REVIEW

Endometriosis and infertility: the role of IVF

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ABSTRACT

The cause and effect relationship between endometriosis and infertility, although traditionally accepted, is difficult to prove because of multiple mechanisms through which endometriosis may interfere with fertility. Both hormonal and surgical treatment of endometriosis improve, but do not completely restore fertility in affected women. Endometriosis, especially in its advanced stages, has become a frequent indication for ART, and more specifically, for IVF/ET. The success rates of IVF/ET in endometriosis appear to be comparable to those seen in other diagnostic entities according to most reports. Several studies, however, indicate lower fertilization, lower oocyte/embryo quality, and lower embryo implantation rates in women with endometriosis leading to the overall lower IVF/ET success rates. It is not clear what is the mechanism of such adverse effects, and neither is the reason for the contradictory data. Some studies implicate abnormal autoantibodies, which can be demonstrated in about 60% of women with endometriosis. Abnormal autoantibodies, especially of the antiphospholipid group, bind to the oocyte/embryo and trophoblast, interfering with their development and function, and to platelets, inducing thrombosis in the spiral arteries of the endometrium and in the placenta. They may be responsible for abnormal fertilization, poor embryo development and low implantation and pregnancy rates. They may also cause higher pregnancy wastage. Suppression of abnormal autoantibodies or use of anticoagulants has been associated with improved reproductive performance and improved IVF/ET results. It is likely that the individual variability in autoantibody levels, empirical use during the IVF protocol of drugs that lower their production or prevent their effects, as well as modifications in the IVF laboratory techniques, which prevent oocyte/embryo exposure to such autoantibodies, are the reasons for contradictory reports.
Key words: Endometriosis, infertility, IVF, Autoantibodies

INTRODUCTION

Women affected by endometriosis seek medical attention because of infertility or chronic pelvic pains. There is, however, no general consensus regarding the effect of endometriosis on fertility. Furthermore, the cause and effect relationship between endometriosis and infertility is unclear and has been questioned. Endometriosis can be demonstrated at laparoscopy as a coincidental finding in healthy, fertile women without pelvic pain symptoms, and the prevalence of endometriosis in the fertile population ranges from 2% to 18% (1,2). In infertile women the prevalence of endometriosis has been quoted to range between 20% and 68% but formal studies are lacking (3-5). The estimated risk of infertility is 20 times greater in women with endometriosis than in those without (1). It is generally agreed that the treatment of endometriosis, regardless of the method used,

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improves fertility and post-treatment pregnancy rates have been used as indicators of the effectiveness of endometriosis therapy.

The technique of in vitro fertilization/embryo transfer (IVF/ET) was developed in the late 1970's to bypass diseased fallopian tubes, and tubal disease was initially the primary indication for the IVF/ET. Subsequently, the indications expanded to other diagnostic entities, including endometriosis. Currently, IVF and its variants are used liberally in the management of infertility associated with endometriosis. However, the results have been contradictory. Some investigators report comparable IVF outcome in women with and without endometriosis, others have shown an adverse effect of the disease. Most significantly, however, the sequential steps within the IVF/ET process permit better evaluation of the effect endometriosis may have on the reproductive function. As never before, the effect of endometriosis on the ovarian response to stimulation, oocyte quality and fertilization rate, as well as on the early embryo development, quality and implantation rate, can be studied.

MECHANISMS OF INFERTILITY IN ENDOMETRIOSIS

The exact mechanism of infertility in endometriosis remains unclear, and probably more than one is involved. It is generally agreed that in severe endometriosis mechanical factors play a predominant role. The cause or causes of infertility in minimal or mild endometriosis are less clear, and at times questioned. In women with untreated mild endometriosis undergoing artificial insemination with donor sperm, at least two reports (6,7) demonstrated monthly fecundability rates decreased to one-sixth to one-third of normal controls. However, another group (8) reported normal fecundity in such women. It has been suggested that decreased fertility in endometriosis may be associated with altered folliculogenesis and ovulatory dysfunction, increased sperm phagocytosis, abnormal tubal transport impaired fertilization and implantation, inhibition of early embryo development, luteal phase defect and immunologic alterations. Each one of these factors may play a role in some, but not in all affected women.

