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Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options

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Abstract

Endometriosis is a common condition in women of reproductive age. In addition to pain, endometriosis may also reduce fertility. The causes of infertility in women with endometriosis may range from anatomical distortions due to adhesions and fibrosis to endocrine abnormalities and immunological disturbances. In some cases, the various pathophysiological derangements seem to interact by mechanisms so far not fully understood.

Whether surgery should be offered as a treatment option in endometriosis-associated infertility has become controversial, partly due to its modest or undocumented effect. Medical or hormonal treatment alone has little or no effect and should only be used in conjunction with assisted reproductive technology (ART). Of the various methods of ART, intrauterine insemination, due to its simplicity, can be recommended in women with minimal or mild peritoneal endometriosis, even though insemination may yield lower success rate than in women without endometriosis. In vitro fertilization (IVF) is an effective treatment option in less advanced disease stages, and the success rates are similar to the results in other causes of infertility. However, women with more advanced stages of endometriosis have lower success rates with IVF.

Keywords

endometriosis, infertility, surgery, insemination, IVF

Key Message

Infertility in women with endometriosis is common, and possible causes are numerous. Many treatment alternatives exist, but with the exception in vitro fertilization, documented effect is modest or none.

Introduction

Endometriosis is a chronic inflammatory disease in women of reproductive age and can cause both pain and infertility. The gold standard for diagnosing endometriosis is laparoscopy, preferably including histological verification by biopsy of suspected lesions. Since surgery is invasive and costly, the true prevalence of endometriosis in women of

reproductive age remains uncertain. The estimated overall prevalence of endometriosis in population-based studies varies from 0.8% to 6% (1-3); however, in subfertile women the prevalence seems to be considerably higher, ranging from 20 to 50%, but with significant variation over time periods and the age of patients (4,5). In a large cohort study on women of reproductive age, the risk of infertility was two-fold increased in women below 35 years with endometriosis compared to women without endometriosis(6). Endometriosis is therefore a frequent cause of infertility, either by itself or in conjunction with other fertility-reducing factors.

Material and methods

In this narrative review, literature search was performed in PubMed, Medline and Embase from March to November 2016 using the key words and MeSH terms endometriosis, infertility, surgery, assisted reproductive technology (ART), intrauterine insemination, in vitro fertilization, and intracytoplasmic sperm injection. In addition, international and national data registers and guidelines on outcome of ART were checked. The search was restricted to sources in English language. Preferably, data from meta-analyses and randomized controlled trials of recent origin were used; however, when such data did not exist, observational studies were also included.

Classification

Endometriosis may exist in various forms, from just a few implants on the pelvic peritoneum to extensive adhesions and organ infiltration, and even lesions outside the pelvis. It has been assumed that clinical outcomes, including pain and subfertility, correlate with the extent of endometriosis, which is usually categorized by one of several classification systems. In fertility studies, the American Fertility Society (later named The American Society for Reproductive Medicine, ASRM) classification has been the most commonly used, first published in 1979 and revised twice, latest in 1996 (American Society for Reproductive Medicine 1997) (7). The revised ASRM classification is a scoring system based on localization and size of implants and extent of adhesions. A point score defines four classes: minimal, mild, moderate, and severe endometriosis. This scoring system does not take into account the depth and thereby the invasiveness or appearance of the endometriotic lesions.

Unfortunately, it has for many years remained unclear whether the ASRM classification has any prognostic significance regarding prediction of a woman's fertility potential (8).

A more recent classification system is the Endometriosis Fertility Index (EFI). This classification system is based on the point scores from the ASRM system combined with additional anamnestic and post-surgical information (9). The EFI gives a score from zero to ten points, and the score predicts well results from subsequent non-IVF treatments. After three years, those with a point score of 0 – 3 had only 10 % probability of becoming pregnant, while those with the highest score of 9 – 10 points had an approximately 75 % success rate. Similar results were found in external validations of the EFI (10,11), the latter study including results from both non-IVF and IVF treatment.

Etiology/pathogenesis

Although many theories exist as to the development of endometriosis, the most generally accepted one is that it may be initiated by retrograde menstrual flux through the Fallopian tubes. Epithelial progenitor cells derived from the shedding of endometrial tissue can implant on the peritoneum, ovaries, or in the rectovaginal pouch. Once established, these hormone-responsive and cyclically active endometriotic lesions drive acute then chronic inflammatory reactions, and lead to pelvic adhesions, pain, and infertility. Individual susceptibility to endometriosis, however, is influenced by genetic, anatomical, endocrine, and environmental factors (12).

