Effect of endometriosis on IVF/ICSI outcome: stage III/IV endometriosis worsens cumulative pregnancy and live-born rates

Paula Kuivasaari¹, Maritta Hippeläinen, Maarit Anttila and Seppo Heinonen

Department of Obstetrics and Gynaecology, Kuopio University Hospital, 70211 Kuopio, Finland

¹To whom correspondence should be addressed. E-mail: kuivasaa@hytti.uku.fi

BACKGROUND: Women with endometriosis often need IVF to conceive—most women need several cycles of treatment. METHODS: To evaluate the impact of moderate to severe endometriosis on cumulative IVF outcome, we carried out an observational study on 98 consecutive women who underwent IVF or ICSI treatment and had endometriosis diagnosed by laparoscopy or laparotomy and classified as minimal to mild endometriosis (American Society for Reproductive Medicine I/II) (n = 31) or moderate to severe endometriosis (American Society for Reproductive Medicine III/IV) (n = 67). The reference group consisted of 87 consecutive women with tubal infertility. The main outcome measures were cumulative pregnancy and live birth rates. RESULTS: There was a significantly lower pregnancy rate per fresh embryo transfer after pooled cycles (1–4) among women with stage III/IV endometriosis (22.6%) compared to stage I/II group (40.0%) or tubal infertility (36.6%). After 1–4 IVF/ICSI treatments, including frozen embryo transfer, 56.7% of the women with stage III/IV endometriosis were pregnant and 40.3% gave birth. The corresponding values were 67.7/55.8% when endometriosis was stage I/II and 81.6/43.7% in the controls respectively. CONCLUSION: Stage III/IV endometriosis means a worse prognosis for IVF/ICSI treatments compared to milder stages or tubal factors. Lower implantation and multiple pregnancy rates offer some support to our practice to continue two embryo transfers in this group.

Key words: embryo transfer/endometriosis/infertility/IVF and ICSI outcome/pregnancy

Introduction

Endometriosis is a disease of reproductive-aged women characterized by endometrial glands or stroma in sites other than the uterine cavity, usually the peritoneum or ovaries. Endometriosis is one of the most challenging diseases for gynaecologists helping infertile women to conceive. Many factors have been suggested to cause infertility in women with endometriosis, including pelvic adhesions, ovulatory dysfunction, disturbed folliculogenesis and defective implantation (Pellicer et al., 1995; Cahill et al., 1997; Selam and Arici, 2000; Navarro et al., 2003; Brosens et al., 2004). Using IVF it is possible to bypass some disturbances of reproductive function.

Several studies have shown that women with endometriosis have a lower ovarian response to gonadotrophins (Azem et al., 1999; Al-Azemi et al., 2000; Aboulghar et al., 2003). In addition, Al-Azemi et al. (2000) found that women with endometriosis needed more HMG ampoules per cycle, while the control group of tubal factor subjects maintained a constant ovarian response over the five analysed cycles. One reason for a reduced ovarian response may be previous ovarian resection. Aboulghar et al. (2003) investigated women with severe endometriosis who had had previous surgical treatment and found that these patients had a significantly higher withdrawal rate than the control group with tubal infertility. Of the endometriosis patients, 29.7% discontinued because of poor ovarian response, the corresponding rate for tubal factor patients being only 1.1%. In contrast, in a study carried out by Donnez et al. (2001), preceding vaporization of the internal cyst wall of endometriomas did not impair ovarian function; there were no differences in ovarian response to stimulation between women with endometriosis and women with tubal infertility.

Data on the impact of endometriosis on the results of IVF treatment are controversial. Olivennes et al. (1995) found that pregnancy rates were no different from those of women with tubal infertility, whereas Bergendal et al. (1998) found that patients with endometriosis had a reduced response to ovarian stimulation, a lower number of oocytes and a reduced fertilization rate, but not a reduced pregnancy rate. In a recent meta-analysis of 22 published studies (Barnhart et al., 2002) the conclusion was that women with endometriosis have a reduced pregnancy rate (<35%) compared with that in women with tubal infertility. In addition, other indicators, such as circulating estradiol levels, numbers of retrieved oocytes, and decreased fertilization and implantation rates, have shown similar results (Azem et al., 1999). Furthermore, the severity of endometriosis is likely to affect the outcome of assisted reproduction, women with stage III and IV disease having lower fertilization rates.
compared with those with stages I and II. Overall, the data from the study carried out by Barnhart et al. (2002) suggest that endometriosis affects fertility not only by distorting normal pelvic anatomy but also by having effects on developing follicles, oocytes and embryos.