Mechanical factors. In advanced endometriosis, fertility is compromised, with untreated patients rarely conceiving. Pelvic adhesions and scarring can distort the pelvic anatomy and block oviducts, thereby mechanically interfering with ovulation, ovum capture by the fimbria and/or ovum/embryo transport.

Ovulatory dysfunction. Various forms of ovulatory and/or hormonal dysfunctions have been reported in association with endometriosis, but it is not clear whether their prevalence in endometriosis is higher than in general infertility. For example, endometriosis has been diagnosed in anovulatory women with oligomenorrhea and polycystic ovaries, but the prevalence of anovulation seems to be similar in both the endometriosis and general infertility patients. We reported lower preovulatory estradiol peaks, smaller leading follicles and greater number of smaller follicles at the time of LH surge (9). Cheesman et al (10) reported two distinct midcycle peaks of LH, two or three days apart, suggestive of inappropriate feedback mechanisms. Ronnberg et al (11) described reduced LH receptors in ovarian follicles and corpora lutea in endometriosis patients, suggesting an LH receptor defect. Others have reported abnormalities in the prolactin and luteal phase progesterone levels. Luteinized unruptured follicle (LUF) syndrome, a form of ovulatory dysfunction, is considered a common cause of infertility in endometriosis. The prevalence of LUF in endometriosis was originally reported at 79% (12) but subsequent studies report lower figures of 30% to 40% (13-15). We found no difference in the incidence of LUF in infertile women with and without endometriosis (14). The process of follicular rupture and oocyte release is a complex event modulated primarily by the local concentrations of prostaglandins such as $PgF_{2\alpha}$, PgE_2, PgI_2, and prostacyclin. Abnormal prostaglandin levels and administration of prostaglandin synthetase inhibitors have been associated with the development of LUF. It is unlikely that LUF recurs during consecutive cycles.

Prostaglandins. Prostaglandins produced in the female reproductive system play a critical role in

several reproductive processes. In endometriosis, alterations in the concentration and/or secretion of several prostanoids have been observed in the fallopian tubes, uterine and ectopic endometria, menstrual flow and peritoneal fluids. However, measurements of prostaglandin concentrations in vivo are difficult to perform because of their instability, and many reports, especially those pertaining to the peritoneal fluid concentrations are contradictory. Furthermore, prostanoid concentrations in the peritoneal fluids as well as the fluid volume vary during the menstrual cycle, making interpretation of some of the studies difficult. There is no disagreement, however, that the endometriotic implants and peritoneal macrophages, activated in endometriosis, produce high levels of several prostaglandins. A recent study demonstrated that peritoneal macrophages from women with endometriosis produced in vitro significantly more $PgF_{2\alpha}$, and PgE_2 than macrophages of healthy controls (16). Abnormal prostaglandin metabolism has been implicated as a cause of infertility in endometriosis (17). Increased tissue and peritoneal fluid prostaglandin levels may interfere with tubal transport of gametes and/or embryos, since prostaglandins mediate tubal muscular contractility. However, the link between endometriosis and tubal dysfunction remains unclear. Prostaglandins may also affect follicular rupture, corpus luteum function, implantation and embryogenesis. They may also contribute to the alteration of the immune function observed in endometriosis. We have reported prostaglandin-dependent suppression of cellular immunity in women with advanced endometriosis (18). The variable, inconsistent effects of endometriosis on fertility could be explained by variable concentrations of prostanoids in the peritoneal fluid and pelvic tissues. This variation in concentration could be dependent on the activity of the endometriotic lesions, their cumulative size, and the amount of lesion exposed to the peritoneal fluid.

