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

Running headline: Endometriosis-associated infertility

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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 patterns seem to interact by mechanisms so far not fully understood.

Whether surgery should 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, and preferably in combination with hormonal follicle stimulation, may 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.

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, which 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 2% (1,2); 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 (3,4). 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 (5). 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 September 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 (RCT) of recent origin was 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)(6). The revised AFS classification is a scoring system of 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 (7).

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 (8). The EFI predicts spontaneous fertility potential after surgery, as affirmed by external validation (9), and has also been validated for assisted reproduction treatment in a comparison of the revised ASRM score and EFI score (10)

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 (11).

Clinical experience suggests that, at least in some women with established endometriosis, the disease is progressive and brings about increasingly worsened pain and subfertility (12). 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 (7). 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 (13). 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 (14). Nonetheless, superficial peritoneal lesions are more closely associated with infertility than endometrioma and deeply infiltrating endometriosis (15). 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. 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, angiogenesis, and fibrosis.

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 (16). In mice, activated Th1 helper cells contribute to formation of peritoneal adhesions (17); alternatively activated macrophages (M2) promote growth and survival of endometriotic lesions, whereas inflammatory M1 macrophages modulate their absorption (18). In women, most data support an increased presence of inflammatory mediators (cytokines, chemokines, and prostaglandins) in the peritoneal fluid in endometriosis (19). The concentration of peripheral Tregs is reduced, whereas intraperitoneal Tregs is increased (26). Intraperitoneal Tregs may suppress effector T-cells and promote proliferation and invasion of endometrial stromal cells (20). Notably, a recent paper identified an endometriosis-related cytokine profile, which could be linked to macrophage activation (21).

Chronic inflammation in endometriosis may impair fertility by several pathways. Increased concentration of IL1b, IL8, IL10 and TNF□ in follicles adjacent to endometriomas is associated with reduced ovarian response (22). IL1 and IL6 may inhibit sperm motility (23,24), and inflammatory mediators of the peritoneal fluid may also contribute to sperm DNA damage (25). In addition, oxidative stress, prostaglandins and cytokines may interfere with oocyte-sperm interaction, impair embryo development, and hinder implantation (26).

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 LH concentration (27). 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 (28,29).

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 (30). Furthermore, progesterone induces the expression of 17□-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 (31). Indeed, an increased estrogenic milieu induces inflammatory responses in the endometriotic tissue, characterized by elevated levels of many inflammatory cytokines (32).

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 (33). 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 (34).

In fertile women, the dominant follicle will rupture and release the oocyte-cumulus complex within 38 hours after the LH 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 been shown to have a higher prevalence of LUF syndrome than women without endometriosis (35). 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 (36).

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 (37).

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 GnRH 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 (38). 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 (39). 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 these 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 (40), while in the other paper (41), reported an increased 1.94 odds ratio for a live birth. 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 (42). 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 the 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 (43). 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 (44).

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 (45).

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 (46).

Assisted reproduction

Assisted reproductive technology (ART) comprise 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. In vitro fertilization (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 may 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 (47). As in smaller previous reports, 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 (48-55). 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 (53).

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 (56). 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 (57,58). The Society for Assisted Reproductive Technology (SART) and ASRM collect data on a vast number of IVF treatments (59). 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 (60).

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.

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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

Table2. Outcome of intrauterine insemination in women with minimal/mild endometriosis or unexplained infertility

Author	Unexplained inf.		Endometriosis	
	No. cycles	No. Pregnancies (%)	No. cycles	No. Pregnancies (%)
Yovich -88	134	12 (9.0)	65	5 (7.7)
Omland – 98	119	40 (33.6)	49	8 (16.3)
Nuojua-Huttunen - 99	413	63 (15.3)	138	9 (6.5)
Singh - 2001	265	36 (13.6)	300	20 (6.7)
Göker - 2002	140	25 (17.9)	39	2 (5.1)
Werbrouck –2006	122	25 (20.5)	137	28 (20.4)
Ahinko-Hakamaa - 2007	637	90 (14.1)	126	15 (11.9)
Jeon - 2013	271	48 (17.7)	47	2 (4.3)

Table3. Cumulative results of IVF in endometriosis and tubal infertility from the ASRM/SART registry 2010 – 2013

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