DEBATE

What is the optimal medical management of infertility and minor endometriosis?

Analysis and future prospects

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By asking the question ‘What is the optimal medical management of infertility and minor endometriosis?’, it is assumed that endometriosis has a detrimental effect on fertility. The published data suggest that oocyte dysfunction may contribute to infertility associated with endometriosis. This is expressed as a reduction in fertilization and implantation rates; implantation rates to a lesser extent, though still significant. Other evidence for oocyte dysfunction exists, not all of which is consistent. Suppression of ovulation and menstruation to treat endometriosis-associated infertility is not effective. However, ovulation induction, perhaps with intrauterine insemination, does result in pregnancy rates higher than in control cycles, while stimulated IVF success rates are equivalent to those of other diagnostic groups. For the future, angiogenesis is critical to the support of endometriotic deposits and targeted therapies are promised; their role in improving fertility has not yet been explored.

Key words: endometriosis/infertility/medical treatment

Introduction

What is the optimal medical management of infertility when associated with endometriosis? Does endometriosis have any relevance to fertility? Does it affect it in any way? The evidence for a relationship between endometriosis and fertility and the benefits of medical treatment of endometriosis are discussed in this paper. Appropriate medical treatments for infertility related to endometriosis are proposed.

Moderate to severe (major) endometriosis is a destructive disease, and benign only in its classification as having no abnormal meiotic activity. In many other respects, it is a ‘malignant’ disease that causes considerable anatomical destruction and symptomatology, particularly pain. Severe endometriosis also significantly impairs fertility, as demonstrated in studies looking at both natural (Olive and Lee, 1986) and assisted conception (Matson and Yovich, 1986; Dlugi et al., 1989; Pal et al., 1999; Olive and Pritts, 2001). Medical treatment has very little to offer infertility patients with major endometriosis. It is only of value to discuss the role of medical intervention in minimal and mild non-adhesive endometriosis [Stages I and II by the American Classification (American Fertility Society, 1985; American Society for Reproductive Medicine, 1997)]. These have been grouped together as minor endometriosis to distinguish these degrees from moderate and severe (Stages III and IV).

Evidence for a relationship between endometriosis and fertility

Evidence from population and prevalence studies, studies of fertilization and implantation rates and endocrine studies can be used to discuss and explore the relationship between endometriosis and fertility.

Prevalence studies of subfertility

When investigating infertility, endometriosis prevalence rates at laparoscopy exceed those in fertile controls (21–47 versus <5%) (Hassan, 1976; Drake and Grunert, 1980; Strathy et al., 1982). When re-laparoscoped 2 years later, 20% of women with a previously normal pelvis and otherwise unexplained infertility had macroscopic endometriosis (Pepperell and McBain, 1985). Significantly lower 3 year cumulative conception rates were observed in women with endometriosis compared with controls (36 versus 54%) (Akande et al., 2001). When donor insemination is used to control for male and coital factors for subfertility, reduced conception rates are consistently demonstrated in women with endometriosis compared with controls (36 versus 54%) (Akande et al., 2001). When donor insemination is used to control for male and coital factors for subfertility, reduced conception rates are consistently demonstrated in women with endometriosis compared with controls (36 versus 54%) (Akande et al., 2001).
stimulation (49 versus 69%). In Table I, two studies conflict with the majority (Mahadevan et al., 1983; Matson and Yovich, 1986). This may be due to chance or differences in design. In some studies, the endometriosis had been previously treated (Mahadevan et al., 1983). In most, this was not clarified, though some explicitly excluded such previously treated patients (Wardle, 1985; Mahmood, 1991a; Cahill, 1997). Most included only women with minor endometriosis, but some included severe disease, reporting no differences in women with or without severe disease (Matson and Yovich, 1986). One study of women with severe disease reported fewer mature follicles, reduced fertilization rates and fewer oocytes (though not significantly so), suggesting that anatomical distortion may interfere with ovarian responsiveness to stimulation (Dlugi et al., 1989). Considerable heterogeneity in control groups was sometimes present, e.g. couples whose primary infertility cause was sperm disorder (Mahadevan et al., 1983).

Implantation rates after standard IVF treatment in women with endometriosis compared with controls are summarized in Table II. As in Table I, most patients with endometriosis had minor disease. Reduction of implantation rates was reported in three studies, though this was significant in only one. Overall the implantation rate of individual embryos was reduced (11 versus 13%, \( P < 0.05 \)).