Peritoneal macrophages. Macrophages act as effectors in cell-mediated cytotoxicity. Chronic inflammatory changes associated with the presence of endometriotic implants include an increased number of activated macrophages in the peritoneal fluid. Halme (19) has studied patients with mild endometriosis and has shown 46% activation of peritoneal macrophages in endometriosis patients versus 15% activation for macrophages in controls. These activated macrophages may have a deleterious effect on sperm, including increased sperm phagocytosis and decreased motility. Fertilization and gamete interaction may also be affected as sperm have shown an impaired ability to penetrate zona-free hamster oocytes in the presence of peritoneal macrophages from women with endometriosis. Activated macrophages release a variety of cytokines which may be the mediators of at least some of the macrophages' damaging effects.

MANAGEMENT OF INFERTILITY IN ENDOMETRIOSIS

Several approaches to the management of endometriosis are available, and factors such as patient's age, symptoms, fertility status, stage of the disease, and prior treatments should be considered in the selection process. However, in infertile women with endometriosis, pregnancy is the major objective, and management of infertility rather than endometriosis becomes a main goal, especially since endometriosis and its symptoms are likely to improve during pregnancy. It is generally agreed that the presence of endometriosis does not preclude other infertility factors, and that all infertile women with endometriosis should undergo a complete infertility evaluation. All identifiable infertility factors should then be corrected to facilitate pregnancy before attempting treatment of endometriosis. Typically, ovulation induction with or without artificial insemination is performed during four to six cycles with concomitant suppression of abnormal autoantibodies if present. In women with early endometriosis, a randomized, controlled trial demonstrated that ovulation induction with insemination for four months produced a cumulative live birth rate of 30% as compared to 10% without treatment (20).

Considering that endometriosis is typically diagnosed during laparoscopic surgery, the laparoscopist should have adequate skills, instruments and power sources to resect, ablate or

fulgurate endometriotic lesions and adhesions at the time of diagnosis. There is probably no place in the 1990's for just a diagnostic laparoscopy without resection of endometriotic lesions and adhesions in a symptomatic or infertile woman. After laparoscopic resection or ablation of early endometriosis, monthly fecundity rates were 6.1% as compared to 3.2% in the diagnostic laparoscopy-only group, with the 36-week cumulative pregnancy rate of 37.5% vs. 22.5% respectively, according to a recent, randomized study (21). However, the 6.1% monthly fecundity rate after laparoscopic destruction of endometriosis was far below the expected 20% monthly fecundity rate of fertile women. It is possible that women who did not conceive had incomplete resection of the lesions or had biochemical changes causing infertility which were not corrected by the surgery. Such patients should undergo further evaluation and treatment.

Medical treatment of endometriosis with GnRH-analogs or danazol is an alternative approach to surgery, especially in the less advanced disease. Danazol may be of special advantage in women with abnormal autoantibodies and recurring implantation failures or early pregnancy losses, since the drug has been shown to suppress not only endometriosis but also abnormal autoantibodies (22). Post treatment pregnancy rates are increased with both GnRH-analogues and danazol, but are inversely related to the stage of the disease prior to treatment. In older, uncontrolled observational studies, cumulative pregnancy rates after medical treatment were reported in the range of 45 to 75%. However, a recent meta-analysis of previously reported controlled trials, was unable to demonstrate beneficial effects on fertility of any medical treatment (23). In advanced endometriosis, when large endometriomas and/or adhesions are present, medical treatment is usually incomplete. Resection of the lesions as well as surgical correction of the pelvic anatomy should be considered. Furthermore, it should be kept in mind that the medical therapy does not destroy endometriotic lesions. Endometriosis atrophies and becomes resorbed during the hypoestrogenic state induced with these regimens. This process takes several months during which conception can not take place, and therefore lengthy medical treatment of endometriosis may not be appropriate for an infertile woman in her late 30's. Considering the rather rapid decline in female fertility after the age of 35, any infertility treatment that requires several months is less than optimal. Recent advances in the reproductive technologies, combined with the increasing demands for improved cost-effectiveness of medical procedures, have brought new trends to the management of infertility in general. In the 1990's, infertile couples are being managed more aggressively, treatment methods are more focused, and less effective therapies are being abandoned in favor of Assisted Reproductive Technologies (ART). This trend is clearly evident in the management of infertility associated with endometriosis. Lengthy medical treatment methods are being replaced by surgery, and/or IVF. It should be noted, however, that according to a recent study, repeated surgery in advanced endometriosis has little or no benefit on fertility (24). Therefore, patients with advanced endometriosis, and especially those with extensive adhesive disease, should be directed to the ART procedures early in treatment.

