Pentoxifylline versus placebo in the treatment of infertility associated with minimal or mild endometriosis: a pilot randomized clinical trial

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The present study is the first prospective randomized controlled trial of the effect of pentoxifylline on future fertility in infertile women with asymptomatic minimal or mild endometriosis. After completion of a basic infertility workup and laparoscopy, patients were entered into the study and randomly allocated to receive either a 12 month course of oral pentoxifylline (800 mg/day) (n = 30) or an oral placebo (n = 30). Those patients with other infertility factors were included in the study only if the factors were correctable and ultimately determined to be non-contributory. Life-table analysis was used to compare pregnancy rates between the two groups over a 12 month period that started immediately after laparoscopy. The 12 month actuarial overall pregnancy rates were 31 and 18.5% in the pentoxifylline and placebo groups respectively. However, this difference was not statistically significant by the χ²-test. Similarly, the Cox regression method showed no differences between the hazard of pregnancy in the two groups studied (odds ratio, 0.56; 95% confidence interval, 0.18–1.67). Therefore, there is no evidence from this study that immunomodulation with pentoxifylline aids fertility in those women with minimal or mild endometriosis. Further studies including more infertile patients with endometriosis are desirable in order to confirm our results.

Key words: endometriosis/immunomodulation/infertility/pentoxifylline

Introduction

The association between the occurrence of endometriosis and infertility has long been recognized but endometriosis is an enigmatic and controversial disease. Much uncertainty exists regarding its pathophysiological characteristics and its treatment. Although the treatment approach towards minimal to mild endometriosis during the past two decades has been mostly hormonal in nature, a quantitative overview of controlled trials in endometriosis-associated infertility shows that medical therapy is an ineffective treatment for this condition (Evers, 1989, 1993; Hughes et al., 1993; Adamson and Pasta, 1994). The limited efficacy of hormonal therapy may be explained on the basis that this treatment approach does not affect the pathophysiology of the condition. On the other hand, since endometriosis is, to a large extent, a microscopic disease, a surgical approach cannot be expected to eradicate the disease (Gleicher, 1995).

Despite intense research efforts over the past 50 years, the pathophysiological mechanisms of endometriosis and endometriosis-associated infertility remain to be completely clarified (Hill, 1992). Recently, however, different studies have suggested that immunological mechanisms are involved in the pathophysiology of endometriosis-associated reproductive failure (Mahmood and Templeton, 1990; Hill, 1992; Ramey and Archer, 1993; D’Hooghe and Hill, 1996; Oral et al., 1996; Prentice and Ingamells, 1996; Vinatier et al., 1996; Martínez-Román et al., 1997). On the other hand, considerable evidence already exists in animal models to suggest that immunomodulation, through a variety of non-specific immunomodulators such as pentoxifylline, affects both endometriotic implant growth and endometriosis-associated infertility (Steinleitner et al., 1991a, b, c; Nothnick et al., 1994). On this clinical and experimental evidence, and since all other treatment concepts have failed, it has been stressed that prospective trials of immunological treatments are urgently needed (Evers, 1993; Nothnick et al., 1994; Gleicher, 1992, 1995). The present report is the first prospective, randomized clinical study comparing immunomodulation and placebo for treatment of endometriosis-associated subfertility.

Materials and methods

The study was a prospective randomized controlled blind trial, of the effect of pentoxifylline on future fertility in infertile women with asymptomatic endometriosis; it was approved by the Ethics Committee of the Hospital Clinic i Provincial, Barcelona, Spain. A total of 60 consecutive eligible patients were recruited after a laparoscopy for infertility at which minimal or mild endometriosis had been diagnosed. All patients had complained of at least 12 months of primary infertility and no woman had previous pelvic surgery, clinical or laparoscopic-laparotomic diagnosis of endometriosis or previous therapy for this condition. Infertility diagnostic evaluation included assessment of ovulation, semen analysis, post-coital test, basal body temperature records, mid-luteal serum progesterone and prolactin concentrations, late luteal endometrial biopsy, hysterosalpingogram (and hysteroscopy when necessary), and laparoscopy (Balasch et al., 1996a). Patients with other infertility factors were included if those factors were correctable and ultimately assessed to be non-contributory. All patients with other pelvic disorders such as adhesions and tubal obstructions in addition to endometriosis were excluded.

