

The Role of Endometrioma Surgery in Assisted Reproductive Treatments

Yardımla Üreme Tedavilerinde Endometrioma Cerrahisinin Yeri

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ABSTRACT Association between endometriosis and infertility was well established, and different mechanisms have been postulated depending on the stage of endometriosis. However, effect of endometrioma(s) when considered independent of the stage is still unclear. Accordingly, surgical removal of endometrioma(s) is also controversial in a patient who has a pregnancy-wish. Conflicting results are seen regarding the impact on assisted reproductive treatments (ART) outcome of endometrioma surgery. We specifically propose that patients with endometrioma(s) who underwent several failed ART attempts do not get benefit from surgical removal which would be a wastage of time. Even opinions exist that ART has superseded surgery as first-line therapy for endometriosis. The main drawbacks of endometrioma surgery which are subsequent decrease in ovarian reserve and delay for a new ART cycle become even more significant in an infertile couple with recurrent ART failures. Well-designed studies are required examining utility of endometrioma surgery in ART programmes to adopt an evidence-based approach.

Key Words: Endometriosis; endometrioma; reproductive techniques, assisted

ÖZET Endometriozis ve infertilite birlikteliği literatürde net olarak ifade edilmektedir, nedensel ilişkide ise endometriozisin evresine göre farklı mekanizmalar öne sürülmektedir. Öte yandan hastalığın evresinden bağımsız olarak ovaryan endometriomanın infertiliteye etkisi hala netleşmemiştir. Bu sebeple çocuk sahibi olmak isteyen bir kadında endometrioma cerrahisi tartışmalıdır. Literatürde endometrioma cerrahisinin yardımla üreme tedavi (YÜT) sonucuna etkisi ile ilgili farklı sonuçlar bulunmaktadır. Bu yazı ile YÜT uygulanan kadınlarda endometrioma cerrahisinin yeri tartışılmıştır. Özellikle tekrar eden YÜT başarısızlığı olan kadınlarda endometrioma cerrahisinin faydalı olmadığı ve zaman kaybına yol açacağı öne sürülmektedir. Son zamanlarda endometriozisin ilk basamak tedavisinde bile YÜT'nin cerrahiye üstün olduğu ifade edilmektedir. Endometrioma cerrahisinin over rezervinde azalmaya yol açma olasılığı ve de yeni bir tedavi siklusunu için zaman kaybı oluşturması tekrar eden YÜT başarısızlığı olan infertil çiftlerde daha da önem kazanmaktadır. Ovaryan endometrioma cerrahisinin YÜT programlarında yararı ile ilgili kanıta dayalı yaklaşımlar oluşturabilmek için iyi planlanmış çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Endometriozis, endometrioma; yardımla üreme tedavileri

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Endometriosis might be defined simply as the existence of both stromal and epithelial components of endometrial cells in locations other than the uterus. Endometriosis affects about 10% of women of reproductive age and is more frequently diagnosed in patients with infertility than in a normal population.¹ The prevalence was suggested to be 0.5 to 5% in fertile and 25 to 40% in infertile women. Although the exact nature of

the relation between endometriosis and infertility still remains uncertain, subfertility is a well-known result of endometriosis.² The debate continues on what makes the conception more difficult in endometriosis patients.

ENDOMETRIOSIS AND INFERTILITY

Although it is well-known that endometriosis is associated with infertility, the causal relationship is as yet undetermined, unless adhesive disease is found. Mechanical alterations of the reproductive tract might explain the association between advanced stage endometriosis and infertility, however the issue of how mild to moderate endometriosis can impair fertility is one of the most discussed ones in the literature.³ Application of ART's provided new insights into the possible mechanisms underlying the relation between endometriosis and infertility. ART's proposed two parameters for the poor success rates in women with endometriosis; poor oocyte/embryo quality and poor endometrial quality.

A. OOCYTE/EMBRYO QUALITY IN ENDOMETRIOSIS-ASSOCIATED INFERTILITY

The follicular environment strongly affects the oocyte included within it which surely has an impact on the quality and the progression of the resulting embryo. Therefore follicular components, oocytes and the resulting embryos were investigated either by clinical studies in IVF or oocyte donation cycles or by basic studies using molecular markers looking for differences between patients with and without endometriosis. Contradictory results have been reported possibly due to different study designs, controls, sample sizes and different methods of detection.