EFFECT OF ENDOMETRIOSIS ON IVF CYCLE PARAMETERS

The IVF/ET cycle consists of several steps, each one contributing to the ultimate IVF outcome. They include ovarian stimulation, oocyte aspiration, in vitro fertilization, embryo culture in vitro, and embryo transfer. Each one of these steps can be individually controlled and analyzed for an effect of endometriosis on reproductive function.

The response to ovarian stimulation, as evidenced by peak estradiol levels, the number of large follicles, and the number of oocytes retrieved, appears to be similar in women with and without endometriosis. A decreased number of oocytes in advanced endometriosis reported by some programs have been attributed to technical difficulties during laparoscopic retrieval (25), or to a tendency for fewer and smaller follicles (26). It is quite likely that women with advanced endometriosis and repeat ovarian surgeries have decreased ovarian reserve and lower response to stimulation. Ovarian endometriomas greater than 2

cm. during the IVF cycle have also been associated with lower response to stimulation, lower fertilization, fewer embryos transferred and lower pregnancy rates (27).

There is no agreement regarding the effect of endometriosis on fertilization in vitro. Lower fertilization rates have been reported repeatedly by one group (28,29), and more recently, in a retrospective but well controlled analysis by another (30). The majority of investigators, however, report similar in vitro fertilization rates in women with and without endometriosis (Table 1).

Similarly, there is no agreement regarding the effect of endometriosis on embryo quality and implantation rates. Simon et al (31) reported that in their oocyte donation program, embryos derived from the oocytes donated by women with endometriosis had 7% implantation rate, as compared to 16.2% for embryos from oocytes of fertile donors, 23.6% from women with polycystic ovaries, and 18.7% from women with tubal infertility. The authors attributed this finding to the decrease in the oocyte/embryo quality in endometriosis. When women with endometriosis and tubal disease were compared in the same study, embryo implantation rates in endometriosis were also lower, 5.8% versus 13.4% in tubal disease (31). Interestingly, a recent study reported lower implantation rates in stage I and II endometriosis than in stage III and IV (2.8 vs. 5.5%) (32). A control group (tubal factor infertility) in that study had implantation rates of 8.1%.

Nevertheless, a comparable number of studies indicate no adverse effect of endometriosis on embryo implantation rates. A high implantation rate of 19.5% in endometriosis was reported by Oliveness et al (33), while Bergendal et al (30), reported a 22% implantation rate in endometriosis as compared to 23% in tubal factor infertility. The results of contradictory reports need to be interpreted with caution, taking into account the design of each study, clinical and laboratory protocols and patient selection. Interestingly, endometriosis in the donor oocyte recipients seems to have no adverse effect on embryo implantation. In a study of 239 consecutive recipients, there was no apparent difference in the implantation rates in the presence of endometriosis (n = 55, implantation rate 12%) or in its absence (n = 184, implantation rate = 13%) (34). Also in the already quoted study by Simon, the implantation rate in donor oocyte recipients with endometriosis was 25% (31).

EFFECT OF ENDOMETRIOSIS ON IVF PREGNANCY RATES

The adverse effect of endometriosis on the number of oocytes retrieved or fertilization in vitro, can be compensated, and should not interfere with the IVF outcome. With the same number of embryos transferred, all investigators (28-30,35) reported similar pregnancy rates in endometriosis and controls. The decrease in the implantation rates, however, can not be readily compensated for. It is, therefore, not a surprise that essentially all investigators who reported lower implantation rates also observed lower pregnancy rates in endometriosis (Table 1).

