Endometriosis as a cause of decreased ovarian reserve: Any new hope?

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Decreased Ovarian Reserve (DOR)

- Diminished ovarian reserve (DOR) predicts the suboptimal ovarian response to stimulation, however it does not predict cycle fecundity.

- The European Society of Human Reproduction and Embryology (ESHRE) has recently proposed the Bologna's criteria, by which DOR is defined by the presence of at least two of the below features including: 1) age >40 years or other risk factor for DOR; 2) abnormal ovarian reserve test (ORT) characterized by antral follicles count (AFC) less than 5-7 follicles or antimullerian hormone (AMH) less than 0.5-1.1 ng/mL (3.57-7.85 pmol/L), and 3) previous poor ovarian response (less than three follicles) after a conventional stimulation protocol (Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli Let al. Eshre consensus on the definition of ‘poor response’ to ovarian stimulation for in vitro fertilization: the Bologna criteria. HumReprod 2011;26:1616-24).
Two episodes of poor response despite maximal stimulation can also label a patient as poor responder in the absence of advanced age or abnormal ORT (Polyzos NP, Devroey P. A systematic review of randomized trials for the treatment of poor ovarian responders: Is there any light at the end of the tunnel? Fertil Steril 2011;96:1058-61.)

DOR is however different from menopause or premature ovarian failure (POF) in which cycles are an ovulatory/irregular, and FSH levels are elevated. In general, the term DOR may sometimes be perceived as primary ovarian insufficiency. (Cooper AR, Baker VL, Sterling EW, Ryan ME, Woodruff TK, Nelson LM. The time is now for a new approach to primary ovarian insufficiency. Fertil Steril 2011;95:1890-1897.)
What measures represent ovarian reserve?

- ORTs are generally classified into biochemical, dynamic and ultrasonographic tests.
- Basal FSH
- Estradiol
- Inhibin B
- AMH
- Clomiphene citrate challenge test (CCCT)
- Gonadotropin agonist stimulation test (GAST)
- Exogenous FSH ovarian reserve test (EFORT)
- AFC
- Ovarian volume
- Ovarian blood Flow
Factors affecting the ovarian reserve

- Aging and environmental factors
- Blood Group
- Autoimmune, metabolic diseases and infections
- Genetic abnormalities
- Cigarette smoking
- Chemotherapy, radiation
- Gynecologic surgeries
- Endometriosis
Endometriosis as a cause of DOR

- The condition is known to leave a significant negative effect on ovarian reserve. Both superficial and deep infiltrating endometriosis (DIE) decrease the ovarian reserve, ovulation rate and response to ovulation induction. (Shah DK. Diminished ovarian reserve and endometriosis: Insult upon injury. Semin Reprod Med 2013;31:144-9.)

- Endometrioma per se may contribute to DOR. A considerable body of molecular, histological and morphological evidence suggests that in cases of endometrioma, normal ovarian cortical tissue adjacent to the cyst is replaced by fibrosis leading to reduce follicular density and eventually DOR. Stretching of the tissue nearby the cyst however has no role in declined ovarian reserve. (Sanchez AM, Vigano 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. Hum Reprod update 2014;20:217-30.)
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- To assess the negative effects of endometrioma on ovarian follicle density, an analysis of prospectively collected biopsy samples of ovarian tissue revealed fibrosis and loss of cortical stroma while the change was not observed in samples of the contralateral cyst-free ovary. In addition, the follicular density was significantly lower in cystic versus the opposite normal ovary. (Kitajima M, Defrere S, Dolmans MM, Colette S, Squifflet J, Van Langendonckt Aet al. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertil Steril 2011;96:685-91.)

- As already pointed out, AFC and AMH are the most reliable markers for ovarian reserve and given the unique characteristics of AMH in progressive disease like endometriosis, its assay can potentially predict the ovarian reserve decrement. (Sanchez AM, Vigano 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. Hum Reprod update 2014;20:217-30.)
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Several clinical studies have shown negative effects of surgical treatment of endometrioma on ovarian reserve which could result from the removal of normal follicles adjacent to endometrioma, electrocautery related thermal injury to the normal ovarian cortex and the consequent inflammatory responses. (Esinler I, Bozdag G, Arikan I, Demir B, Yarali H. Endometrioma ≤3 cm in diameter per se does not affect ovarian reserve in intracytoplasmic sperm injection cycles. Gynecol Obstet Invest 2012;74:261-4.)

Along these lines, a recent meta-analysis demonstrated negative impact of surgical resection of endometrioma on ovarian reserve evolvable by AMH. Based on this analysis, serum AMH level after surgery of endometrioma decreased by 38%. (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.)
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As compared to AMH, AFC can better reflect the damage to single ovary. Furthermore, while AMH reflects the ovarian reserve of both ovary, AFC directly expresses the reserve of single ovary. As a result, in patients with unilateral injury to ovary, AFC is superior to AMH for the evaluation of ovarian reserve. Likewise, in the assessment of surgery-associated damages to ovary, AFC is the preferred value to measure. (Muzii L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. Hum Reprod 2014;29:2190-8).

