Impact of ovarian endometrioma on assisted reproduction outcomes

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Abstract

The effects of ovarian endometrioma on fertility outcomes with IVF and embryo transfer have been causally related to poor outcomes. The objective of this meta-analysis was to evaluate the ovarian reserve and ovarian responsiveness to ovarian stimulation and assisted reproduction outcomes in patients with ovarian endometrioma. The odds for clinical pregnancy were not affected significantly in patients with ovarian endometrioma compared with controls, with an overall odds ratio of 1.07 from three studies [95% CI: (0.63, 1.81), \(P = 0.79\)]. The overall pregnancy rate was similar with an estimated odds ratio of 1.17 [95% CI: (0.85, 1.60), \(P = 0.34\)]. Decreased ovarian responsiveness to ovarian stimulation in patients with ovarian endometrioma may be due to a reduced number of follicles in these patients compared with controls (\(P = 0.002\)). Prospective randomized controlled trials are needed to assess whether surgical treatment versus no surgical treatment improves pregnancy outcomes in patients with ovarian endometrioma undergoing assisted reproduction cycles.

Keywords: embryo quality, in-vitro fertilization, intracytoplasmic sperm injection, ovarian endometrioma, retrieved oocytes

Introduction

Endometriosis is a disease characterized by ectopic growth of endometrial stroma and glands, and affects about 5 million women of reproductive age in North America (Esfandiar, 2005). Among women with infertility, 30–50% are diagnosed with endometriosis laparoscopically (Mahmood and Templeton, 1991; Redwine, 1999). The association between endometriosis and infertility is still a topic of debate, and remains controversial. The presence of ovarian endometrioma is a common and specific manifestation of the disease, and may arise as a consequence of metaplasia of the coelomic epithelium or inversion with invagination of the ovarian cortex after local implantation of the endometrium on the ovarian surface (Donnez et al., 1996). Ovarian endometriomas are a manifestation of deep ovarian endometriosis. The management of ovarian endometrioma remains controversial, since some studies have not reported improvement in pregnancy rates with surgical treatment in the context of assisted reproduction (Garcia-Velasco et al., 2004) and others have reported adverse fertility outcomes (Dlugi et al., 1989).

Among women in their reproductive years, endometriosis has a prevalence of 10–15% (Counseller and Crenshaw, 1951; Somigliana et al., 2004). Laparoscopic evidence of ovarian endometrioma was reported in 17% of women with chronic pelvic pain and infertility (Milingos et al., 2006). Symptoms such as chronic pelvic pain, dysmenorrhea, infertility and dyspareunia affect quality of life in women suffering from endometriosis. There is an immense expense in terms of the cost of treatment and the emotional burden. The mechanism of the pathogenesis of infertility associated with endometriosis is controversial. In the most severe form, infertility is ascribed to adhesions, tubal blockage and anatomical distortion, but the mechanisms involved in mild to moderate disease are poorly understood.
Cumulative pregnancy rates in patients with pelvic endometriosis and ovarian endometriomas are not significantly different, according to the revised staging by the American Society of Reproductive Medicine (Guzick et al., 1997). However, increasing tubal adhesive involvement associated with the endometrioma leads to reduced pregnancy rates.

Unfortunately, medical therapy has not been found to be an effective treatment for endometrioma-associated infertility in endometriomas greater than 4 cm. However, assisted reproductive technologies are being increasingly employed to help women with endometriosis to conceive. Endometriosis is one of the main indications for the use of IVF-embryo transfer and currently represents 10–25% of all patients who seek this treatment. Women with ovarian endometrioma have been reported to have a reduced ovarian response to ovarian stimulation as measured by fewer retrieved follicles, fewer aspirated oocytes and lower peak oestradiol concentrations. This is also associated with poor quality of oocytes, which may lead to lower fertilization rates, a smaller number of embryos available for transfer, and higher miscarriage rates (Yanushpolsky et al., 1998).

Ovarian endometriomas are predominantly haemorrhagic lesions. Ovarian endometriomas result from the implantation of ectopic endometrium on surfaces of the ovaries and subsequent invagination and invasion of the endometrium into the ovarian cortex (Brosens, 2004). The cytology of ovarian endometrioma reveals the presence of glandular and flattened endometrial epithelium, endometrial stroma and haemosiderin-laden macrophages (Nezhat et al., 1992). Transvaginal sonography can diagnose ovarian endometriomas greater than 2 cm in diameter (Moore et al., 2002). Diminished ovarian reserve and reduced ovarian response to ovarian stimulation and compromised follicular development have all been implicated in endometriosis-associated infertility (Wardle et al., 1985; Yovich et al., 1985). Patients with ovarian endometriomas can present with infertility alone or infertility associated with chronic pelvic pain (Milingos et al., 2006). IVF and embryo transfer can be successfully used to treat infertility associated with endometriosis.