When ICSI is used, oocyte factors (as well as sperm defects) may be overcome, partly by selection of metaphase II oocytes. Two recent studies using ICSI comparing patients with endometriosis with controls found no reduction in fertilization, cleavage (Minguez et al., 1997) or implantation rates (Bukulmez et al., 2001) in women with endometriosis. No reduction in implantation rates was noted when ICSI treatment was used in women with endometriosis compared with controls (15 versus 13%) (Minguez et al., 1997). In addition, to add to the evidence for an oocyte dysfunction, no reduction in implantation rates was found in recipients of donor oocytes according to whether the recipient had endometriosis or not (12 versus 13%) (Sung et al., 1997).

**Evidence for a disorder of pituitary or ovarian function**

Endocrine and ultrasound studies in women with minor endometriosis suggest that ovulatory dysfunction contributes to their infertility. Abnormalities observed include reduced follicular growth rate (Doody et al., 1988), reduced preovulatory follicle functional capacity (estradiol levels over the 4 days before ovulation) (Tummon et al., 1988; Cahill et al., 1995), impaired LH surge pattern and amplitude (peak LH levels and sum LH levels during the surge) (Cheesman, 1982; Bancroft, 1992; Cahill, 1995), reduced oocyte fertilizing ability (Cahill et al., 1997) and disturbed early luteal function (Cheesman, 1982). Luteal phase abnormalities include indistinct early luteal phase rises in basal temperature and delayed return to the low temperature phase at menstruation (Swolin and Skogsberg, 1985). A slow rise in progesterone may explain the initial slow rise in temperature (Cheesman, 1982) while increased ovarian progesterone and reduced estradiol secretion during the follicular phase may explain the delayed fall in temperature (Ayers et al., 1987). Follicular maturation in subsequent cycles may be altered by impaired luteolysis.

**Follicular endocrinology**

Preovulatory follicle function is estimated by steroid measurements in follicular fluid (FF) and by determining granulosa cells steroidogenic capacity when collected at oocyte recovery for IVF. Studies of unstimulated cycles are more relevant to natural fecundability but difficult to undertake. In such unstimulated cycles, two studies of FF sex steroid concentrations found no differences between women with endometriosis and controls (Mahmood et al., 1991a; Cahill et al., 1995). In the latter paper (Cahill et al., 1995), endogenous gonadotrophin levels were also measured. No difference was found in FSH

<table>
<thead>
<tr>
<th>Stimulation used/author and year of publication</th>
<th>Tubal</th>
<th>Endometriosis</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Oocytes</td>
<td>Embryos (%)</td>
<td>Oocytes</td>
<td>Embryos (%)</td>
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<tr>
<td>Unstimulated cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mahmood et al., 1991a</td>
<td>8</td>
<td>5 (62)</td>
<td>19</td>
</tr>
<tr>
<td>Cahill et al., 1997</td>
<td>59</td>
<td>41 (69)</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>46 (69)</td>
<td>47</td>
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<tr>
<td>Gonadotrophin-stimulated cycles</td>
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<tr>
<td>Mahmadevan et al., 1983</td>
<td>594</td>
<td>476 (80)</td>
<td>32</td>
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<tr>
<td>Wardle et al., 1985</td>
<td>149</td>
<td>77 (52)</td>
<td>82</td>
</tr>
<tr>
<td>Matson and Yovich, 1986</td>
<td>174</td>
<td>132 (75)</td>
<td>547</td>
</tr>
<tr>
<td>Dlugi et al., 1989</td>
<td>81</td>
<td>69 (85)</td>
<td>20</td>
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<td>Mills et al., 1992</td>
<td>937</td>
<td>642 (68)</td>
<td>643</td>
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<tr>
<td>Lelaider et al., 1993</td>
<td>7181</td>
<td>5726 (80)</td>
<td>784</td>
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<tr>
<td>Simon et al., 1994</td>
<td>1162</td>
<td>670 (58)</td>
<td>922</td>
</tr>
<tr>
<td>Bergendal et al., 1998</td>
<td>1068</td>
<td>836 (78)</td>
<td>702</td>
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<td>Hull et al., 1998</td>
<td>8517</td>
<td>5118 (60)</td>
<td>2559</td>
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<td>Azem et al., 1999</td>
<td>1041</td>
<td>729 (70)</td>
<td>1398</td>
</tr>
<tr>
<td>Total</td>
<td>20904</td>
<td>14475 (69)</td>
<td>7689</td>
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concentrations, but LH concentrations were significantly reduced in women with endometriosis. Reduced LH concentrations in FF were associated with impaired fertilization of oocytes in vitro, despite normal FF FSH and steroid levels (Verpoest et al., 2000). The inference might be drawn that lower LH levels were associated with the reduced fertilization associated with endometriosis. In both unstimulated and stimulated cycles, production of estradiol and progesterone is reported to be reduced (Harlow et al., 1996). Further evidence for an ovarian dysfunction comes from glucocorticoid abnormalities reported in the FF of women with minor endometriosis (Smith et al., 2002).