Nevertheless, this measurement has little implications in endometriosis. In a large RCT, we evaluated the effects of surgical resection of endometrioma on the above markers through their measurement before and after the operation. According to our findings, patients with endometrioma showed a significantly decreased level of AMH from the baseline. This significant decline was irrespective of patients’ age, cyst size and bilaterality or multicity of the pathology. (Alborzi S, Keramati P, Younesi M, Samsami A, Dadras N. The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas. Fertil Steril 2014;101:427-34.)
In addition, increased serum FSH and E2 were observed.

However, surprisingly the ultrasonographic AFC was increased post-operatively. The study conclude that one possible reason for this discrepancy between AFC and AMH as two reliable marker for ovarian reserve could be related to difficulty in the evaluation of AFC in the presence of endometrioma. As such, while AFC is not seen as a reliable ovarian reserve marker following the laparoscopic resection of endometrioma, AMH can be sought as a useful test. (Alborzi S, Keramati P, Younesi M, Samsami A, Dadras N. The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas. Fertil Steril 2014;101:427-34.)
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- In cases of bilateral endometrioma, a more noticeable decrease in AMH was reported. In addition, laparoscopic stripping of endometrioma was shown to result in progressive decline in serum AMH concentration. (Celik HG, Dogan E, Okyay E, Ulukus C, Saatli B, Uysal Set al. Effect of laparoscopic excision of endometriomas on ovarian reserve: Serial changes in the serum antimullerian hormone levels. Fertil Steril 2012;97:1472-8.)

- The excision of ovarian endometrioma in young subjects may lead to a decreased ovarian reserve secondary to unintentional damage to the normal cortical tissue and follicle loss during the procedure. For this reason, minimal invasive surgical techniques should be performed. The choice of surgical approach is laparoscopic excision of the lesion with care to avoid injury to the healthy ovarian cortex. (Busacca M, Vignali M. Endometrioma excision and ovarian reserve: a dangerous relation. J Minim Invasive Gynecol 2009;16:142-8.)
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- Comparing the laparotomic versus laparoscopic unilateral benign cystectomy and unintentional ovarian tissue removal with the benign cyst, a randomized trial substantiated that the nature of ovarian cyst was a significant factor for the ovarian reserve decline, whereas the type of surgical treatment (laparotomy versus laparoscopy) had no significant effect on inadvertent ovarian tissue removal with the cyst. (Alborzi S, Foroughinia L, Kumar PV, Asadi N, Alborzi S. A comparison of histopathologic findings of ovarian tissue inadvertently excised with endometrioma and other kinds of benign ovarian cyst in patients undergoing laparoscopy versus laparotomy. Fertil Steril 2009;92:2004-7.)

- Some other studies have tried to ascertain the role of various surgical techniques for endometriosis on ovarian reserve. According to such reports, repeated surgeries are associated with a severe decline in ovarian reserve. Moreover, considerable surgical skills and dexterity are required to preserve normal ovarian tissue. (Jadoul P, Kitajima M, Donnez O, Squifflet J, Donnez J. Surgical treatment of ovarian endometriomas: State of the art? Fertil Steril 2012;98:556-63).
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- In a prospective RCT on 100 patients with endometrioma who complained of pain or infertility, we compared two laparoscopic surgical approaches towards endometrioma. Our findings indicated a higher pregnancy rate as well as lower recurrence of symptoms and signs in ovarian cystectomy method rather than fenestration and coagulation. (Alborzi S, Momtahan M, Parsanezhad ME, Dehbashi S, Zolghadri J, Alborzi S. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. Fertil Steril 2004;82:1633-7.)

- We also performed a meta-analysis and re-emphasized the fact that the best surgical method for achievement of higher pregnancy is clear. In this meta-analysis, we concluded that laparoscopic cystectomy is a preferred choice over fenestration and coagulation when treating patients with endometrioma due to the lower recurrence of pain and the higher subsequent pregnancy rate. (Alborzi S, Zarei A, Alborzi S, Alborzi M. Management of ovarian endometrioma. Clin Obstet Gynecol 2006;49:480-91.)
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- A recent trial suggested that striping of endometrioma left no adverse effect on the ovarian reserve. In addition, this report suggested no significant pre- and post-operative changes with regard to FSH, LH level, AFC, volume and stromal blood flow of ovary on cycle day 2. Meanwhile, histopathologic examination of cyst wall showed that 27% of cases had follicle loss. (Bhat RG, Dhulke S, Ramachandran A, Bhaktha R, Vasudeva A, Kumar P et al. Laparoscopic cystectomy of endometrioma: good surgical technique does not adversely affect ovarian reserve. J Hum Reprod Sci 2014;7:125-9.)