The purpose of this study was to investigate whether or not the stage of endometriosis affects the outcome of IVF, and the specific aim was to look at the cumulative pregnancy and live-born rates after four treatment cycles using women with tubal infertility as a control group. Such data would be useful for patient counselling.

Materials and methods

The material consisted of 98 consecutive women who underwent IVF or ICSI treatment at Kuopio University Hospital between October 1996 and May 2003. All of them had endometriosis diagnosed by laparoscopy (77.6%) or laparotomy (22.4%). Endometriosis was scored according to the revised classification of the American Fertility Society (1997). In operation, adhesions were freed in 45 patients, endometriomas resected in 36 patients, and electrocoagulation was used in 46 cases. The control group comprised 87 consecutive women with tubal infertility. Tubal infertility was diagnosed by laparoscopy in 77.0% and by laparotomy in 6.9% of the women. In the rest of the women (16.1%) the diagnosis was made by hysterosalpingosonography (HSSG) (Spalding et al., 1998); they did not have any clinical signs of endometriosis and ultrasonography was clean. Excluded from the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by the study were those women who: (i) had repeatedly high early cycle FSH level (>15–20 IU/l) and/or had no noticed follicles in ovaries by

Table I. Characteristics of the subjects

<table>
<thead>
<tr>
<th>Reference group</th>
<th>Endometriosis stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I/II</td>
</tr>
<tr>
<td>No. of patients</td>
<td>87</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.7 ± 4.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.4 ± 4.5</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>4.2 ± 2.7</td>
</tr>
<tr>
<td>Primary infertility (%)</td>
<td>39.4</td>
</tr>
<tr>
<td>Smoking (&gt;5 cigarettes per day, %)</td>
<td>31.0</td>
</tr>
<tr>
<td>Chronic illness (%)</td>
<td>13/87 (14.9)</td>
</tr>
<tr>
<td>Ovarian resection</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless stated otherwise. *P < 0.05. **P < 0.01 in comparison with the reference group.

Table II shows the overall outcomes of the IVF/ICSI cycles separately for women in the reference group and women with minimal to mild or moderate to severe endometriosis. There were no statistically significant differences in the mean number of oocytes, fertilization rate or quality of embryos between the groups.

The overall pregnancy rate per fresh embryo transfer was 31.7%, and of these pregnancies, 66.4% resulted in live-born infants in a total of 392 cycles analysed in this study. These rates are comparable to those achieved in our unit in general. Detailed results are shown in Table II. Pregnancy rates after all four fresh embryo transfers were not significantly different in women with minimal to mild endometriosis and in the reference pregnancy rates.

Effect of endometriosis on IVF/ICSI outcome

Results
When compared against the reference group, the pregnancy rate in women with moderate to severe endometriosis was significantly lower ($P = 0.009$). There were no significant differences in miscarriage rate between the groups. One pregnancy was terminated because of a fetal structural anomaly (anencephaly).

Women with stage III/IV endometriosis had the highest overall drop-out rate from the treatment (52.2%). The drop-out rate was 38.7% in women with milder endometriosis and the corresponding rate was 44.8% in women with tubal factor infertility. There were no significant differences between these numbers. We recorded no differences in the mean numbers of oocytes yielded or the mean ages of women continuing their treatment cycles versus those who dropped out (data not shown).

Figure 1 shows the cumulative live birth results. The cumulative pregnancy and live-born rates resulting from four IVF treatments without frozen embryo transfers were 64.5 and 51.6% in women with stage I/II endometriosis, 44.8 and 32.8% in women with stage III/IV endometriosis and 69.0 and 43.7% in the reference group respectively. With frozen embryo transfers included, the equivalent rates were 67.7 and 55.8% in women with stage I/II endometriosis, 56.7 and 40.3% in women with stage III/IV endometriosis and 81.6 and 43.7% in the reference group respectively.

Finally, we compared the present results with those of four earlier studies having similar study design (Table III). The pooled data showed that the mean number of oocytes obtained per cycle and the pooled fertilization rate were significantly lower in women with endometriosis. Similarly, according to the pooled results, women with stage III/IV endometriosis also had a significantly lower pregnancy rate than the reference group, 14.3 versus 28% ($P < 0.001$). The corresponding rate was 23.1% in women with stage I/II endometriosis ($P = 0.183$).

Women with minimal to mild endometriosis had a better live-birth rate (20.0%) than women with moderate to severe endometriosis (11.4%) or women with tubal factor infertility (18.7%).