Compromised follicular development and poor embryo quality have been reported to result in impaired fertility outcomes with ovarian endometrioma. This meta-analysis was conducted to evaluate the effects of ovarian endometrioma on ovarian responsiveness to ovarian stimulation and pregnancy outcomes with assisted reproduction.

Materials and methods

Search strategy

This meta-analysis was initiated with studies identified by an extensive search of Medline-Ovid, EMBASE, Cochrane Collaboration database, BIOSIS and Meeting Abstracts from 1986 to 2005, with the help of a professional librarian as well as manual searching of review articles and cross references. The overall strategy employed for study identification and data extraction is outlined in Figure 1. The following keywords were used to search the databases: ovarian endometrioma, IVF, intracytoplasmic sperm injection, retrieved oocyte, embryo quality, fertilization rate, implantation and pregnancy rate. Articles were evaluated for relevance by examining titles and abstracts.

Evaluation of relevant studies: blinding and scoring of studies

Articles and reviewers were ‘blinded’ during the evaluation period. The methods, results, tables and figures from each study were extracted, and each article was assigned an identification number by an individual other than the two scorers. Quantitative or qualitative report of results was blacked out in each article to enable unbiased scoring of study quality. Data points or graphs were blacked out of figures, while axes and captions were still included for evaluation. Summary statistics, P-values or descriptions were blacked out of tables and texts, while labels such as comparison groups and parameters measured were left viewable. Two evaluators blinded to the concluding results, authors, journal, and year of the articles evaluated each study on its methodological merits.

Four overarching categories of bias were appraised with the questionnaire and the scoring system: selection or follow-up bias, confounding bias, information or detection bias, and other sources of bias such as misclassification. Each study was scored using the same set of questions for each type of bias. Specific answers for different questions were given more weight than others as shown in the point system used to total the scores for each category of bias. A higher score indicated that the study met most of the criteria required to avoid introducing bias in the study. If the total points for more than one category of bias fell below an acceptable range, the study

![Figure 1. Steps in the meta-analysis.](image-url)
was automatically excluded from the final analysis. If the total points for only one category fell below the acceptable range, the study was re-examined to determine whether, indeed, the overall study was likely to be biased, and, if not, whether it could be included in the meta-analysis.

**Study description**

**Study 1 (Canis et al., 2001)**

This was a retrospective cohort study with patient information extracted from an IVF database. Patients were excluded if oocyte retrieval was performed laparoscopically. If patients underwent IVF and gamete intra-Fallopian transfer (GIFT) or intracytoplasmic sperm injection (ICSI) cycles, only the IVF cycles were included.

Three groups of patients were retrospectively selected from the IVF–embryo transfer records. The first group consisted of patients who had undergone laparoscopic ovarian cystectomy for ovarian endometriomas >3 cm in diameter. The second group consisted of women treated for endometriosis with laparoscopy but without deep ovarian endometriosis. The third group consisted of patients with tubal infertility. The endometriosis and tubal infertility groups were age matched with those with ovarian endometrioma.

The study concluded that laparoscopic cystectomy is valuable in the management of ovarian endometriomas as there was no diminution of response to ovarian stimulation. In addition, the number of embryos and pregnancy rates were similar in the endometrioma group and the endometriosis group without deep ovarian endometriosis.

**Study 2 (Donnez et al., 2001)**

This study reported outcomes per cycle with multiple observations per individual.

A series of 85 patients who had undergone laparoscopic cystectomy for ovarian endometrioma and had failed to become pregnant were compared with a control group of 287 patients with tubal factor infertility. Both groups were treated with IVF–embryo transfer. IVF–embryo transfer outcomes were analysed in both groups to assess if laparoscopic surgery for ovarian endometriomas adversely affects IVF outcomes.