There is no agreement regarding the benefits of medical treatment of endometriosis before IVF/ET. Some investigators report improved results after pre-treatment with danazol (36) or GnRH-agonists (37,38). Others indicate a lack of an apparent effect (39). When women with active, and no evidence of active disease were compared, there was no difference in the pregnancy rates (33,40). Similarly, there was no effect of the stage of endometriosis on the IVF outcome (33,40,41). However, there may be an adverse effect of endometriomas. A recent report indicates higher early pregnancy losses in women with suspected ovarian endometriomas with slightly but not significantly lower implantation and pregnancy rates as compared to controls without endometriomas (42). The study, however, was limited by a small number of patients, and a lack of definitive diagnosis of endometriosis in either group.

THE ROLE OF AUTOANTIBODIES

About two decades ago, Weed and Arguembourg (43) reported deposits of IgG and complement in the uterine endometrium of women with endometriosis, providing an indirect evidence for the antigen-antibody reaction. They postulated that autoantibodies against the ectopic endometrium

Table I. IVF cycle parameters and IVF/ET success rates in women with endometriosis: Recent Literature Review

Authors	No. of cycles/ cases	No. of follicles ≥ 14 mm (Mean±SEM)	No. of eggs retrieved (Mean)	Fertilization rate (%)	No. of ET (Mean)	No. of transfers	No. of pregnancies	Implantation (Pregnancy) rate/ transfer
Inoue et al, 1992								
Endometriosis								
Stage I	111	---	---	---	---	171	52	--(30)
Stage II	78	---	---	---	---	123	39	--(32)
Stage III	51	---	---	---	---	76	24	--(32)
Stage IV	69	---	---	---	---	106	32	--(30)
No Endometriosis	372	---	---	---	---	701	189	--(27)
Mills et al, 1992								
Endometriosis	67	4	8	48	2.5	63	17	12(27)
No endometriosis	198	4	7	65*	2.8	198	53	12(27)
Simon et al, 1994								
Endometriosis								
Stage I/II	14/9	---	9.6	56	3.6	12	2	6.9(17)
Stage III/IV	82/50	---	9.6	54	3.4	67	10	5.6(15)
Total	96/59	---	9.6	44	3.5	79	12	5.8(15)
No endometriosis	96/78	---	12.1	58	3.5	91	34	13.4*(37)*
Dmowski et al, 995								
Endometriosis								
Stage I	49/37	12.3	8.5	61	3.5	42	11	--(26)
Stage II	40/22	11.5	8.0	59	3.8	34	11	--(32)
Stage III	21/19	11.6	8.0	62	3.9	21	8	--(38)
Stage IV	9/6	12.4	8.4	71	4.0	9	1	--(11)
No endometriosis	118/109	10.4	7.3	61	3.5	100	25	--(25)
Oliveness et al, 1995								
Endometriosis								
Stage I	64/51	---	9.0	67	3.2	57	28	--(49)
Stage II	18/13	---	12.7	52	3.2	15	8	--(53)
Stage III/IV	11/8	---	7.1	66	3.3	10	5	--(50)
Endometriomas	61/44	---	9.5	65	3.3	57	27	--(47)
Total	360/214	---	8.4	58	2.9	290	104	19.5(36)
No endometriosis	160/111	---	7.9	52	3.3	136	57	--(42)
Pagidas et al, 1996								
Endometriosis								
Stage III & IV	37/23	---	8.5	64	---	---	16	16(44)
No endometriosis	414/312	---	11*	59	---	---	10	10(34)
Arici et al, 1996								
Endometriosis								
Stage I/II	43/18	---	11	67	4.3	42	5	2.8(12)
Stage III/IV	46/17	---	5.3	78	3.3	39	7	5.5(18)
Total	89/35	---	8.1	71	3.8	81	12	3.9(15)
No endometriosis	195/85	---	9.1	69	3.8	179	45	7.9*(25)*
Huang et al, 1997								
Endometriosis								
Stage I/II	27/27	4.5	6.8	53	3.9	---	---	9.2(27)
Stage III/IV	48/48	4.8	7.6	61	3.6	---	---	9.1(22)
No endometriosis	-/60	7.2	9.9*	73*	4.7	---	---	9.4(32)
Kim et al, 1997								
Endometriosis	111/42	10.1	9.3	77	3.4	---	36	--(32)
No endometriosis	165/87	10.5	10.1	85	3.6	---	62	--(38)
Bergendal et al, 1998								
Endometriosis	65/48	10.6	10.8	60	2.0	57	22	22(39)
No endometriosis	98/98	11.1	10.9	78*	2.1	98	39	23(40)