**Discussion**

A poorer success with IVF with an increase in severity of endometriosis is also obvious according to our data. The overall cumulative outcome of IVF/ICSI treatment was favourable, however. It could be speculated that the results may have been even better if the women had been ready to continue treatments. The number of drop-outs was surprisingly large, especially among women with severe endometriosis (50%), and this may affect the overall results. Pregnancies in women with endometriosis more often resulted in live-born infants than those in the tubal factor group. Women with endometriosis had fewer miscarriages and ectopic pregnancies than women with tubal infertility, but on the other hand the women with tubal infertility were older and they smoked more often than those with moderate to severe endometriosis, which may be one reason for the observed higher rate of miscarriages. At the end,
more than half of the woman with minimal to mild endometriosis left the clinic with the baby, but only \(\sim 40\%\) of the women with tubal infertility or severe endometriosis.

In addition to the overall outcome of the IVF/ICSI treatment, several interesting observations can be drawn from this study. First, women with moderate to severe endometriosis were treated earlier than women with less severe disease, although their infertility history was a few months shorter. Second, women with moderate to severe endometriosis discontinued infertility treatment more often than the other women. Third, the outcome of IVF/ICSI treatment was relatively constant within each group, independent of the order of the treatment cycle. Fourth, the rate of multiple pregnancies was highest in women with stage I/II endometriosis.
The present results also have several clinical implications. The AFS classification is useful in predicting the outcome of infertility treatment and can be used for counselling purposes. Women with endometriosis should be treated in good time, especially when a woman has an active disease. The present results also support the idea of using single embryo transfer in women with stage I/II endometriosis, whereas the observed low pregnancy rate in women with stage III/IV disease requires further studies before deciding on an optimal policy in these cases. On the other hand, difficulties such as painful stimulation and challenging puncture, encountered by patients with endometriosis in the IVF treatment would favour the use of two-embryo transfer.

Martikainen et al. (2001) investigated one- versus two-embryo transfer after IVF/ICSI. In that study the cause of infertility was not taken into consideration. The outcome was that two-embryo transfer did not result in a significantly better pregnancy rate than single embryo transfer; 47.1 versus 32.4%. Since our endometriosis III/IV group showed lower single and multiple pregnancy rates than the other groups, it is possible to draw the conclusion that their endometrial receptivity had deteriorated. However, on the basis of the results of a study by Diaz et al. (2000), this conclusion is not necessarily valid. In that study there were 25 women with stage III/IV endometriosis and 33 women with other causes of infertility. When oocytes from a single donor were donated to recipients in both groups, pregnancy, implantation and miscarriage rates were not found to be affected in women with endometriosis when compared with the control group. Further studies are therefore needed to address the issue of whether single embryo transfer should be recommended to women with moderate to severe endometriosis.

All in all, we found that women with stage III/IV endometriosis had worse IVF/ICSI results compared with women with less severe disease or women with tubal infertility.

Women with impaired ovarian reserve were excluded from our IVF programmes and this may somewhat bias the results. However, the effect of such bias would rather underestimate than overestimate the outcome difference between women with stage I/II and III/IV endometriosis. Overall, these limited clinical data support the idea of some kind of defective implantation. Even though the same numbers of good quality embryos were transformed, the implantation rate per embryo (data shown before) and pregnancy rate appeared to be lower among women with endometriosis compared to the controls. The frequency of multiple pregnancies also seemed to be lower. An explanation for the present results is beyond the scope of this study, but may be related to mechanisms related to angiogenesis, the immune system, and/or endometrial receptivity (Bergqvist et al., 1997; Toya et al., 2000).

Clinically, ovarian resection is one possible explanation for the present results, but on the other hand, the need for operative treatment also reflects more severe disease. In a study by Tinkanen and Kujansuu (2000) there were 100 women with stage III/IV endometriosis with a history of surgery for ovarian endometriosis or with prevailing ovarian endometriosis. The patients were divided into two groups, 55 women with no ovarian endometriosis and 45 women with recurrent endometrioma. The pregnancy rate was 38% in the endometrioma group and 22% in the group without endometriomas. The results of the study suggest that the presence of ovarian endometriosis does not reduce fertilization or implantation rates, but the radical nature of resection could reduce ovarian capacity.

According to our data, 40.3% of women with stage III/IV endometriosis gave birth after one to four IVF/ICSI treatments. The success trend (Figure 1) is rising slowly, but the inconvenience caused by ovarian stimulation may be a limiting factor, especially when the activity of the illness increases along the course of treatments. However, more patients need to be studied to attain better predictability of the treatment success.

References


Submitted on February 20, 2005; resubmitted on May 21, 2005; accepted on May 24, 2005