Diagnosis of endometriosis was made in all cases by laparoscopy as previously reported (Balasch et al., 1996b; Martínez-Román et al., 2008).
A systematic laparoscopic evaluation of all pelvic peritoneal surfaces was carried out in all patients. Endometriosis was staged according to the revised American Fertility Society (AFS, 1985) scoring. Superficial ovarian and peritoneal endometriosis was classified as recently suggested by Brosens et al. (1993) as follows: red lesion (flame-like lesion, or a haemorrhagic vesicle or a vascularized polypoidal or papular lesion); black lesion (a puckered, black lesion); white lesion (scarred tissue with or without some pigmentation). Biopsies of suspicious lesions were taken when the visual diagnosis of endometriosis was in doubt (four cases). Biopsy of the endoscopically suspected endometriosis revealed the presence of endometrial glands and stroma in three cases, while the remaining biopsy showed endometrium-like stroma alone. The latter case was considered as negative for endometriosis. All laparoscopies included tubal dye perfusion.

Patients were entered immediately after laparoscopy and all of them gave written informed consent. They were assigned according to a computer-generated randomization list to one of the following treatments: oral pentoxifylline (Elorgán, Grupo Roche SA, Barcelona, Spain) 400 mg twice daily \( n = 30 \) or an oral placebo \( n = 30 \) to be taken twice daily. Patients were then observed for pregnancy for 12 months. During this period, other infertility factors such as male problems, ovulatory defects, and cervical mucus abnormalities, were treated with appropriate therapeutic modalities including intrauterine insemination with husband or donor semen and/or ovulation induction. It is important to note that patients who had been treated for additional correctable infertility factors before laparoscopy, received the same additional infertility treatments during the same number of cycles after endometriosis was diagnosed. This was also true for those patients empirically treated with intrauterine insemination plus ovulation induction before laparoscopy (two women in the pentoxifylline group and one case among patients receiving placebo). Thus, patients were their own control for additional infertility factors which adds to the homogeneity of the study groups. Pregnancy was confirmed by ultrasonography.

Groups were compared by \( \chi^2 \) analysis and the Mann–Whitney \( U \)-test. We calculated with the actuarial method the cumulative proportion of women who became pregnant, and the curves obtained and pregnancy rates in both groups were analysed by Cox regression method, \( \chi^2 \)-test, and Fisher’s exact test.

**Results**

A total of 60 eligible consecutive patients were entered into the study between November 1993 and December 1995. Thirty of these patients were designated as ‘pentoxifylline patients’ and 30 as ‘placebo patients’. One woman in the pentoxifylline group and three of the placebo patients were discarded because they refused to start treatment after being randomized (one case) or because of the patient’s failure to continue taking the medication (three cases). Thus, in total, the responses of 56 patients to pentoxifylline \( n = 29 \) or placebo \( n = 27 \) were evaluated. All these 56 patients took the drug or placebo regularly and actively tried to become pregnant during the study period.

Baseline characteristics of the patients and the distribution of other infertility factors in each study group are shown in Table I. There were no significant differences between groups regarding age, duration of infertility, prevalence of endometriosis by revised AFS (1985) classification, and diagnosis of appearances of the condition. The frequency of additional correctable infertility factors and additional infertility treatments were also similar for both study groups.

The 12 month actuarial overall pregnancy rates were 31% and 18.5% in the pentoxifylline and placebo groups, respectively. However, this difference was not statistically significant by the \( \chi^2 \)-test. Similarly, the Cox regression method showed no differences between the hazard of pregnancy in the two groups studied (odds ratio, 0.56; 95% confidence interval, 0.18–1.67) (Figure 1). One patient in each study group became pregnant but miscarried at 7 and 8 weeks gestation, respectively. Both women conceived again under the same treatment and carried to term. These two pregnancies were not included for statistical analysis of results. When patients were categorized as pregnant or non-pregnant, according to treatment regimen, again the presence of corrected additional infertility factors did not appear to influence the rate of pregnancy by Fisher’s exact test (Table II).