* Results significantly different between endometriosis and controls.

causing early implantation failures and spontaneous abortions. Other investigators, using different techniques, confirmed high frequency of antiendometrial antibodies in the peripheral circulation and other body fluids of women with endometriosis (44,45). In addition to antiendometrial antibodies, about 60% of women with endometriosis also produce autoantibodies to a variety of cell derived antigens. These are IgG, IgM and IgA isotype antibodies to several phospholipids, histones, polynucleotides, and single and double stranded DNA (46). These and other autoimmune phenomena have prompted some to speculate that endometriosis may be a form of an autoimmune disease (46). However, not all women with endometriosis are autoantibody positive, and because most have other alterations in the immune function, alternative theories to explain the immune system involvement in this disease have also been proposed (47).

In women with autoimmune diseases, such as systemic lupus erythematosus, the presence of abnormal autoantibodies has been associated with high pregnancy wastage. In healthy women with abnormal autoantibodies, there is also a high incidence of reproductive failure. Recurrent spontaneous abortions, intrauterine growth retardation, intrauterine fetal death, and pregnancy induced hypertension leading to pre-eclampsia have all been reported. In such patients, thrombosis in placental vessels and thrombocytopenia are a frequent finding. These conditions in otherwise healthy women without evidence of the autoimmune disease have variously been referred to as lupus anticoagulant syndrome (LACS) (48), reproductive autoimmune failure syndrome (RAFS) (49), anticardiolipin syndrome (ACLS) (50), or antiphospholipid syndrome (APLS) (51). It appears that all acronyms may refer to the same subclinical form of an autoimmune disease affecting reproductive performance. It is unclear at this time what is the role of autoantibodies in this condition and what is the mechanism of antifertility effects. It has been suggested that autoantibodies induce thrombosis in spiral arteries of the endometrium and in the placenta, causing infarctions and decreased blood supply to the conceptus (52). Others have proposed that abnormal autoantibodies, especially of the antiphospholipid group, bind to the trophoblast and alter its function (53). Several studies indicate that suppression of abnormal autoantibodies with corticosteroids, as well as anticoagulant therapy, such as aspirin and/or heparin may improve reproductive performance in affected patients (54).

In evaluating abnormal autoantibodies in patients undergoing IVF, several investigators have reported a high prevalence of autoantibodies in failed IVF cycles (55-57). El-Roeiy and associates (56) demonstrated higher concentration of autoantibodies in the follicular fluids than in sera. The initial concern that the IVF procedures may somehow lead to the development of abnormal autoantibodies was, however, not substantiated. Fisch and colleagues (58) who measured antiphospholipid antibodies before, during and after the IVF cycle, indicated that although the IVF patients had higher levels of autoantibodies than normal controls, there was no change in the autoantibody level as a result of the IVF cycle. On the other hand, several studies have demonstrated that the presence of autoantibodies affects the IVF outcome. Birkenfeld and colleagues (55) reported that 18 of 56 patients (32%) who failed IVF/ET were autoantibody positive as compared to none of 14 who conceived with IVF, and 7 of 69 (10%) in an unselected group of new IVF candidates. Geva and associates (59) went a step further. They measured several autoantibodies in a group of 21 women who had chemical but no clinical pregnancies as a result of the IVF cycle. The prevalence of autoantibodies in this group was 33.3% as compared to none of 21 women who conceived and delivered with the IVF/ET. We recently analyzed IVF cycle parameters including pregnancy rates in women with endometriosis who were autoantibody positive or negative (40). There was no difference between the groups in any of the cycle parameters, including the response to ovarian stimulation, number of follicles produced, number of eggs retrieved, percentage fertilized, or number of embryos transferred. There was, however, a significant difference in the pregnancy rates: 22.9% in autoantibody positive, and 45.7% in autoantibody negative patients.