In contrast to the above studies, Pellicer and co-workers found significant, apparently favourable, increases in FF progesterone and decreases in testosterone concentrations in patients with endometriosis, together with increased granulosa cell steroidogenesis (Pellicer et al., 1998).

The nuclear state of granulosa cells undergoing mitotic division has been studied using flow cytometry. Women with moderate and severe endometriosis have abnormal cell cycles and a higher incidence of apoptotic cells in their granulosa cells compared with other infertile women (Toya et al., 2000). These data complement earlier findings of impaired granulosa cell viability in women with minor endometriosis (Cahill, 1998). These aberrant nuclear events may be responsible for poorer quality oocytes with impaired fertilizing ability.

In summary, studies of altered steroid concentrations within the preovulatory follicles of women with endometriosis are not consistent. Any dysfunctional steroidogenesis that does exist may be due to altered mitotic activity in granulosa cells, altered glucocorticoid exposure or gonadotrophin sensitivity or exposure.

**Does the evidence support a causal or casual relationship?**

In Stage I (minimal) and Stage II (mild) endometriosis (American Fertility Society, 1985; American Society for Reproductive Medicine, 1997), it is often stated that the evidence for the relationship between endometriosis and fertility is unclear. Can superficial endometriosis in the pelvis really affect fertility? A considerable body of evidence would suggest that these women have got some oocyte dysfunction that leads to reduced fertilization and implantation rates. The environment that the oocyte is subjected to may also be affected by altered glucocorticoid balance or sex steroidogenesis. That this is the case still does not confirm whether endometriosis is causal or casual in this relationship. One model to explain the oocyte dysfunction links this with the abnormalities of LH secretion seen during the LH surge and the lower fertilization rate observed in some studies. This may result from inadequate follicular phase drive, perhaps from FSH or some other intra-ovarian paracrine hormone. Stimulation of FSH secretion in the early follicular phase by clomiphene or by exogenous gonadotrophins may be beneficial in improving fertility.

The much debated Canadian study of laparoscopic surgical treatment suggested that altering the peritoneal environment had a beneficial effect on conception rates (Marcoux et al., 1997). A second similar study from Italy found no significant difference in 1 year pregnancy rates (Parazzini, 1999). When the results of these studies were combined (Olive and Pritts, 2001), there was still a higher chance of pregnancy following surgical treatment, though the effect was small [odds ratio (OR) = 1.7, 95% confidence interval (CI) 1.1–2.5]. Thus, the presence of endometriosis may be causative in itself, or may be additive to other factors leading to infertility. This provides an imperative to treat it, even though the ‘proven’ treatments are surgical rather medical.

**Current state of knowledge on the medical treatment of endometriosis-associated infertility**

Medical treatments for endometriosis alter the hormonal balance of the menstrual cycle and produce chronic anovulation, endometrial decidualization (a pseudo-pregnancy) or atrophy (a pseudo-menopause). The endometriotic implants will respond similarly to become ultimately atrophic.
The main categories of the medical treatments used for pain are the progestogens (usually medroxyprogesterone acetate or norethisterone), gestrinone, danazol and the GnRH agonists. These have been extensively studied in the treatment of pain associated with endometriosis. They all have similar levels of efficacy and for all these treatments, between 80–90% of women will have improvement in symptoms (Hughes et al., 2001; Olive and Pritts, 2001).

Because these drugs are effective for symptoms (principally pain), they have been used extensively in the management of infertility associated with endometriosis. A number of studies have investigated these drugs in comparison with other drugs, with a placebo or with no treatment. These have been summarized by meta-analysis in a Cochrane review (Hughes et al., 2001). There was no difference in efficacy as measured by the likelihood of clinical pregnancy whichever drug was used, or indeed if no treatment or a placebo was used.

It has taken some time for this message to be widely disseminated, but it is now clear that there is no role for these drugs in the management of endometriosis-associated infertility. Indeed, because many women have a delay in return to normal ovulatory function after such drugs, the lack of any positive effect is accentuated. Some have claimed a benefit in a small number of women with particular markers for uterine receptivity (Lessey, 2000). However, the weight of evidence is in favour of not treating these women.

Appropriate medical treatments of endometriosis-associated infertility

Current therapies

From the evidence provided earlier, no medical suppressive treatment appears to be of any value, and suppression of endometriosis is unhelpful. Does this imply that non-adhesive, non-cystic endometriosis is of no consequence to fertility? Results from laparoscopic surgical treatments would seem to suggest that the removal of the endometriotic tissue, and whatever it is producing improves fertility (Marcoux et al., 1997; Parazzini, 1999).