Clinical experience suggests that, at least in some women with established endometriosis, the disease is progressive and brings about increasingly worsened pain and subfertility (13). There seems to be an association between the extent of disease and the degree of reduced spontaneous fertility in endometriosis, although the strength of this association is variable (8). Among women with minimal/mild endometriosis, approximately 50% will be able to conceive without treatment, while in women with moderate disease, only 25% will conceive spontaneously, and few spontaneous conceptions occur in case of severe disease (14). Indeed, the rate of spontaneous pregnancy is comparable among women with minimal/mild endometriosis and women with unexplained infertility, indicating that minimal/mild endometriosis may have just a modest effect on fertility (15). Nonetheless, superficial peritoneal lesions are more closely associated with infertility than endometrioma and deeply

infiltrating endometriosis (16). Extensive disease with pelvic adhesions and obliteration of the cul-de-sac, however, may result in infertility due to occlusion of the tubal ostium compromising sperm passage, further aggravated by the embedment of the ovaries in adhesions. Nonetheless, in the absence of major mechanical distortions in moderate endometriosis, alternative pathomechanisms of endometriosis-associated infertility must be considered (Table 1).

Chronic intraperitoneal inflammation is a characteristic feature of endometriosis (17-19). According to a likely disease model, endometriotic peritoneal implants induce an acute inflammatory reaction, which is associated with recruitment and activation of T-helper and Treg cell subsets. After resolution of the acute phase, monocytes/macrophages maintain a chronic inflammation, which contributes to peritoneal adhesion formation and angiogenesis. This model is supported by animal experiments and some human data. In baboons, peritoneal inoculation of menstrual endometrium induces depletion of peripheral Treg cells, which increasingly accumulate in the ectopic endometrial tissue and contribute to survival of the lesions (20). In mice, activated Th1 helper cells contribute to formation of peritoneal adhesions (21); alternatively activated macrophages (M2) promote growth and survival of endometriotic lesions, whereas inflammatory M1 macrophages modulate their absorption (22). In women, most data support an increased presence of inflammatory mediators (cytokines, chemokines, and prostaglandins) in the peritoneal fluid in endometriosis (23). The concentration of peripheral Tregs is reduced, whereas intraperitoneal Tregs is increased (24). Intraperitoneal Tregs may suppress effector T-cells and promote proliferation and invasion of endometrial stromal cells (25. The macrophages in the ectopic lesions are typically polarized towards M2, however, there is a bias towards M1 among macrophages of the eutopic endometrium in women with endometriosis (26). Notably, a recent paper identified an endometriosis-related cytokine profile, which could be linked to macrophage activation (27).

Chronic inflammation in endometriosis may impair fertility by several pathways. Increased concentration of IL1b, IL8, IL10 and TNF alpha in follicles adjacent to endometriomas is associated with reduced ovarian response (28). The level of IL6 in peritoneal fluid from women with endometriosis is elevated and this cytokine may inhibit sperm motility (29,30), and inflammatory mediators of the peritoneal fluid may also contribute to sperm DNA damage (31). In addition, oxidative stress, prostaglandins and cytokines may interfere with oocyte-sperm interaction, impair embryo development, and hinder implantation (32).

Dysfunction of the hypothalamo-pituitary-ovarian axis may contribute to infertility in patients presenting with a prolonged follicular phase, low serum estradiol levels, and reduced peak luteinizing hormone concentration (33). Pituitary dysfunction in endometriosis would predict disturbed folliculogenesis, reduced oocyte quality and/or a reduced endometrial receptivity. Indeed, these abnormalities have been demonstrated in some studies, but the findings are equivocal (32,34).

Normal secretion of progesterone and responsiveness of endometrium to its effect during the luteal phase is mandatory for the transition of the endometrium from a proliferative to a secretory and receptive stage. In endometriosis, reduced expression of progesterone receptors in the endometrium may cause progesterone resistance (35). Furthermore, progesterone induces the expression of 17beta-hydroxysteroid dehydrogenase type 2 (HSD17B2), which metabolizes the biologically potent estradiol to the less potent estrone. In women with endometriosis and progesterone resistance, endometrial function may be afflicted by an increased estrogenic bioactivity upon loss of HSD17B2 activity (36). Indeed, an increased estrogenic milieu induces inflammatory responses in the endometriotic tissue, characterized by elevated levels of many inflammatory cytokines (37).