- A more recently proposed laparoscopic surgical technique for ovarian endometrioma has applied a combined approach. Such a technique was found to be a suitable alternative to the classic technique in endometrioma with cyst bed stripping. (Donnez J, Lousse JC, Jadoul P, Donnez O, Squifflet J. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. Fertil Steril 2010;94:28-32.)
Endometriosis as a cause of DOR

Given the progressive nature of endometrioma and the possibility of irreversible ovarian cortical injury, early diagnosis of the pathology is crucial. In addition, the treatment of endometriosis should be performed before devascularization and occurrence of follicular loss. The endometrioma-induced devascularization in the cyst bed can be predicted by transvaginal color Doppler sonography. (Brosens I, Puttemans P, Gordts S, Campo R, Gordts S, Benagiano G. Early stage management of ovarian endometrioma to prevent infertility. Facts Views Vision ObGyn 2013;5:309-14.)

According to a recent report which compared patients with endometrioma with those who concomitantly suffered from endometrioma and DIE, both AFC and the number of retrieved oocyte in IVF were more significantly reduced in the DIE-endometrioma group. (Papaleo E, Ottolina J, Vigano 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 Obstet Gynecol Scand 2011;90:878-84.)
Endometriosis as a cause of DOR

- Post-operative evaluation of patients with DIE, revealed that laparoscopic resection of the lesions as well as laparoscopic bowel resection ameliorated pain, improved the clinical outcome, sexual function, quality of life and increased both spontaneous and IVF resulted pregnancy rates. Based on these data, laparoscopic resection of DIE in infertile patients resulted in more pregnancy rate. (Meuleman C, Tomassetti C, D'Hoore A, Buyens A, Van Cleynenbreugel B, Fieuws Set al. Clinical outcome after co(2) laser laparoscopic radical excision of endometriosis with colorectal wall invasion combined with laparoscopic segmental bowel resection and reanastomosis. Hum Reprod 2011;26:2336-43.)
Treatment of poor responders considering endometriosis

- Dose of gonadotropins
- Antagonist
- The use of estradiol
- Recombinant LH
- Growth hormone
- DHEA
- Aspirin
- Natural cycle IVF
Future hopes

- Elective oocyte cryopreservation offers hope to women who plan to defer childbearing for professional or social reasons. While the idea of preserving oocyte to ensure future fertility potential may be seen intriguing for any reason, insufficient data on this issue has discouraged physicians to recommend its widespread use. Furthermore, cryopreservation after the age of 38 is not shown to yield any favorable outcome. (Borini A, Levi Setti PE, Anserini P, De Luca R, De Santis L, Porcu Eet al. Multicenter observational study on slow-cooling oocyte cryopreservation: Clinical outcome. Fertil Steril 2010;94:1662-8.)

- Meanwhile, oocyte cryopreservation is considered as a practical and beneficial strategy in distinct female children such as girls with turner syndrome or cancer who are at an increased risk for POF. (Oktay K, Bedoschi G. Oocyte cryopreservation for fertility preservation in postpubertal female children at risk for premature ovarian failure due to accelerated follicle loss in turner syndrome or cancer treatments. J Pediatr Adolesc Gynecol 2014;27:342-6).
Studies have revealed that mesenchymal stem cells (MSCs) may significantly decrease the rate of apoptosis in primordial follicles and prevent the loss of follicles in the grafted ovarian tissues. Taken together, the use of MSCs transplantation of the cryopreserved ovarian tissue can now be deemed as a useful strategy to optimize fertility preservation and restoration. (Xia X, Yin T, Yan J, Yan L, Jin C, Lu C et al. Mesenchymal stem cells enhance angiogenesis and follicle survival in human cryopreserved ovarian cortex transplantation. Cell Transplantation 2014 [Epub ahead of print]).

In general, stem cell mitochondria can be considered as an optimal source for supplementation of oocytes with compromised quality. (Schatten H, Sun QY, Prather R. The impact of mitochondrial function/dysfunction on ivf and new treatment possibilities for infertility. Reproductive Biology and Endocrinology 2014;12:111)
Conclusions:

- DOR predicts the suboptimal ovarian response to stimulation. Although it differs from premature ovarian failure it is a real concern for the patient and her clinician.

- Among different tests to evaluate DOR, AMH measurement seems to be the test of choice.

- There are many factors such as aging, autoimmune and metabolic diseases, infections, genetic abnormalities and iatrogenic causes for DOR.

- Endometriosis due to its high prevalence may be considered as the leading cause of DOR and its treatment which at present time is laparoscopic cystectomy for endometrioma and resection of DIEs, should be carefully discussed with the patient especially for its potential harmful effect on the ovarian reserve.
Conclusions:

- This is especially true for those patients with bilateral endometrioma and those with diminished ovarian reserve prior to the operation, who may benefit from direct referral to ART.

- There are some newer protocols for poor responding patients which may be useful and these patients may benefit from natural cycle IVF.

- Oocyte and ovarian tissue cryopreservation offer hope for patients with DOR and new techniques, such as ovarian transplantation and transfer of mitochondria to improve the quality of oocyte, may become a part of the routine treatment procedures in the near future.