i. Clinical Studies

In programs of assisted reproduction, some studies have shown that the number and the quality of oocytes, the fertilization and the implantation rates may be reduced in women with endometriosis, but this observation has not been confirmed by other investigators. Some authors described altered oocyte/embryo quality in patients with endometriosis

compared to healthy controls.^{4,5} Furthermore, studies in oocyte donation programmes support the theory of poor quality oocytes produced by the ovaries of the endometriosis-affected women.² When the outcomes of oocyte donation cycles were analysed according to the origin of the oocytes donated, women who received embryos derived from endometriotic ovaries demonstrated a significantly reduced implantation rate.⁶ The results of the mentioned study support the thesis that infertility in endometriosis patients is not related to an altered endometrial receptivity, but is related to a diminished quality of follicular environment/oocyte/resulting embryo component. In another study, embryo quality between endometriosis and tubal factor patients were compared and the results revealed a significant increase in the ratio of arrested embryos in endometriosis patients.⁵ Pal et al. investigated the impact of severity of endometriosis on the outcome of in vitro fertilization comparing patients with stage I/II (or minimal/mild) and II-I/IV (or moderate/severe) according to the revised American Fertility Society (rAFS) classification.⁷ They found that the number, maturity and quality of the oocytes, implantation, clinical pregnancy, and miscarriage rates were comparable between patients with varying severity of endometriosis. However, fertilization rates for oocytes of patients with stages III/IV were found to be significantly impaired compared to those with stages I/II. The reduced fertilization potential of the oocytes obtained from patients with severe endometriosis in the absence of male-factor infertility was suggested to be due to an adverse biological impact of the advanced disease on the oocytes.

ii. Basic Studies

Oocyte development and maturation was considered to be affected by the alterations in the follicular microenvironment which is comprised of the endocrine and paracrine factors secreted by the granulosa cells and present in the follicular fluid. To address this issue, plasma, follicular fluid and granulosa cell culture studies were performed to document the implications of molecules associated with steroidogenesis, angiogenesis and apoptosis. Some of those molecules investigated were progesterone

teron, estradiol, androstenedione, testosterone, IL-6, IL-1 β , VEGF, IL-8, TNF- α , natural killer cells, B lymphocytes, monocytes, prostaglandin F2 α , mul-lerian inhibiting substance, inhibin A, inhibin B, activin B and endothelin-1.⁸⁻¹⁵ There is an epidemiological evidence to support the association between endometriosis and recurrent implantation failure after assisted reproduction.¹⁶ This relation was suggested to be due to alterations in humoral and cell-mediated immunity in women with endometriosis. These immunological changes may negatively affect the folliculogenesis and the oocyte quality resulting in an embryo with decreased ability to implant.¹⁶ The results from the studies are highly controversial. Further prospective studies should be designed to assess the significant role of these molecules in the pathophysiology of endometriosis.

B. ENDOMETRIAL RECEPTIVITY IN ENDOMETRIOSIS-ASSOCIATED INFERTILITY

The other edge of implantation, that is, the endometrial receptivity was also suggested to be altered and therefore responsible, at least in part, for the subfertility seen in endometriosis patients.³

i. Clinical Studies

To address the issue of implantation further, oocyte donation programmes were analysed which are good models to reveal the impact of endometrial component in endometriosis patients. In a study by Sung et al. recipients were divided into groups containing women with and without endometriosis.¹⁷ Implantation and pregnancy rates were found to be similar. In another prospective study, oocytes from a single donor were donated to recipients with stage III-IV endometriosis and to those without the disease.¹⁸ Outcomes assessed included implantation, pregnancy, miscarriage and live birth rates which were not different between the groups. Similarly, in a study by Simon et al., it was shown that patients with endometriosis undergoing IVF with oocyte donation had the same chances of implantation and pregnancy as other recipients when oocytes originated from donors without known endometriosis.⁶ Some investigators proposed that a good quality embryo

might overcome the slight decrease observed in endometrial receptivity.³

ii. Basic Studies

Many investigators evaluated the molecular and morphological markers of endometrial receptivity in endometriosis. Studies regarding pinopod formation, integrins, anti-endometrial antibodies, transforming growth factor beta (TGF- β), glutathione peroxidase, apoptosis and Fas-L were performed.¹⁹⁻²⁶ The role of endometrial alteration in endometriosis-associated infertility still remains undetermined. Future studies regarding endometrial aspect should be well-designed, randomized and controlled in order to avoid results complicating the interpretation of the pathophysiology of this interesting disease.