Oocyte donation is an instructive clinical model to dissect the effects of endometrial receptivity from oocyte competence in endometriosis-associated infertility. A recent review of oocyte donation studies found that patients receiving oocytes from donors with endometriosis achieve lower implantation and pregnancy rates, whereas the status of the recipient does not influence treatment outcome (38). This suggests that a reduced fertility potential in women with endometriosis may be the result of poor oocyte quality rather than a defective endometrium. Nevertheless, elevated levels of anti-endometrial antibodies have been detected in serum from women with endometriosis, and binding of such antibodies to endometrial antigens may cause implantation failure (39).

In fertile women, the dominant follicle will rupture and release the oocyte-cumulus complex within 38 hours after the luteinizing hormone surge. Occasionally, the follicle undergoes luteinization but fails to rupture and release the ovum, a condition termed luteinized unruptured follicle syndrome (LUF). LUF syndrome cannot be diagnosed by hormonal assays, only by repeated ultrasound scans demonstrating the presence of unruptured follicles. Women with endometriosis have a higher prevalence of LUF syndrome than women without endometriosis (40). In addition, non-steroid inflammatory drugs (NSAIDS)

that are often prescribed for dysmenorrhea, have been shown to increase the risk of LUF syndrome. NSAIDS inhibit cyclooxygenase with a resulting low prostaglandin production in the ovaries, inhibition of matrix metalloproteinases, and loss of follicle rupture (41).

In the uterus, coordinated muscular contractions enhance sperm transport to the Fallopian tubes where spermatozoa undergo capacitation and hyperactivation in order to reach the ampullary part of the tube and fertilize the ovum. After fertilization, the embryo is passively transported through the Fallopian tube to the uterine cavity. In endometriosis, uterotubal dysperistalsis may contribute to infertility because of disturbed transport of gametes and embryos (42).

Treatment

Treatment of endometriosis-associated infertility has been based on three modalities: medical treatment, surgery, and assisted reproduction.

Medical treatment

Medical treatment of endometriosis-associated infertility has followed two strategies: 1) suppression of follicle growth with the aim to induce amenorrhea and thereby suppress development and growth of endometriotic lesions with the aim to increase subsequent fertility; 2) stimulation of follicle growth and ovulation. Suppression of ovulation with Gonadotropin-releasing hormone agonists, progestins, danazol, or oral contraceptives have all been shown not to improve fertility in women with endometriosis; indeed, such treatments seem rather to postpone pregnancy and imply side effects (43). For stimulation of follicle growth and ovulation, clomiphene citrate has most commonly been prescribed, either alone or in combination with gonadotropins. More recently, aromatase inhibitors have also been used for follicle stimulation (44). However, these studies most often tested combinations of various treatments, and therefore the efficacy of ovarian stimulation isolated from other procedures in endometriosis-associated infertility remains to be documented.

Surgery

Surgery has previously played an important role in the treatment of endometriosis-associated infertility. When considering the efficacy of surgical treatment, the disease stage (minimal/mild, moderate/severe and endometriomas) and outcomes compared to alternative treatment modalities must be taken into account.

In minimal/mild endometriosis without disruptive anatomy, the objective of surgery is to destroy or remove all or most of the endometriotic implants. In such women, two meta-analyses published in 2014 concluded that removal or destruction of endometriosis improves fertility. In one of the studies, summarizing data from two randomized trials, clinical pregnancy rate improved by a risk ratio of 1.44, 95% confidence interval (CI) 1.24 – 1.68 (45), while the other study, reported an increased odds ratio for a live birth, odds ratio 1.94, 95% CI 1.20 – 3.16 (46). These meta-analyses were dominated by a large Canadian multicenter trial, in which the monthly fecundity rate and 36-week cumulative probability of having a pregnancy increased from 2.4% and 17.7% respectively after diagnostic laparoscopy to 4.7 and 30.7% after laparoscopic surgery (47). Although these results indicate a superiority of laparoscopic surgery compared to diagnostic laparoscopy, one may question whether a 30% cumulative probability of becoming pregnant during 36 weeks justifies surgical treatment, when one single IVF-attempt will usually have a similar success rate. Nonetheless, one should also consider the age of the patient, the costs, and reimbursement, when recommending treatment alternatives.