**Discussion**

It has been estimated that 25–50% of infertile women have evidence of endometriosis, and 30–50% of women with endometriosis are infertile (Mahmood and Templeton, 1990; Christman and Halme, 1992). Therefore, endometriosis is one of the most important gynaecological diseases affecting the fertility potential of women. Most infertile women having endometriosis present with minimal to mild forms of the disease for which no definite therapeutic approach exists. In fact, it has been recently stressed that, in endometriosis-associated subfertility, it has never been proven satisfactorily that medical treatment works, and the same holds for surgery and laser laparoscopy (Evers, 1989, 1993; Hughes et al., 1993; Adamson and Pasta, 1994; Gleicher, 1992, 1995). Thus, it now seems well established that endometriosis is neither an endocrinological nor a surgical disease and novel approaches of treating infertility associated with minimal or mild endometriosis are urgently needed (Evers, 1993; Gleicher, 1992, 1995).

Endometriosis has, in recent years, been characterized by a large number of immunological abnormalities in the host and there is substantial evidence that immunologic factors play a role both in the pathogenesis of endometriosis and endometriosis-associated reproductive failure (Mahmood and Templeton, 1990; Hill, 1992; Ramey and Archer, 1993; D’Hooghe and Hill, 1996; Oral et al., 1996; Prentice and Ingamells, 1996; Vinatier et al., 1996). Thus, in a recent study (Martinez-Román et al., 1997) investigating immunologic factors in fertile and infertile women with and without endometriosis, we concluded that immunologic mechanisms of endometriosis-associated infertility exist but these peritoneal immunological factors in infertile women with endometriosis are a function more of their subfertility than of their ectopic endometrial implants. This is supported by the lack of immunologic abnormalities observed among fertile women with endometriosis. These immunological abnormalities are lacking in patients with unexplained infertility.

If peritoneal macrophages are involved in the pathogenesis of endometriosis and endometriosis-associated subfertility,
Figure 1. Overall 12 month probability of becoming pregnant in 56 subjects with minimal or mild endometriosis according to treatment allocation.

Table I. Baseline characteristics and additional correctable infertility factors in the pentoxifylline and placebo groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pentoxifylline group (n = 29)</th>
<th>Placebo group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.2 ± 3.8</td>
<td>32.4 ± 3.1</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>3.3 ± 1.9</td>
<td>4.2 ± 2.6</td>
</tr>
<tr>
<td>AFS stage (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25 (86)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>II</td>
<td>4 (14)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Laparoscopic appearance (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>red lesion</td>
<td>5 (17)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>black lesion</td>
<td>25 (86)</td>
<td>23 (85)</td>
</tr>
<tr>
<td>white lesion</td>
<td>10 (34)</td>
<td>10 (37)</td>
</tr>
<tr>
<td>Additional infertility factors (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>16 (55)</td>
<td>16 (59)</td>
</tr>
<tr>
<td>male factor</td>
<td>4 (13.7)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>oligo-ovulation</td>
<td>4 (13.7)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>luteal phase defect</td>
<td>2 (6.9)</td>
<td>0</td>
</tr>
<tr>
<td>poor post-coital test</td>
<td>3 (10.3)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>hyperprolactinaemia</td>
<td>0</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Additional infertility treatments (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUI + ovulation induction</td>
<td>9 (31)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>ovulation induction</td>
<td>6 (20)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>bromocriptine</td>
<td>0</td>
<td>1 (3.7)</td>
</tr>
</tbody>
</table>

AFS = American Fertility Society.
IUI = intrauterine insemination.
There were no significant differences between the groups.

Table II. Patients with minimal to mild endometriosis who conceived in both treatment groups

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pentoxifylline (n = 29)</th>
<th>Placebo (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases No. conception (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected additional infertility factors</td>
<td>16 4 (25)</td>
<td>16 3 (19)</td>
</tr>
<tr>
<td>Corrected additional infertility factors</td>
<td>13 5 (38)</td>
<td>11 2 (18)</td>
</tr>
</tbody>
</table>

There were no significant differences between the groups by the Fisher exact test.