Management of endometriosis-associated infertility

Management of infertility related to endometriosis is a source of controversy and so far no consensus has been reached. Quite often complex decisions must be made regarding the management of the endometriosis patient who has a pregnancy-wish. Medical treatment has no place in infertility treatment, however laparoscopic surgical treatment of minimal and mild endometriosis has been demonstrated to increase fecundity. Many papers exist in the literature to assess the impact on fertility of surgery to eradicate endometriosis. Recently, opinions exist that ART has superseded surgery as first-line therapy for endometriosis.²⁷ Furthermore, these authors say "infertility surgery is dead: only the obituary remains?". The rationale is that the time to pregnancy is faster and success rates are quite high with ART in endometriosis patients.

Removal of endometrioma(s) is a wastage of time in infertile women with several failed assisted reproductive treatments

Endometriomas are endometriotic deposits within the ovary. The origin of endometrioma is unclear. Most investigators think that it results from a deposit of endometrium passed through the fallopian tube, causing adherence of the ovary to the pelvic peritoneum and progressive folding of the ovary inwards.²⁸⁻³⁰ According to this theory, an endometri-

oma is a pseudocyst, the wall being the inverted ovarian cortex. Therefore, removal of the wall might involve normal ovarian tissue which may decrease the ovarian reserve.³¹

The effect of an ovarian endometrioma on IVF outcome is still a matter of debate. In a meta-analysis, ovarian responsiveness to ovarian stimulation and assisted reproduction outcomes in patients with ovarian endometrioma were evaluated.³² The results of the meta-analysis indicate that ovarian endometrioma has adverse effects on follicle number and oocytes retrieved but not on embryo quality or pregnancy outcomes. It was reported in that meta-analysis that the odds for clinical pregnancy were not affected significantly, although ovarian responsiveness to ovarian stimulation was decreased in patients with ovarian endometrioma compared with controls which may be due to a reduced number of follicles in these patients. The presence of an endometrioma during IVF cycles has been associated with the need for greater amounts of gonadotropins and fewer oocyte yield, suggesting that the endometrioma may be compromising ovarian function.³³ Barnhart et al., in a meta-analysis, reported that endometriomas negatively impacted ART success, however they did not address whether surgical correction improved the outcome.³⁴

On the contrary, a study using sibling oocytes demonstrated similar outcomes in oocyte recipients with advanced stage endometriosis compared with controls, and showed that endometriomas did not negatively affect implantation rates.¹⁸ Another study compared two patient groups with previous removal of an endometrioma, one of which had no visible endometriomas while the other group had a visible endometrioma <4 cm at the initial ultrasound.³⁵ They found no differences between the two groups regarding the pregnancy rates per embryo transfer. Similarly, Sung et al. concluded that the presence of endometriomas in women undergoing ovum donation is not a determinant of success.¹⁷ Garcia-Velasco et al. also demonstrated no adverse effect of endometrioma on IVF outcome.³⁶ Similarly, Pal et al. reported that the outcome of IVF-ET was unaffected by increasing severity of

endometriosis.⁷ They suggested that IVF may compensate for or overcome the reduction in the biological potential of the oocytes associated with severe disease, thus accounting for a comparable outcome irrespective of the severity of endometriosis. Some other investigators also proposed that the presence and the extent of endometriosis had no negative effect on implantation and pregnancy rates.^{6,37,38}

As seen, the results are controversial and it is unclear whether endometriomas have an impact on IVF outcome. Therefore, the main question to be answered should be whether surgical removal of endometriomas improves outcome and the benefits outweigh the risks of surgery. Surgical removal of an endometrioma carries the standard surgical risks of infection, bleeding and injury to the internal organs and also ovarian reserve may be impaired because of inadvertent removal or the thermal injury of the nearby ovarian cortex.

Endometrioma aspiration alone is not recommended due to the high rate of recurrence and also high infection and abscess risk.^{39,40} In a study which investigated whether aspiration of endometriomas at the beginning of the treatment improved ART outcomes, it was concluded that the number of oocytes retrieved and the clinical pregnancy rates were not different between aspirated and nonaspirated groups.⁴¹ Some investigators proposed that surgical pretreatment was not necessary for ovarian endometrial cysts before IVF, but cyst aspiration may be beneficial after several failed attempts of IVF.⁴²

Whether the excisional or ablative laparoscopic approach is more effective is also controversial. The technique of ovarian endometrioma capsule excision may lead to removal of healthy ovarian tissue.⁴³ Capsule ablation may lead to thermal damage to the underlying ovarian cortex and also a risk of incomplete destruction of the endometriotic tissue.⁴⁴ Thus both procedures may lead ovarian cortical damage and hence a decrease in the ovarian reserve.