In moderate/severe endometriosis, the goal of surgery is to restore normal anatomy of the pelvis and remove large endometriomas. Unfortunately, there are no randomized controlled trials on the effect of surgery in women with moderate/severe endometriosis-associated infertility versus medical or no treatment, and observational studies are often flawed by not adjusting for possible confounding factors (48). A historical meta-analysis on observational studies suggested that laparoscopic surgery was superior to medical treatment or no treatment in endometriosis, but the stage of the disease was not reported in many of the included studies in that paper (49).

The benefit of medical treatment before or after surgery is uncertain. In theory, suppression of endometriosis prior to surgery may reduce inflammation and aid removal of the lesions, but may also make minor foci invisible. Postoperative hormonal suppression may prevent

recurrence of endometriosis, however, neither preoperative nor postoperative medical treatment seems to have any overall clinical effect in systematic reviews (50).

Excision of endometriomas in infertile women has been controversial, given the risk of damage to ovarian reserve. In terms of clinical effect, systematic reviews fail to identify benefits of endometrioma surgery, neither aspiration nor cystectomy, on IVF outcome (51).

Assisted reproduction

Assisted reproductive technology (ART) comprises several treatment modalities that combine some kind of hormonal follicle stimulation with preparation and handling of gametes to bypass pathological barriers of reproduction. In principle, ART can be divided into in vivo or in vitro procedures depending on whether or not oocytes have been extracted from the ovaries, fertilized and cultured in a laboratory before transfer back into the uterus or in some cases the Fallopian tubes. There are many ART variants, particularly in vivo procedures. The most frequently used in vivo procedure is intrauterine insemination (IUI) with or without follicle stimulation, followed by gamete intrafallopian transfer (GIFT). Insemination of spermatozoa directly into the Fallopian tube or intraperitoneally has also been reported, but the studies are few and usually with a limited number of patients and treatment cycles, therefore these will not be described here. IVF with transfer of one or more embryos into the uterus is by far the most common in vitro procedure in couples with normal sperm counts. In cases of severely reduced sperm quality or previous failure of fertilization with IVF, intracytoplasmic sperm injection (ICSI) is used. A combination of IVF with transfer of zygotes/embryos by laparoscopy to the Fallopian tubes have also been described, but again, the number of papers and cycles reported are few. In this paper we will focus on insemination and IVF procedures.

Intrauterine insemination

Intrauterine insemination (IUI) with partner or donor sperm is a simple procedure that has been subject to many studies looking for optimal treatment of couples with minimal/mild endometriosis and normal semen quality. Unfortunately, several of these studies have methodological weaknesses, like combination of IUI with ovarian stimulation, not reporting

the stage of endometriosis, or performing ablative surgery just prior to the IUI treatment. Thus, the effect of IUI per se remain unclear.

In a large multicenter cohort study including 3371 couples and 14968 treatment cycles from the Netherlands, the presence of endometriosis was a risk factor for treatment failure (52). As in smaller previous reports (53-55), this study also showed superior outcomes when IUI was combined with ovarian stimulation with clomiphene citrate or gonadotropins. However, the outcome data in this paper were not tabulated according to disease stage.

When evaluating treatment benefits in endometriosis, it is important to select fair intervention and comparison groups. Indeed, IUI is typically not offered to women with moderate/severe endometriosis, because of a probable affection of the Fallopian tubes. Therefore, it may be more appropriate to compare minimal/mild endometriosis-associated infertility to unexplained infertility during IUI treatment. Table 2 presents cohort studies reporting these comparisons (56-63). Based on these studies, patients with minimal/mild endometriosis-associated infertility achieve lower success rates with stimulation and IUI compared to women with unexplained infertility. However, shortly after ablation of minimal/mild endometriosis, clinical pregnancy rate per treatment cycle and cumulative birth rate were similar in endometriosis and unexplained infertility, indicating a detrimental effect of endometriosis on fertility (61).

