The association of minimal and mild endometriosis without adhesions and infertility with therapeutic strategies

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Summary

Introduction: Mild endometriosis may be present in fertile or infertile women. When present in infertile women it could be merely an innocent bystander, and some other problem could be causing the difficulty in conceiving, or it may in some way be directly responsible for the infertility problem. Sometimes to achieve a pregnancy, only these other infertility factors need to be treated with no specific treatment for the endometriosis per se. However there are some data suggesting that sometimes treating the endometriosis surgically may be helpful.

Methods: The pregnancy outcome in women with probable endometriosis vs those without this entity (based on serum CA-125 levels) was compared with treatment rendered only to correcting ovulatory defects with no specific treatment rendered to the endometriotic lesions during the first six months of therapy. Another study evaluated the efficacy of laparoscopic removal of endometriosis vs leaving the lesions untouched on pregnancy outcome in women who failed to conceive after at least eight months of all infertility factors corrected.

Results: No difference in pregnancy outcome was found in women with probable endometriosis vs none after six months of correcting ovulation defects. However, for the minority not conceiving after such therapy removing the endometriosis surgically significantly improved fertility rates in the next eight months.

Conclusions: The probable presence of endometriosis based on symptoms, signs, or serologic evidence should prompt careful evaluation and treatment of subtle ovulatory problems, e.g., luteal phase defects and luteinized unruptured follicle syndrome. Therapeutic strategies for those women failing to conceive after 6-8 months of conservative therapy could be laparoscopic removal of observed endometriotic implants or consideration of in vitro fertilization.

Key words: Endometriosis; Luteal phase defect; Progesterone; Luteinized unruptured follicle; Laparoscopy; In vitro fertilization.

Mild endometriosis and subfertility

Studies from over a decade ago demonstrated that minimal or mild endometriosis without adhesive disease was found to be associated with decreased fecundity [1-4]. A more recent study evaluating 3-year conception rates confirmed these studies [5].

Theoretical ways that minimal or mild endometriosis could be associated with reduced fertility potential could be related to ovarian function (ovarian factor) or to the endometrial environment (uterine factor) or to function of the fallopian tubes (tubal factor).

Mechanism for subfertility and therapeutic options

Ovulatory dysfunction and treatment considerations:

There are some data linking endometriosis with luteal phase defects [6-9]. This may possibly be related to follicular maturation defects [9-11] or to impaired luteinizing hormone (LH) surge pattern and amplitude [6, 11, 12]. Thus, if endometriosis is associated with reduced fecundity through these mechanisms, the treatment rendered should be no less successful than in women with similar ovulatory dysfunction but without endometriosis. Though not all agree, we favor the exclusive treatment with luteal phase supplementation with vaginal progesterone (P) if the follicle appears mature rather than using follicle maturing drugs (follicular size of 18-24 mm and serum estradiol (E2) > 200 pg/ml) [13]. This might be a type of problem seen when the problem is related to problems with the LH surge [6, 11, 12]. If follicular maturation problems are the cause [6-8], then follicle maturing drugs should be used [13]. However, when follicular maturation defects are detected, our data suggest a higher miscarriage rate if one does not also support the luteal phase with extra P [13, 14].

In fact, untreated endometriosis has been found to be associated with a higher rate of miscarriage [15-17]. However, when patients with endometriosis were treated with luteal phase P without treating the endometriosis, no increased rate of miscarriage was seen compared to controls without endometriosis [18].

The inadequate LH mid-cycle surge [6, 11, 12] or reduced LH concentration in follicular fluid [11, 19] could also lead to the failure of the oocyte to rupture from the follicle [20-24]. There have been data suggesting that endometriosis may be associated with a higher incidence of luteinized unruptured follicle syndrome [25]. Non-surgical treatment has included injections of 10,000 units of human chorionic gonadotropin (hCG) or hCG mixed with 150 IU of human menopausal gonadotropin (hMG) or follicle stimulating hormone (FSH) [23] or leuprolide acetate in dosages of 1 mg 12 hours apart x3 beginning at peak follicular maturation [26].

Endometrial environment and treatment considerations:

An adverse effect of endometriosis on uterine receptivity has been suggested by Muscato *et al.* and Yovich *et al.* [27, 28]. There have been some experimental data supporting this concept [29, 30]. However, the study that gave the most credence to this concept was that of Lessey *et al.* who demonstrated aberrant integrin expression in the endometrium of women with endometriosis [31]. Previous investigations from this group found that the integrin alpha and beta-3 vitronectin receptor appears on endometrial cells only after day 19 of the normal menstrual cycle, the time of the opening of the implantation window [32]. They also discovered that beta3-subunit expression is absent during this time in infertile women with maturational delay of the endometrium [32].