There were no significant differences in the studied parameters such as number of ampoules, number of follicles, number of mature oocytes, concentration of oestradiol and day of human chorionic gonadotrophin (HCG) injection between the ovarian endometrioma and the control group. An additional analysis was performed in the group of patients who had received cystectomy comparing the ovary that had undergone cystectomy to the contralateral normal ovary, which acted as a control. No statistically significant difference in ovarian response was seen between the two groups. The proportion of clinical pregnancies was 37.4 and 34.7% in the endometriosis and the tubal factor control group respectively. Vaporization of the internal cyst wall did not seem to compromise the ovarian reserve.

**Study 3 (Marconi et al., 2002)**

This was a retrospective follow-up study.

Thirty-nine patients underwent surgery for ovarian endometrioma by stripping of the pseudo-capsule and minimal bipolar cauterization in order not to avoid compromising the vascular supply of the ovaries. Thirty-nine tubal infertility patients in a similar age group served as controls.

Several parameters such as serum oestradiol concentrations, number of follicles and oocytes retrieved were similar in both the cases and controls. Thus, ovarian cystectomy did not compromise the ovarian reserve. The study concluded that laparoscopic stripping of the cyst wall with careful electrocoagulation does not affect the ovarian reserve.

**Study 4 (Pabuccu et al., 2004)**

This was a prospective follow-up study.

One hundred and seventy-one patients divided into four groups were examined. All four groups were similar with regard to age, duration of infertility, body mass index (BMI) and FSH and oestriadiol concentrations on day 2 of the menstrual cycle. The first group consisted of patients with endometriomas that were aspirated at the start of combined ovarian stimulation. The second group was comprised of patients with non-aspirated endometriomas. The third group included patients with a history of surgery for endometriomas, but with no endometriomas presently. The fourth group included only patients with tubal factor infertility. All patients had undergone ICSI.

There were no significant differences in the implantation rates between the endometrioma group and the tubal infertility group.

**Study 5 (Suzuki et al., 2005)**

This study reported outcomes per cycle with multiple observations per person.

There were no significant differences in age and BMI between the groups compared. Three study groups were included: group A (n = 50) was composed of patients with a diagnosis of endometrioma confirmed by aspiration and the characteristic appearance of the aspirated fluid. Group B consisted of patients with endometriosis diagnosed at laparoscopy, but without endometriomas. Group C consisted of patients with tubal factor infertility who served as the unexposed cohort.

The study concluded that ovarian endometrioma has adverse effects on follicle number but not on embryo quality or pregnancy outcomes. This study also reported that the detrimental effects of ovarian endometrioma could possibly be overcome by laparoscopic treatment.

**Study 6 (Yanushpolsky et al., 1998)**

This was a prospective follow-up study.

Thirty-seven patients with ovarian endometriomas were included; all had a cyst fluid CA-125 concentration of >10^4 IU/
Eight patients with complex ovarian cysts were excluded because the cyst fluid concentrations were <10^5 IU/ml. Fifty-seven women without any complex ovarian cysts served as the comparison group.

Emphasis is placed on the need to distinguish endometrioma from complex ovarian cysts, as complex haemorrhagic cysts do not have an unfavourable impact on IVF outcomes. The endometriomas were aspirated at the time of oocyte retrieval, and CA-125 concentrations were estimated in the cyst fluid.

This study concluded that endometriomas have adverse effects on oocyte and embryo quality.

Data extraction

Preformatted data extraction sheets were utilized to extract the data by one of the reviewers. The data were then entered into a spreadsheet. The outcomes reported were variable; some studies reported the odds of chemical or overall pregnancy (detection of HCG) and others reported the odds of clinical pregnancy rates. Some authors reported the odds of pregnancy per cycle with multiple cycles per woman while other reported odds with only one observation per woman.

The outcomes or measures of interest for which data were extracted included dichotomous variables such as clinical pregnancy, chemical/overall pregnancy, and spontaneous abortion for which the overall odds were calculated and continuous variables such as average fertilization rate, implantation rate, number of oocytes retrieved, peak oestradiol concentration, total FSH used, and number of mature follicles for which a weighted mean was calculated. Population and study characteristics such as type of comparison group, whether ovarian endometrioma was treated, and unit of measurement (i.e. variables were measured per patient or per cycle) were also extracted for further subgroup analyses.

Data analysis

Data analyses were carried out using the RevMan software (version 4.2.8) developed by the Cochrane collaborative for the purpose of meta-analysis (www.cochrane.org). A random effects model was used for both the dichotomous and continuous data, as it was intended to extrapolate conclusions to other situations beyond only those in the studies included in the analysis. Outcomes that had significant heterogeneity were examined to determine whether the unit of measurement (by cycle or by patient) was the source of heterogeneity. Because by-cycle measurements, with multiple cycles observed for some individuals in the study, were less common, these were the first to be excluded from the final models if there was significant or close to significant heterogeneity. A P-value <0.05 was used as the cut-off point for significance testing in all statistical tests.