either the disruption of macrophage function or interference in the release of secretory products should result in regression or suppression of endometriosis and/or its associated symptoms (Ramey and Archer, 1993). Experimental studies by Steinleitner et al. (1991a, b, c) support this contention. These authors showed that the intraperitoneal transfer of hyperactivated macrophages, but not of basal state macrophages, into syngeneic mice significantly inhibited fertilization. This fertility-lowering effect of activated macrophages was reversed by periovulatory administration of pentoxifylline, a methylxantine derivative. Similarly, they found that peri-ovulatory treatment with pentoxifylline abrogated the adverse influence of endometrial explants on fertilization in the rodent model. A variety of mechanisms has been proposed to account
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for these observations (Steinleitner et al., 1991a, b). Pentoxifylline inhibits phagocytosis and generation of toxic oxygen species and proteolytic enzymes by macrophages and granulocytes in vitro and in vivo; it inhibits tumour necrosis factor production in vitro; and it reduces the inflammatory action of tumour necrosis factor and interleukin 1 on granulocytes in vitro. Thus, pentoxifylline influences both the production of inflammatory mediators and the responsiveness of immunocompetent cells to inflammatory stimuli. Pentoxifylline has also been used to enhance sperm motility and the outcome of in-vitro fertilization in couples suffering from male infertility (Tournaye et al., 1994; Matson et al., 1995). Therefore, a direct effect on sperm motility has also been advocated by Steinleitner et al. (1991a, b) to explain their results. Finally, it should be noted that a recent experimental study showed that pentoxifylline can modulate rat endometriotic implant growth and production of implant-specific proteins (Nothnick et al., 1994).

From their studies, Steinleitner et al. (1991a, b) and Nothnick et al. (1994) concluded that immunomodulation of peritoneal inflammatory cell hyperactivation with pentoxifylline may represent a new modality specifically to treat the essential pathophysiology of endometriosis-associated subfertility. Evers (1993) and Gleicher (1995) stressed that since all other treatment concepts have failed, there is nothing to lose by designing new experimental treatment approaches towards endometriosis that are based on immunomodulation. However, so far, such studies in the human have not been reported.

The present study represents the first report investigating the possible beneficial effect of pentoxifylline for treatment of endometriosis-associated infertility in women. As critically stressed by Evers (1989, 1993) in reviewing clinical trials on medical treatment of endometriosis, at present it would be unethical not to start randomized studies with no treatment in one arm. In addition, this author emphasizes the need for measuring the result of treatment in subfertility patients in terms of pregnancy rate. Both aspects were considered in our study and our results revealed that 31% of patients who received pentoxifylline therapy conceived, whereas only 18.5% of those patients who received a placebo conceived. However, pregnancy rates in the two groups were not found to be statistically significant. Therefore, there is no evidence from this study that immunomodulation with pentoxifylline aids fertility in those women with minimal or mild endometriosis. Our study has three possible limitations. The first one is that the present investigation was undertaken as a pilot study and included a limited number of patients. Considering the difference in pregnancy rates between the two treatment arms obtained in our study, a sample size >800 patients would be necessary in order to provide 80% statistical power of avoiding a type II error, and a 5% chance of making a type I error. Therefore, multicentre prospective trials of immunological treatments are warranted. However, it should be noted that the number of patients included in the present report was similar to the number of cases included in the only five randomized controlled clinical trials on hormonal therapy for endometriosis-associated subfertility treatment having no treatment or placebo as a randomly allocated option in one arm of the study and pregnancy rates as one of their endpoints (Seibel et al., 1982; Thomas and Cooke, 1987; Bayer et al., 1988; Telimaa, 1988; Fedele et al., 1992). A second limitation of our study, which is also shared with those previous studies on hormonal therapy, is that 40–45% of patients had additional infertility factors. However, a thorough infertility evaluation was carried out in all patients, those cases with untreatable confounding factors were excluded, and all defects thought to be contributing to subfertility were corrected. In addition, $\chi^2$ analysis showed that these confounding factors had no significant effect on pregnancy rates among the two study groups. Finally, pentoxifylline dosage (800 mg/day) used in our study was selected arbitrarily on the basis of the manufacturer’s recommendations while a dosage of 400–1200 mg/day was used for the treatment of idiopathic male factor infertility (Tournaye et al., 1994). This dose, however, is twice as high as the dose of pentoxifylline (5 mg/kg body weight) successfully used to modulate endometriotic implant growth and production of implant-specific proteins in the rat model (Nothnick et al., 1994).

In summary, the present pilot study failed to show any impact of treatment of asymptomatic endometriosis with pentoxifylline on future fertility. Further studies including more patients ideally having endometriosis but not additional infertility factors are desirable in order to confirm our results.

References


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