alterations to clinical impact. The Journal of Steroid Biochemistry and Molecular Biology. 2016;**155**:35-46

[47] Sanchez AM, Viganò P, Somigliana E, Panina-Bordignon P, Vercellini P, Candiani M. 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. 2014;**20**(2):217-230. DOI: 10.1093/humupd/dmt053

[48] Glister C, Hatzirodos N, Hummitzsch K, Knight PG, Rodgers RJ. The global effect of follicle-stimulating hormone and tumour necrosis factor α on gene expression in cultured bovine ovarian granulosa cells. BMC Genomics. 2014;**15**:72. DOI: 10.1186/1471-2164-15-72

[49] Hong CY, Park JH, Seo KH, et al. Expression of MIS in the testis is downregulated by tumor necrosis factor alpha through the negative regulation of SF-1 transactivation by NF-kappa B. Molecular Cellular Biology. 2003;**23**:6000-6012

[50] Cheong YC, Shelton JB, Laird SM, Richmond M, Kudesia G, Li TC, et al. IL-1, IL-6 and TNF-alpha concentrations in the peritoneal fluid of women with pelvic adhesions. Human Reproduction. 2002;**17**(1):69-75

[51] Kondera-Anasz Z, Sikora J, Mielczarek-Palacz A, Jońca M. Concentrations of interleukin (IL)-1alpha, IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2005;**123**(2):198-203

[52] Sikora J, Mielczarek-Palacz A, Kondera-Anasz Z. Imbalance in cytokines from interleukin-1 family—Role in pathogenesis of endometriosis. American Journal of Reproductive Immunology. 2012;**68**(2):138-145

[53] Brännström M. Potential role of cytokines in ovarian physiology: The case for interleukin-1. In: Leung PCK, Adash EY, editors. The Ovary. 2nd ed. Amsterdam: Elsevier-Academic Press; 2004. pp. 261-271

[54] Kharfi A, Boucher A, Akoum A. Abnormal interleukin-1 receptor type II gene expression in the endometrium of women with endometriosis. Biology of Reproduction. 2002;**66**(2):401-406