Results

A search of the electronic databases yielded 439 studies. Of these, a total of 29 articles were found to be relevant by examining the abstracts and titles. Twenty-one original articles contained data relevant to the analysis. One of these articles was excluded due to duplication, and 13 were excluded from the main analysis because there was no unexposed group, or because the exposed group had endometriosis rather than ovarian endometrioma (Figure 2). One of the studies was excluded because the methodology of recruitment, diagnosis and follow-up was not clear (Suganuma et al., 2002). Subsequent analysis was performed to examine whether there were significant differences in reproductive outcomes of patients with endometriosis in comparison to those with ovarian endometrioma. After grading each of the remaining seven studies on quality, only six studies remained (Table 1). One article was excluded because there was no indication as to the characteristics of the studied populations (Chang et al., 1997). The data on outcomes, which were examined in fewer than two studies, are not presented in the meta-analysis. So far as is known, this is the first meta-analysis to consider the effects of ovarian endometrioma on fertility outcomes with assisted reproduction techniques.

Significant heterogeneity was found in the initial analysis of many of the outcomes that included studies measuring characteristics by cycle along with studies taking measurements for individual patients. Therefore, studies reporting per-cycle characteristics were excluded from all analyses in which there was significant or borderline significant heterogeneity.

A total of six studies were included in the final meta-analysis with a total study population of 782 (exposed n = 293, unexposed n = 489). One of the included studies reported 80 cycles in patients with endometriomas (n = 50) and 283 cycles in tubal infertility controls (patient numbers were not reported for the controls) (Suzuki et al., 2005). The study population consisted of couples affected by ovarian endometrioma or with a history of ovarian endometrioma in the female partner; all were undergoing IVF–embryo transfer. Four of the studies examined a group of patients with ovarian endometriomas who had undergone laparoscopic cystectomy (Table 1). A total of three studies had patients with ovarian endometrioma, which were aspirated either at the beginning of ovarian stimulation or at the time of oocyte retrieval (Table 1). One of the studies conducting endometrioma aspiration at the time of oocyte retrieval utilized this as a diagnostic test (Yanushpolsky et al., 1998). Endometriomas were distinguished from other ovarian cysts by measuring CA-125 concentrations in the aspirated fluid.

A second study examined three groups, with one of the groups consisting of patients with ovarian endometriomas, which were aspirated at the beginning of ovarian stimulation. The other two groups consisted of patients with endometriosis but without endometriomas and the control group with tubal factor infertility (Suzuki et al., 2005). The majority of studies included patients with tubal infertility as the unexposed cohort. However, one study recruited all women with no complex cysts to serve as the unexposed cohort. Patients underwent IVF–embryo transfer in four of the studies and ICSI in two studies. Pituitary desensitization was performed using the long protocol with gonadotrophin-releasing hormone (GnRH) agonists. Ovarian stimulation was performed with recombinant FSH alone in two of the studies (Marconi et al., 2002; Pabuccu et al., 2004) and a combination of human menopausal gonadotrophin and Metodrin or clomiphene in some of the studies (Yanushpolsky et al., 1998; Canis et al., 2001; Donnez et al., 2001).
The odds of clinical pregnancy were not different for patients with ovarian endometrioma when compared with the controls; the overall odds ratio was 1.07 from three studies [95% CI: (0.63, 1.81), \( P = 0.79 \)] (Figure 3). There was no heterogeneity found between studies examining this outcome (\( P = 0.65 \)). The odds of overall or chemical pregnancy, as measured by HCG assay, were similar between the exposed and unexposed, with an overall estimated odds ratio of 1.17 [95% CI: (0.85, 1.60), \( P = 0.34 \)] (Figure 4). The results of this meta-analysis are in agreement with the results of many of the studies reporting that patients with endometriomas have fewer oocytes harvested (Figure 5), but their chances of pregnancy are comparable (Garcia-Velasco and Arici, 1999; Tinkanen and Kujansuu, 2000; Loo et al., 2005). The possible explanations of reduced number of oocytes can be the deleterious effects of endometriosis on folliculogenesis, impaired follicular environment, reduced rates of follicular growth resulting in poor quality oocytes. Losses of ovarian volume and follicles have been reported with the laparoscopic ovarian cystectomy procedure (Exacoustos et al., 2004). The reduction in ovarian response following surgery has resulted in many authors advocating conservative management for patients with infertility.