If part of endometriosis-associated infertility is due to follicular development, does ovulation induction make any difference in women with minor endometriosis? One small but well designed study of follicular development in spontaneous and clomiphene (with or without FSH) induced cycles in women with minor endometriosis addressed this question (Mahmood et al., 1991b). Clomiphene alone did not improve follicular development, though clomiphene and FSH did (P < 0.01).

In women with minor endometriosis, the use of clomiphene for ovulation stimulation results in a higher pregnancy rate than the use of danazol for ovarian suppression (OR = 2.9, 95% CI 1.2–7.1 versus 1.02, 0.5–2.3) (Simpson et al., 1992). A number of reports have examined the role of ovulation induction in the medical management of minor endometriosis (Deaton et al., 1990; Fedele et al., 1992; Tummmom et al., 1997). These studies are heterogeneous in their protocols, in the drugs used for ovulation induction and whether intrauterine insemination was used. It is therefore difficult to combine their data with any degree of common analysis. Each study does show a consistent increase in cycle fecundity rate following the particular intervention. One non-randomized study examined pregnancy rates after expectant management, clomiphene or HMG following surgical treatment of endometriosis (Karabacak et al., 1999). In this, the cycle rates for fecundity for expectant management, clomiphene and HMG were 0.221, 0.066 and 0.174 respectively (expectant versus HMG, P = 0.005). In addition, the relative risk (RR) of pregnancy was higher if the duration of infertility was <5 years (RR = 1.42, 95% CI 1.02–2.05). The negative effect of increasing age is borne out by the findings of others (Snick et al., 1997).

These studies suggest some improvement in fertility from ovulation induction. In systematic reviews of the role of ovulation induction and/or intrauterine insemination in unexplained infertility, most trials reported in favour of the use of clomiphene (Hughes 1997; Hughes et al., 2000). The common OR for pregnancy per patient for this intervention was 2.37 (95% CI 1.22–4.62), suggesting a significant treatment benefit. However, the presence of endometriosis in persistent infertility is associated with a significant reduction in the likelihood of pregnancy (OR = 0.45, 95% CI 0.27–0.76).

The additional operative element of assisted conception may exclude it from consideration as medical treatment. If not, then it forms an important arm of the treatment plan for couples with minor endometriosis. Success rates in IVF for women with minor endometriosis are generally comparable with other female diagnostic groups (Mills et al., 1992; Hull et al., 1998), because although fertilization rates are reduced, sufficient embryos are obtained and implantation rates are at worst minimally affected. Therefore, early recourse to assisted conception is valid after failure of other methods of medical management or even as a primary treatment in older women.

Imminent or future therapies

Is there any treatment likely to alter these management options in the near future? Possibly. The role of new vessel formation in endometriosis is critical to the progression of the disease. Angiogenesis is also important in many other aspects of medicine, not just in obstetrics and gynaecology where tumour development and pre-eclampsia are important areas of study. The controlling role of vascular endothelial growth factor (VEGF) in many aspects of medicine and particularly in endometriosis is recognized. The potential roles for therapeutic intervention have been reviewed elsewhere (McLaren, 2000), but in essence these focus on VEGF production, bioavailability and receptor binding. Some endocrine manipulations have shown interesting alterations in receptor numbers and VEGF immunoreactivity in normal endometrium (Macpherson et al., 1999; Charnock-Jones et al., 2000). Both etonorgestrel and a combined oral contraceptive (20 µg ethinyl estradiol and 150 µg desogestrel) pill reduced VEGF immunoreactivity, while etonorgestrel increased progesterone receptor numbers and the combined pill decreased it. The therapeutic application of these findings is not yet established. Nonetheless, agents such as those that can alter angiogenesis (antibodies, soluble receptors, tyrosine kinase inhibitors and inhibitors of matrix-
metalloproteinase) may soon be available for use clinically to inhibit the progression of endometriosis (Smith, 2001a).

However, their role in the management of minor endometriosis is likely to be limited (Smith, 2001b).

**Conclusion**

When endometriosis is associated with infertility, there is a reduction in fertility beyond that seen in women with unexplained infertility. There are consistent findings of oocyte dysfunction and reduced fertilizing ability in women with minor endometriosis and a number of studies suggest additional disorders of gonadotrophin release and exposure to the follicle. Although new medical treatments are under development, no currently available medical treatments for suppression of endometriosis have been shown to improve fertility, whereas there may be a role for surgical treatment. Ovulation induction with clomiphene, exogenous gonadotrophins and intrauterine insemination, and assisted conception are all effective treatments for the infertile woman with minor endometriosis. Probably in that order, they should be used for the medical management of infertility associated with minor endometriosis.

**References**