Studies were performed to examine the relationship between endometrioma surgery and subse-

quent response to gonadotropin stimulation. In a study comparing patients who underwent laparoscopic ovarian cystectomy with endometriomas >3cm to patients who had endometriomas and no surgery, the outcome parameters assessed which were implantation, clinical pregnancy and miscarriage rates were all similar, however, significantly more gonadotropins were required and lower peak E2 levels were achieved in patients who had surgery.³⁶ Two more investigators reported decreased ovarian reserve after endometrioma surgery.^{45,46} However, surgical technique is highly dependent on the operator skill and therefore studies may not be generalizable.

Decreased ovarian reserve is the major hesitation of the clinician when the endometrioma surgery is considered. Tissue planes are often difficult to dissect and inadvertent removal of the adjacent normal ovarian cortex occurs because of the nature of the disease. In patients with endometrioma(s) who underwent several failed ART's before, ovarian reserve becomes even more important. Hence, surgical removal of endometrioma(s) in such a patient before a new treatment might cause harm more than a benefit. Moreover, it is not clear yet whether IVF outcome improves following endometrioma surgery whether excisional, ablative or aspiration. The general opinion is that the surgical management should only be reserved for cases in which ART was not initially effective.²⁷ However, based on the studies including women with previous endometrioma surgery who underwent ART, we further support that there exists no role or benefit of surgery after a failed ART attempt. We suggest that a new assisted reproduction cycle is better to be started without the removal endometrioma, maybe with a different stimulation protocol from the previous one(s), in women with ovarian endometriomas who previously underwent several failed ART's. Therefore, we support that no benefit of endometrioma surgery exists in couples with recurrent ART failures. Moreover, recurrent ovarian surgery should be avoided.

In a study, cumulative endometriosis recurrence rate 36 months after the start of ovarian hyperstimulation was given as 63% in patients

who underwent fertility surgery for endometriosis stage III or IV.⁴⁷ Therefore, infertility surgery before ART seems to be a temporary solution with a controversial benefit. Another study of endometriosis patients with stage III and IV reported that more than half the patients in fact remained sterile in spite of the operation.⁴⁸ Therefore, early referral for ART should be recommended to women with severe disease. As we all know, the presence of an endometrioma >1 cm puts an individual at stage III or IV disease according to the revised American Fertility Society (rAFS) classification.⁴⁹

In the literature, a clinically relevant decline has been reported in female fecundity when a woman reaches her mid 30s, for which even ART cannot compensate.⁵⁰ Therefore, in a woman with ovarian endometrioma(s) and previous failed ART's, age should be an important limitation in the decision of endometrioma surgery. Ovarian surgery for the treatment of endometriosis reduces the outcome in IVF/ICSI cycles in women >35 years old, and might also decrease pregnancy rates. Therefore, especially for aged infertile patients, non-surgical treatment might be a better option to avoid reduction of the ovarian response.⁵¹

Lastly, a basic study investigated prostaglandin F₂ α concentrations in the follicular fluid comparing women with and without visible endometriosis lesions and concluded that, even if lesions disappeared after treatment, fertility did not increase.⁹ On the contrary in a study, pregnancy rates were found to be increased with an increase in $\alpha\text{v}\beta 3$ expression after the treatment of endometriosis, supporting the surgical or medical treatment of endometriosis.⁵² Similarly, in a review, it has been suggested that the administration of gonadotropin releasing hormone (GnRH) agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by fourfold.⁵³ Studies show considerable variation in methodology, may not have enough statistical power or report results that are exactly the opposite of what has been previously published. Hence, further randomized controlled trials are needed to clarify

the issue.

CONCLUSION

The etiology and physiopathology of endometriosis-associated infertility are still unexplained, despite an enormous effort over many decades. Therefore, approach to a woman with an endometrioma is controversial. In young (<35 years) patients with good ovarian reserve, surgical removal of endometrioma(s) might be considered. However, even in this patient group with a good pregnancy chance, randomized controlled studies should be designed to investigate whether a clear

benefit is obtained with the removal of endometrioma(s). Otherwise, surgery delays time to pregnancy. It should be strongly stressed that patient age is a significant factor when considering the removal of endometrioma(s). We support the thesis that in infertile women with recurrent ART failures, the outcome in the subsequent treatment would not be improved after the removal of endometrioma(s). Those women do not get benefit from the endometrioma surgery. However, well-designed randomised controlled trials examining the utility of endometrioma surgery in ART programmes are required and are necessary to adopt an

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Evidence-based approach

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