Spontaneous abortion was measured in only one study. The odds of spontaneous abortion in those with ovarian endometrioma were significantly increased in comparison with those without; the odds ratio was 5.53 [95% CI: (1.13, 25.11), \( P = 0.03 \)] (Yanushpolsky et al., 1998). The average fertilization rate was considered to be a continuous variable by the content experts rather than a dichotomous one, because the fertilization rate was calculated as the average of the percentage of oocytes fertilized for each individual stimulation cycle per person. This also was not significantly different for those with and without endometrioma. Implantation rate was not evaluated by meta-analysis because it was examined in only one study.

Initially, it was believed that five studies examined the number of oocytes retrieved from stimulation. However, significant heterogeneity was found when the two studies examining per-cycle characteristics were not excluded (chi-squared = 37.69, \( P < 0.00001 \); Donnez et al., 2004; Suzuki et al., 2005). Once excluded, however, the overall effect in the remaining three studies showed that there was, on average, 1.69 fewer oocytes retrieved in those with ovarian endometrioma than in those without ovarian endometrioma [95% CI: (−3.16, −0.23), \( P = 0.02 \)] (Figure 5).

Several studies measured peak oestradiol concentrations, while others measured oestradiol on the day of HCG administration. These two measures were taken separately because statistically significant heterogeneity was evident when they were combined. Peak oestradiol, as estimated from the studies by Donnez et al. and Marconi et al., was not significantly different between the patients with ovarian endometrioma and the controls (Donnez et al., 2001; Marconi et al., 2002). There was no evidence of heterogeneity between these two studies. On the day of HCG administration, oestradiol concentrations were not significantly different in those with endometrioma in comparison with the controls.

Two studies compared the number of mature follicles in these two groups of cases and controls. The definition of a mature follicle differed amongst the studies. Some specified a minimum diameter of 14 mm while others specified 17 mm. Still others specified an intermediate value, or nothing at all. The study by Donnez et al. was excluded due to per-cycle reporting that was thought to be the cause of significant heterogeneity (Donnez et al., 2001). Overall, it was found that the number of follicles in the patients with endometrioma was significantly fewer than the number in the controls (\( P = 0.002 \)) (Figure 6). Patients with ovarian endometrioma had, on average, 0.88 fewer follicles than the controls after stimulation [95% CI: (−1.43, −0.32)] (Figure 6).

The average number of ampoules of gonadotrophins used for each cycle of IVF was calculated in four studies. In two studies, only FSH was used. There was no significant difference between the numbers of ampoules of FSH used in those with endometrioma compared with controls. The same held true for studies that used FSH and HMG. The amount of ampoules measured in these two types of studies, however, could not be combined, as there was significant heterogeneity.
Table 1. Description of each study included in the meta-analysis and the outcomes measured.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
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<td>Marconi et al., 2002</td>
<td>Endometrioma cystectomy</td>
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<td>Tubal infertility</td>
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<td>Yanushpolsky et al., 1998</td>
<td>Aspirated endometrioma</td>
<td>No complex cysts</td>
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Outcomes 1-9: 1 = Clinical pregnancy; 2 = Chemical/overall pregnancy; 3 = Implantation; 4 = Spontaneous abortion; 5 = Fertilization proportion; 6 = Number of oocytes retrieved; 7 = Peak oestradiol or oestradiol on day of human chorionic gonadotrophin; 8 = FSH/human menopausal gonadotrophin or total FSH; 9 = Number of (mature) follicles.

*Contains multiple observations per person as calculations were done by cycle for multiple cycles.

Figure 3. Meta-analysis plot showing odds ratio (OR) for clinical pregnancy of 1.07 from three studies [95% CI: (0.63, 1.81), \( P = 0.79 \)]. PR = pregnancy rate; ET = embryo transfer.

Figure 4. Meta-analysis plot showing overall pregnancy rate (PR) with an estimated odds ratio (OR) of 1.17 [95% CI: (0.85, 1.60), \( P = 0.34 \)].
The overall goal of a systematic review or meta-analysis is to combine results of previous studies to arrive at summary conclusions about a body of research. The meta-analysis was conducted according to the guidelines of the Potsdam consultation (Cook et al., 1995). The reviewers were blinded during the evaluation process and a scoring system was developed to quantify bias that was used to evaluate the literature on infertile women with endometrioma undergoing assisted reproduction. A critical discussion of the methodology has been provided to clarify the process of blinding and scoring of studies that was applied in this meta-analysis.