The question is whether this abnormality merely reflects the association of endometriosis and luteal phase deficiency and is correctable by supplementation of extra P or is this an intrinsic defect not responsive to P. The majority of evidence from in vitro fertilization (IVF) data favor that the infertility that may be related to low beta3-integrin expression is correctable by supplementing P. One such study evaluated whether endometriosis caused endometrial deficiencies that could be sonographically detected [33]. However, no difference in mean endometrial thickness or echo patterns immediately prior to hCG injection in women undergoing IVF-embryo transfer (ET) was found according to the presence or absence of endometriosis [33]. Interestingly, the group with the most advanced endometriosis had the highest pregnancy rates (PRs) [33]. Since all IVF-ET cycles were supported with P, these data left the impression that if low beta3-integrin is associated with infertility and endometriosis, it is remediable by treatment with P. Intrinsic non-correctable endometrial defects should have resulted in low implantation rates even with IVF-ET.

Subsequent IVF data also supported the concept that P-treated women with endometriosis do not have endometrial receptivity problems. Diaz *et al.* did a case controlled study on the impact of Stage III-IV endometriosis on recipients of sibling oocytes [34]. In this approach, donor oocytes from healthy women were shared between two recipients, one with endometriosis and one without. They found no difference in subsequent PRs and implantation rates. Sung *et al.* also demonstrated that endometriosis is not detrimental to embryo implantation in oocyte recipients [35].

One might consider whether some adverse endometrial factors that can be diagnosed by sonography could be found in patients with endometriosis but the controlled ovarian hyperstimulation for IVF overcomes the abnormality. However, a study of non-IVF cycles did not find any differences in endometrial thickness or sonographic echo pattern at the peri-ovulatory time in women with or without endometriosis [36].

Alterations in immune function associated with endometriosis have been hypothesized to possibly contribute to infertility associated with endometriosis [37, 38]. However, the data support deficient cellular immunity or defective natural killer (NK) cell activity [37, 38]. Most studies suggesting immune causes of infertility or miscarriage favor increased rather then decreased NK cellular activity in the endometrium. However, even if endometriosis was found to inhibit endometrial receptivity by immunological damage, it could be merely related to the P deficiency rather than the endometriosis, per se. Progesterone has been found to stimulate the induction of immunomodulatory proteins that inhibit NK cell activity and favor the shift in cytokine dominance from thymic helper (TH) 1 cytokines that favor the cellular immune response to TH2 cytokines that favor a protective humoral response [39-46].

Knowledge obtained from the study of shared oocytes:

Shulman *et al.* evaluated the "best donor" in a shared oocyte program and found that donors with endometriosis and the recipients who shared their oocytes both showed reduced PRs compared to donor recipient pairs with other diagnoses in the donors [47]. Simon *et al.* also found reduced PRs in donors with endometriosis and with their oocyte recipients suggesting that endometriosis has a negative effect on oocyte quality which effects the ability of the embryos to implant [48].

We also evaluated relative outcomes of donor-oocyte recipient pairs and found a clinical and viable PR of 41.2% and 35.3% in donors with endometriosis and 42.9% and 38.1% in their respective recipients [49]. The respective clinical and viable PRs were 50.4% and 48.0% and 60.9% and 51.9% in their respective recipients [49]. The implantation rates in donors with and without endometriosis were 20.4% and 29.4% and 28.4% and 33.2% in recipients receiving oocytes from donors with or without endometriosis [49]. No significant differences were found. These data are consistent with the concept that the presence of endometriosis does not impair oocyte quality or uterine receptivity to any great extent since even the donors with endometriosis who would be exposed to both negative effects on the oocyte and endometrium had a respectable implantation rate of 20.4%. However, if one looks for a trend, the recipients with oocytes from donors with endometriosis had similar percentages to recipients with oocytes from donors without endometriosis but the implantation rates were 40% higher in donors without endometriosis vs donors with endometriosis. This trend might suggest that in contrast to the conclusions of Shulman *et al.* and Simon *et al.* that the mild adverse effect of endometriosis on fertility is probably related to diminished oocyte quality, these data may suggest that uterine receptivity may be even more important despite P supplementation [49]. This could be exaggerated in the presence of controlled ovarian hyperstimulation.

The role of surgical removal of endometriosis:

A study is needed to determine if the presence of endometriosis diminishes fertility potential even when efforts have been made to correct ovulatory defects and sperm-mucus interaction. Such a study without surgical treatment of endometriosis would be difficult to perform if the diagnosis was established by laparoscopy because it would be difficult to justify not removing the endometriotic implants that were seen.