At the time of IVF/ET, some patients had evidence of active endometriosis, while others did not. As expected, active disease was more common in the autoantibody positive than in the

autoantibody negative group (80% versus 36%). This anti-implantation effect of abnormal autoantibodies appears to be reversed by treatment. Birkenfeld and colleagues (55) reported that 7 of 15 autoantibody positive patients who had previously failed IVF/ET conceived during a subsequent IVF/ET cycle while being treated with prednisone and aspirin. In another study, Sher et al (60) reported that treatment with aspirin and heparin increased the pregnancy rate per transfer in autoantibody positive women from 16 to 49%. In our study (40) some patients received corticosteroids during the IVF cycle on an empirical basis. It is interesting to note that all patients with endometriosis who had three or more autoantibodies and conceived were on corticosteroid treatment. When pregnancy rates were analyzed according to the autoantibody status and the use of corticosteroids, the rationale for the use of these steroids in autoantibody positive patients became quite apparent. Autoantibody positive patients undergoing IVF were more likely to conceive if they were taking corticosteroids. On the other hand, there was no effect of corticosteroids in autoantibody negative patients. A more recent study by Kim et al (61) reported similar observations. The prevalence of abnormal autoantibodies was 38.1% in women with endometriosis versus 2.3% in those with tubal disease. As in our study, the pregnancy rates were similar in the overall endometriosis group and controls (Table 1). However, treatment with corticosteroids was associated with a higher pregnancy rate (42.6%) in the treated than in the untreated subgroup (22.8%) of endometriosis patients. There was no effect of corticosteroids in-patients with tubal disease. Abnormal autoantibodies in women with endometriosis can also be suppressed by danazol treatment (22). The immunomodulatory effect of danazol is probably one of the mechanisms responsible for improved reproductive performance after treatment with this drug.

It has been postulated that abnormal autoantibodies in the follicular fluids interfere with oocyte fertilization in vitro and with early embryo development, while those in the peripheral circulation may cause implantation failure. This concept is supported by two recent reports. One indicates that antiphospholipid antibodies bind to the zona pellucida and mouse pre-embryos and interfere with their subsequent development to the blastocyst stage (62). The other demonstrates that antiphospholipid antibodies bind to the human trophoblast and interfere with its function (63).

It should be pointed out, however, that all published studies on the effect of abnormal autoantibodies on the IVF outcome have been almost exclusively retrospective and observational. Their results are, therefore, highly dependent on proper selection of subjects and controls. There are no prospective data to demonstrate the adverse effect of autoantibodies on the gametes or embryos, nor on fertilization, implantation or pregnancy rates in IVF cycles. The beneficial effects of corticosteroids and anticoagulants have not been correlated with autoantibody suppression. On the contrary, a recent prospective study in a large population of 793 consecutive IVF patients was unable to demonstrate the adverse effect of antiphospholipid antibodies on implantation or pregnancy rates (64). The patients in that study did not receive corticosteroids or anticoagulants during the IVF cycle.

It is possible that the inconsistent effect of endometriosis on embryo implantation rates reflects variable concentration of abnormal autoantibodies in the follicular and peritoneal fluids and in the peripheral circulation, and the fact that some women are autoantibody negative. Furthermore, danazol or corticosteroids can suppress abnormal autoantibodies, and their effect can be neutralized by the use of anticoagulants, such as aspirin and/or heparin. Some of these drugs are used empirically before or during the IVF/ET protocol. Similarly, the practice of repeated follicular washing and cumulus corona cell removal during egg collection might dilute or remove the autoantibodies and prevent oocyte/embryo exposure to their effects. Such modifications to the clinical protocol and alterations in the IVF/ET techniques are seldom or never reported.

CONCLUSIONS

The association between endometriosis and infertility, although traditionally accepted, is elusive and difficult to prove in clinical studies.