In vitro fertilization (IVF)

In a now classical meta-analysis, it was shown that infertile women with endometriosis had substantially lower success with IVF compared to tubal factor infertility, including lower ovarian response, reduced implantation rate and pregnancy rate. In addition, a more advanced disease was related to increasingly inferior outcome (64). In two more recent meta-analyses on outcome of IVF in endometriosis, live birth rate was found to be similar in minimal/mild endometriosis and other indications for IVF, while in patients with moderate/severe endometriosis, the results were inferior, including fewer oocytes retrieved, lower implantation rate, and lower birth rate (65,66). The Society for Assisted Reproductive Technology (SART) and ASRM collect data on a vast number of IVF treatments (67). During the period 2010 – 2013, women with endometriosis had a marginally higher cancellation rate and more embryos transferred compared to the tubal factor group, but achieved comparable live birth rate per cycle, Table 3. Since endometriosis may occur together with other infertility diagnoses, data from the ASRM/SART register were used to

compare the results in couples having endometriosis as a sole diagnosis compared to those with endometriosis and additional diagnoses. This analysis showed that women with endometriosis had live birth rate similar to or slightly higher compared to those with other infertility diagnoses (68).

Conclusion

Endometriosis may impair fertility through multiple pathways, including peritoneal inflammation and endocrine derangements, which interfere with ovarian function and ultimately reduce oocyte competence. Removal of superficial peritoneal foci in minimal/mild endometriosis has been shown to improve fertility modestly, while resection of endometriomas and deep infiltrating lesions has an undocumented effect on fertility. Intrauterine insemination is a simple treatment procedure, but with modest effect. IVF is a successful treatment option with results comparable to other causes of infertility.

References

1. Moen MH, Schei B. Epidemiology of endometriosis in a Norwegian county. Acta Obstet Gynecol Scand. 1997;76:559-62.
2. Abbas S, Ihle P, Köster I, Schubert I. Prevalence and incidence of diagnosed endometriosis and risk of endometriosis in patients with endometriosis-related symptoms: findings from a statutory health insurance-based cohort in Germany. Eur J Obstet Gynecol Reprod Biol. 2012;160:79-83.
3. Fuldeore MJ, Soliman AM. Prevalence and Symptomatic Burden of Diagnosed Endometriosis in the United States: National Estimates from a Cross-Sectional Survey of 59,411 Women. Gynecol Obstet Invest. 2016 Nov 8. [Epub ahead of print]
4. Mahmood TA, Templeton A. Prevalence and genesis of endometriosis. Hum Reprod. 1991;6:544-9
5. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril. 2009;92:68-74.
6. J Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, Rich-Edwards JW, Barbieri RL, Missmer SA. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod. 2016;31:1475-82.
7. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine revised classification of endometriosis 1996. Fertil Steril. 1997;67:817-21.

8. Guzick DS, Silliman NP, Adamson GD, Buttram Jr VC, Canis M, Malinak LR et al. Prediction of pregnancy in infertile women based on the American Society for Reproductive Medicine's revised classification of endometriosis. Fertil Steril. 1997;67:822-9.
9. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010;94:1609-15.
10. 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. Hum Reprod. 2013;28:1280-8.
11. Boujenah J, Bonneau C, Hugues JN, Sifer C, Poncelet C. External validation of the Endometriosis Fertility Index in a French population. Fertil Steril. 2015;104:119-23.
12. Taylor RN, Lebovic DI. Endometriosis. In Strauss JF, Barbieri RL (editors). Yen & Jaffe's Reproductive Endocrinology. 7. Edition. Philadelphia PA: Elsevier Saunders, 2014. pp. 565-85
13. Koninckx PRC, Meuleman S, Demeyere E, Lesaffre, and F. J. Cornillie. Suggestive Evidence That Pelvic Endometriosis Is a Progressive Disease, Whereas Deeply Infiltrating Endometriosis Is Associated with Pelvic Pain. Fertil Steril.1991;55:759-65.
14. Olive DL, Stohs GF, Metzger DA, Franklin RR. Expectant management and hydrotubations in the treatment of endometriosis-associated infertility. Fertil Steril. 1985;44**:**35-41.
15. Bérubé S, Marcoux S, Langevin M, Maheux R. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. The Canadian Collaborative Group on Endometriosis. Fertil Steril. 1998;69:1034-41.
16. Santulli P, Lamau MC, Marcellin L, Gayet V, Marzouk P, Borghese B, et al.. Endometriosis-related infertility: ovarian endometrioma per se is not associated with presentation for infertility. Hum Reprod. 2016;31:1765-75.
17. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364:1789-99.
18. Lousse JC, Van Langendonckt A, Defrere S, Ramos RG, Colette S, Donnez J. Peritoneal endometriosis is an inflammatory disease. Front Biosci (Elite Ed). 2012;4:23-40.
19. Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, Tayade C. Pathophysiology and Immune Dysfunction in Endometriosis. Biomed Res Int. 2015;2015:795976.
20. Braundmeier A, Jackson K, Hastings J, Koehler J, Nowak R, Fazleabas A. Induction of endometriosis alters the peripheral and endometrial regulatory T cell population in the non-human primate. Human Reprod. 2012;27:1712-22.
21. Tzianabos AO, Holsti MH, Zheng XX, Stucchi AF,. Kuchroo VK, Strom TB et al. Functional Th1 cells are required for surgical adhesion formation in a murine model. J Immunol. 2008;180:6970-6.
22. Bacci M, Capobianco A, Monno A, a Cottone L, Di Puppo F, Camisa B et al. Macrophages are alternatively activated in patients with endometriosis and required for growth and vascularization of lesions in a mouse model of disease. Am J Pathol. 2009; 175:547-56.