Women with endometriosis frequently exhibit increased serum levels of CA-125 [50-53]. A study was performed to see if correction of follicular dynamics and luteal function and sperm mucus interactions in women with endometriosis would produce similar PRs compared to women without endometriosis. The assumption was made that a much higher percentage of women with increased CA-125 levels >35 U/ml have endometriosis compared to women with normal levels.

The PR after a maximum of six months of therapy in these women with patent fallopian tubes established by hysterosalpingogram was 70.5% in those with normal CA-125 levels and presumed to be devoid of endometriosis vs 79.2% of the group with elevated CA-125 levels with suspected endometriosis ($p = NS$) [54]. Thus these data would support the concept that if the presence of endometriosis without tubal occlusion can reduce fertility potential, the majority of women can achieve pregnancies by the correction of ovulatory dysfunction (including aggressive luteal phase support with P) and sperm-mucus abnormalities [54].

Women who fail to conceive after at least eight cycles of the correction of all apparent infertility factors might be considered as having unexplained infertility. The question arises as to whether the presence of minimal to mild endometriosis can account for the reason for persistent infertility in this recalcitrant group, and even more importantly, would the surgical treatment of the apparent endometriotic implants improve fertility potential?

One study did evaluate the subset of patients who had at least eight cycles of all other infertility factors seemingly corrected and who failed to conceive to see if the removal of mild endometriosis would improve subsequent PRs [55]. Laparoscopy was performed in a group of women who failed to conceive after at least eight corrected cycles. Those women in whom mild endometriosis was found were randomly assigned to electrocoagulation of endometriotic implants or they were left untouched. The previous therapy that failed to produce pregnancies for the first 8+ cycles was now repeated. The PR for those women whose endometriotic implants were fulgurated was 61% during the next eight months vs only 18.5% of the controls whose endometriosis remained untreated ($p < .05$) [55]. This study thus suggested that for a subset of patients with endometriosis, the surgical removal might improve fertility potential. These data were corroborated subsequently by other studies [56-58].

The role of in vitro fertilization

Success rates in IVF for women with minor endometriosis are generally comparable with other female diagnostic groups [59-61]. Though a recent meta-analysis concluded that the presence of endometriosis reduces PRs even with IVF-ET, there were no significant differences with the groups with minimal endometriosis [62]. Furthermore most of the studies included were not prospective [62]. Most studies usually find however fewer oocytes retrieved and thus fewer embryos available for fresh and frozen ET.

Though meticulous attention to details of follicular dynamics and aggressive use of luteal phase P support may correct ovulatory problems related to endometriosis, there may be other ways that endometriosis causes infertility that may be corrected by IVF-ET. For example possible mechanisms associated with infertility and endometriosis may involve defects in ovum transport [63, 64] or peritoneal fluid factors with macrophage activation that may interfere with the fertilization potential of the sperm [65-68].

Endometriosis and oocyte reserve

Barnhart *et al.* found in their meta-analysis adjusted for confounding variables that there were fewer oocytes retrieved from women with endometriosis compared to those without following IVF [62]. We have observed a higher percentage of women with endometriosis to have an increased serum FSH level when undergoing IVF compared to controls. The possibility thus exists that all of the noted ovulatory defects may not be related to the presence of endometriosis itself but to the change in FSH/LH ratios seen with decreasing oocyte reserve.

The decreased oocyte reserve may be related to replacement of normal ovarian tissue with endometriotic implants. Autoimmune mechanisms could also explain decreased oocyte reserve [69]. However, one must also consider an iatrogenic cause, i.e., damage to the ovaries and their blood supply by surgical intervention. Thus in developing a treatment strategy for initial therapy, one must consider the risk/benefit ratio of surgically removing endometriotic implants while concomitantly correcting ovulatory defects to cover the minority of patients where this treatment will improve fertility potential, since it may lower fertility potential in those women where this treatment is not needed by further decreasing an already compromised oocyte reserve and further disturbing the FSH/LH ratio.

Specific medical treatment of endometriosis

Most studies show no fertility benefit from medical treatment with impeded androgens, e.g., danazol or gonadotropin-releasing hormone analogues [70]. Cahill in his treatise on the optimal medical management of infertility and minor endometriosis stated that "medical treatment has very little to offer infertility patients with endometriosis" [61]. However a minority of studies suggest some benefit [71]. My own bias is that this class of drugs has a lot of side-effects. Furthermore, with the consideration that there may be an ongoing more rapid rate of egg loss through autoimmune mechanisms, medical therapy should be discouraged because of the delay in attempting conception and the risk of developing more endometriotic implants. Similarly, if surgical therapy helps restore infertility, but at the price of decreasing oocyte reserve, more delay by combined therapy could result in even further compromise of the oocyte pool.

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