Contradictory reports are most likely secondary to the multiple mechanisms through which endometriosis interferes with fertility. In early endometriosis, substances produced by the ectopic endometrium or by the immune system, activated in response to the ectopic endometrial growth, interfere with several reproductive processes. Cytokines, prostaglandins, abnormal autoantibodies, and as yet unidentified embryotoxic factors have been shown to adversely affect gametes and embryos, and several steps in the reproductive function, such as fertilization, gamete/embryo transport, and embryo implantation. These effects, however, depend on the concentrations of such substances in the fluids surrounding the gametes and embryos, and, in turn, are related to the number, size, and exposure of the endometriotic lesions to body fluids, as well as the immune system response, all of which are individually variable. In advanced endometriosis, additional effects of adhesive disease, endometriomas, and the distortion in the pelvic anatomy should also be considered. Hormonal suppression of endometriosis, or surgical resection of endometriotic lesions, improve but do not completely restore fertility. The effect of surgery and different hormonal regimens on biochemical changes discussed above is variable, and even though endometriosis is suppressed or resected, some of the anti-fertility effects persist. In such cases ovulation induction combined with suppression of abnormal autoantibodies and insemination may further improve fertility. In women who do not conceive with this approach, IVF/ET is the next step in the management of infertility related to endometriosis. In women over 35, and in those with advanced endometriosis, IVF/ET may be justified as a primary approach in the management of infertility. Aspiration of the oocytes with laparoscopically or sonographically guided needle, in vitro fertilization, early embryonic development in the laboratory, and ultimately transfer of the developing embryos into the reproductive system, correct for, or identify problems caused by ovulatory dysfunction, abnormal fertilization, failure of early embryonic development, abnormal ovum pickup/transport or abnormal implantation.

There is no agreement regarding the effect of endometriosis on the IVF cycle parameters and outcome. The disease in its early stages seems to have no effect on the ovarian response to stimulation. In advanced endometriosis, the response may be less than optimal due to a decreased ovarian reserve. Oocyte fertilization rates in vitro according to most studies are similar in women with and without endometriosis. Lower fertilization rates, as reported by some investigators, can generally be compensated for at the time of embryo transfer without affecting the IVF outcome. Contradictory data have been reported regarding the effect of endometriosis on embryo implantation. According to some reports, embryo implantation rates are similar in women with endometriosis and tubal disease, regardless of the activity or stage of endometriosis. Several studies, however, report lower implantation rates in endometriosis than in other reproductive disorders. Furthermore, according to at least one study, women with early stages of endometriosis have lower implantation rates than those with advanced disease. It has been suggested that lower implantation rates in endometriosis are the result of lower quality oocyte/embryos. This concept is supported by reports that embryos derived from oocytes donated by women with endometriosis have lower implantation rates when transferred into healthy recipients than embryos derived from oocytes donated by fertile women or women with other reproductive disorders. Interestingly, however, endometriosis in the recipient does not seem to affect the implantation rate of embryos derived from healthy donors. Considering that low implantation rates can not be readily compensated for, investigators who report this finding also report lower pregnancy rates in women with endometriosis. It is not clear what is the cause of lower embryo implantation rates in endometriosis. Studies from our Institute and from other laboratories suggest that women with abnormal autoantibodies have lower implantation and pregnancy rates than those who are autoantibody negative. Abnormal autoantibodies present in the circulation and follicular fluids of some women with endometriosis are known to adversely affect the reproductive performance. It has been demonstrated that they bind to the oocyte/pre-embryo and to the trophoblast, affecting their survival and function. Treatment with corticosteroids and/or anticoagulants significantly improves IVF implantation and

pregnancy rates in autoantibody positive women. It is likely that the discrepancy in the reported data on embryo implantation rates and IVF/ET outcome in endometriosis is related to the variability in the autoantibody levels. Furthermore, concentrations of autoantibodies in the fluids surrounding oocyte /embryo are individually variable and depend on the drugs used during the IVF protocol as well as on the laboratory techniques.

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