23. Borrelli GM, Carvalho KI, Kallas EG, Mechsner S Baracat EC, Abrão MS. Chemokines in the pathogenesis of endometriosis and infertility. J Reprod Immunol. 2013;98:1-9.
24. Olkowska-Truchanowicz J, Bocian K, Maksym RB, Białoszewska A, Włodarczyk D, Baranowski W, et al. $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells in peripheral blood and peritoneal fluid of patients with endometriosis. Hum Reprod. 2013;28:119-24.
25. Li MQ, Wang Y, Chang KK, Meng YH, Liu LB, Mei J et al. CD4+Foxp3+ regulatory T cell differentiation mediated by endometrial stromal cell-derived TECK promotes the growth and invasion of endometriotic lesions. Cell Death Dis. 2014;5:e1436.
26. Takebayashi A, Kimura F, Kishi Y, Ishida M, Takahashi A, Yamanaka A et al. Subpopulations of macrophages within eutopic endometrium of endometriosis patients. Am J Reprod Immunol. 2015;73:221-31.
27. Beste MT, Pfäffle-Doyle N, Prentice EA, Morris SN, Lauffenburger DA, IsaacsonKB, et al. Molecular network analysis of endometriosis reveals a role for c-Jun-regulated macrophage activation. Sci Transl Med. 2014;222ra16.
28. Opøien HK, Fedorcsak P, Polec A, Stensen MH, Åbyholm T, Tanbo T. Do endometriomas induce an inflammatory reaction in nearby follicles? Hum Reprod.2013;28:1837-45.
29. Punnonen J, Teisala K, Ranta H. Increased levels of interleukin-6 and interleukin-10 in the peritoneal fluid of patients with endometriosis. Am J Obstet Gynecol 1996;174:1522-6.
30. Yoshida S, Harada T, Iwabe T. A combination of interleukin-6 and its soluble receptor impairs sperm motility: implications in infertility associated with endometriosis. Hum Reprod 2004;19:1821-5.
31. Mansour G, Aziz N, Sharma R, Falcone T, Goldberg J, Agarwal A. The impact of peritoneal fluid from healthy women and from women with endometriosis on sperm DNA and its relationship to the sperm deformity index. Fertil Steril. 2009;92:61-7.
32. Pellicer A, Oliveira N, Ruiz A, Remohí J, Simón C. Exploring the mechanism(s) of endometriosis-related infertility: an analysis of embryo development and implantation in assisted reproduction. Hum Reprod. 199510 Suppl 2:91-7.
33. Cahill DJ, Hull MG. Pituitary-ovarian dysfunction and endometriosis. HumReprod Update. 2000;6:56-66.
34. Opøien HK, Fedorcsak P, Omland AK, Abyholm T, Bjercke S, Ertzeid G et al. In vitro fertilization is a successful treatment in endometriosis-associated infertility. Fertil Steril. 2012;97:912-8.
35. Bulun SE, Cheng YH, Yin P, Imir G, Utsunomiya H, Attar E et al. Progesterone resistance in endometriosis: link to failure to metabolize estradiol. Mol Cell Endocrinol. 2006;248:94-103.
36. Lessey BA, Lebovic DI, Taylor RN. Eutopic endometrium in women with endometriosis: ground zero for the study of implantation defects. Semin Reprod Med. 2013;31:109-24.

37. Khan KN, Kitajima M, Inoue T, Fujishita A, Nakashima M, Masuzaki H. 17β-estradiol and lipopolysaccharide additively promote pelvic inflammation and growth of endometriosis. Reprod Sci. 2015;22:585-94.
38. Hauzman EE, Garcia-Velasco JA, Pellicer A. Oocyte donation and endometriosis: What are the lessons? Semin Reprod Med. 2013 ;31:173-7.
39. Sarapik A, Haller-Kikkatalo K, Utt M, Teesalu K, Salumets A, Uibo R. Serum anti-endometrial antibodies in infertile women - potential risk factor for implantation failure. Am J Reprod Immunol. 2010 ;63:349-57.
40. Dmowski WP, Rao R, Scommegna A. The luteinized unruptured follicle syndrome and endometriosis. Fertil Steril. 1980;33:30-4.
41. Smith G, Roberts R, Hall C, Nuki G. Reversible ovulatory failure associated with the development of luteinized unruptured follicles in women with inflammatory arthritis taking non-steroidal anti-inflammatory drugs. Br J Rheumatol. 1996 ;35:458-62.
42. Leyendecker G, Kunz G, Wildt L, Beil D, Deininger H. Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. Hum Reprod. 1996 ;11:1542-51
43. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2014 Mar 10;3:CD009590.
44. Bayar U, Tanriverdi HA, Barut A, Ayoğlu F, Ozcan O, Kaya E. Letrozole vs. clomiphene citrate in patients with ovulatory infertility. Fertil Steril. 2006;85:1045-8.
45. Jin X, Ruiz Beguerie J. Laparoscopic surgery for subfertility related to endometriosis: a meta-analysis. Taiwan J Obstet Gynecol. 2014;53:303-8.
46. Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R et al. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev. 2014 April 3;4:CD011031.
47. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med. 1997;337:217-22.
48. Angioni S, Cela V, Sedda F, Stochino Loi E, Cofelice V, Pontis A et al. Focusing on surgery results in infertile patients with deep endometriosis. Gynecol Endocrinol. 2015;31:595-8.
49. Adamson GD, Pasta DJ. Surgical treatment of endometriosis-associated infertility: meta-analysis compared with survival analysis. Am J Obstet Gynecol. 1994 ;171:1488-504.
50. Yap C, Furness S, Farquhar C. Pre and post operative medical therapy for endometriosis surgery. Cochrane Database Syst Rev. 2004;(3):CD003678.
51. Benschop L, Farquhar C, van der Poel N, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. Cochrane Database Syst Rev. 2010 ;(11):CD008571.
52. Steures P, van der Steeg JW, Mol BW, Eijkemans MJ, van der Veen F, Habbema JD et al. Prediction of an ongoing pregnancy after intrauterine insemination. Fertil Steril. 2004;82:45-51.

53. Chaffkin LM, Nulsen JC, Luciano AA, Metzger DA. A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. Fertil Steril. 1991 ;55:252-7.
54. DiMarzo SJ, Kennedy JF, Young PE, Hebert SA, Rosenberg DC, Villanueva B. Effect of controlled ovarian hyperstimulation on pregnancy rates after intrauterine insemination. Am J Obstet Gynecol. 1992;166:1607-12.
55. Nulsen JC, Walsh S, Dumez S, Metzger DA. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. Obstet Gynecol. 1993;82:780-6.
56. Yovich JL, Matson PL. The treatment of infertility by the high intrauterine insemination of husband's washed spermatozoa. Hum Reprod. 1988;3:939-43.
57. Omland AK, Tanbo T, Dale PO, Abyholm T. Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis. Hum Reprod. 1998;13:2602-5
58. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod. 1999;14:698-703.
59. Singh M, Goldberg J, Falcone T, Nelson D, Pasqualotto E, Attaran M et al. Superovulation and intrauterine insemination in cases of treated mild pelvic disease. J Assist Reprod Genet. 2001;18:26-9.
60. Göker EN, Ozçakir HT, Terek MC, Levi R, Adakan S, Tavmergen E. Controlled ovarian hyperstimulation and intrauterine insemination for infertility associated with endometriosis: a retrospective analysis. Arch Gynecol Obstet. 2002;266:21-4.
61. Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril. 2006;86:566-71.
62. Ahinko-Hakamaa K, Huhtala H, Tinkanen H. Success in intrauterine insemination: the role of etiology. Acta Obstet Gynecol Scand. 2007;86:855-60.
63. Jeon YE, Jung JA, Kim HY, Seo SK, Cho S, Choi YS et al. Predictive factors for pregnancy during the first four intrauterine insemination cycles using gonadotropin. Gynecol Endocrinol. 2013;29:834-8.
64. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in-vitro fertilization. Fertil Steril 2002;77:1148-55.
65. Harb HM, Gallos ID, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. BJOG. 2013;120:1308-20.
66. Hamdan M, Omar SZ, Dunselman G, Cheong Y. Influence of endometriosis on assisted reproductive technology outcomes: a systematic review and meta-analysis. Obstet Gynecol. 2015;125:79-88.

67. American Society for Reproductive Medicine/Society for Assisted Reproductive Technology. Available online at: https://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Educational_Bulletins/endometriosis_and_infertility(1).pdf
68. 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. Fertil Steril. 2016;106:164-171.

Table1. Possible causes for reduced fertility in women with endometriosis.

- Adhesions
- Chronic intraperitoneal inflammation
- Disturbed folliculogenesis
- Luteinized unruptured follicle
- Luteal phase defects
- Progesterone resistance
- Detrimental effects on spermatozoa
- Anti-endometrial antibodies
- Dysfunctional uterotubal motility

Table 2. Outcome of intrauterine insemination in women with minimal/mild endometriosis or unexplained infertility.

Author	Unexplained inf.		Endometriosis		P
	No. cycles	No. Pregnancies (%)	No. cycles	No. Pregnancies (%)	
Yovich -1988	134	12 (9.0)	65	5 (7.7)	0.98
Omland – 1998	119	40 (33.6)	49	8 (16.3)	< 0.04
Nuojua-Huttunen -1999	413	63 (15.3)	138	9 (6.5)	< 0.01
Singh - 2001	265	36 (13.6)	300	20 (6.7)	< 0.01
Göker - 2002	140	25 (17.9)	39	2 (5.1)	0.09
Werbrouck –2006	122	25 (20.5)	137	28 (20.4)	0.99
Ahinko-Hakamaa - 2007	637	90 (14.1)	126	15 (11.9)	0.51
Jeon - 2013	271	48 (17.7)	47	2 (4.3)	<0.05
Total	2101	339 (16.1)	901	89 (9.9)	< 0.01

Table 3. Cumulative results of IVF in endometriosis and tubal infertility from the ASRM/SART registry 2010 – 2013.

	Endometriosis	Tubal infertility	P
No. of started cycles	14201	24741	
Cancellation rate			
< 35 years	6.9% (556/8010)	5.6% (643/11482)	< 0.001
35 – 37 years	9.4% (304/3248)	8.3% (526/6337)	0.08
38 – 40 years	12.4% (270/2182)	10.9% (552/5066)	0.07
>= 41 years	16.2% (123/761)	15.3% (335/2183)	0.59
No. Embryos transferred			
< 35 years	2.0 (14657/7454)	1.9 (20627/10839)	< 0.01
35 – 37 years	2.2 (6347/2944)	2.1 (12376/5811)	0.50
38 – 40 years	3.1 (4949/1573)	2.6 (11565/4504)	< 0.001
>= 41 years	3.1 (1962/638)	2.9 (5424/1848)	0.21
Live pregnancy rate per cycle			
< 35 years	41.0% (3281/8010)	40.2% (4618/11482)	0.30
35 – 37 years	31.4% (1019/3248)	32.6% (2069/6337)	0.21
38 – 40 years	22.9% (500/2182)	23.1% (1171/5066)	0.85
>= 41 years	10.9% (83/761)	11.1% (242/2183)	0.89