Reviewers may be biased because of the knowledge of the institution or researchers involved and the conclusions of the paper (Sacks et al., 1987). Bias on the part of reviewers is defined as inclusion bias (Egger and Smith, 1998). Inclusion bias can be minimized by blinding the reviewers and the documents during the scoring process (Berlin, 1997). However, in the present meta-analysis, an extensive effort was made to blind all the studies for evaluation. In addition, other strategies were employed to evaluate selection bias.

For the evaluation of the studies, a scoring system was developed rather than a checklist, as quantitative scoring systems that are transparent and parsimonious have been recommended (Cook et al., 1995). Application of a checklist to the studies to assess fulfillment of inclusion criteria may not exclude all types of bias because of unequal weight. Some items on the checklist may inappropriately value individual studies over the others. Studies were scored in the meta-analysis with a scoring plan, which was intended to adjust for different types of bias. In some instances, specialty groups have developed and utilized standardized protocols for scoring literature in their fields (Stroup et al., 2000; Dennis et al., 2003). A scoring system was developed to evaluate for different types of bias. The authors discussed and adopted a set of specific questions and point scores to quantify potential bias in the literature under consideration. The system developed to exclude bias was then applied to the blinded manuscripts prior to their inclusion into the meta-analysis. Two reviewers who were experts in content area and methodology scored each study independently, and the final decision on inclusion or exclusion was determined during a discussion between the two reviewers. Some of the studies had to be revisited by both the reviewers and the decision for inclusion of a study was based on the study being biased towards null.

**Figure 5.** Meta-analysis plot showing the effects of endometrioma on number of oocytes retrieved. When the two studies examining per cycle characteristics were excluded (Donnez et al., 2004; Suzuki et al., 2005), 1.69 fewer oocytes were retrieved in those with ovarian endometrioma than in those without ovarian endometrioma [95% CI: (−3.16, −0.23), P = 0.02]. ET = embryo transfer; PT = patient; WMD = weighted mean distribution.

**Figure 6.** Effect of endometrioma on number of follicles – 0.88 fewer follicles than the controls after stimulation [95% CI: (−1.43, −0.32)]. ET = embryo transfer; PT = patient; WMD = weighted mean distribution.

**Discussion**

The overall goal of a systematic review or meta-analysis is to combine results of previous studies to arrive at summary conclusions about a body of research. The meta-analysis was conducted according to the guidelines of the Potsdam consultation (Cook et al., 1995). The reviewers were blinded during the evaluation process and a scoring system was developed to quantify bias that was used to evaluate the literature on infertile women with endometrioma undergoing assisted reproduction. A critical discussion of the methodology has been provided to clarify the process of blinding and scoring of studies that was applied in this meta-analysis.

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This approach has been considered and accepted in other fields for the development of other meta-analyses (Juni et al., 1999; Dennis et al., 2003).

In the present meta-analysis, observational studies were included, as there are no randomized trials in the literature on the subject. Most published data are derived from uncontrolled, observational studies, clinic based studies with small study populations. The study populations are small because of the relative low incidence of endometriosis.

Randomized controlled trials provide the highest level of evidence, but they are cumbersome and expensive and subject to follow-up bias. Prospective randomized controlled trials (PRT) may be borderline unethical in the situation of randomizing patients with endometriomas to IVF. In addition, some PRT may be particularly unfair to infertile couples with ovarian endometrioma who are offered treatment in one arm of the trial, i.e. IVF, when alternative treatment is no intervention. In these instances, treatment delays may expose these couples to the negative influence of advancing age on pregnancy outcome. The Potsdam Consultation stated that it is valid to include observational studies for meta-analysis but only after a thorough evaluation and appraisal process (Cook et al., 1995). However randomized controlled trials are not feasible in many situations, because of the low incidence of endometriosis and, combining data from several smaller clinic based observational studies may be an effective way to combine and summarize clinical data (Stroup et al., 2000). All the observational studies were scrutinized with an elaborate scoring system for bias.

Ovarian endometriomas constitute definite disease, thus selection bias will not result because of lack of under ascertainment of cases. The likelihood of bias amongst controls was limited, as patients with documented fertility i.e. women undergoing tubal ligation were the control group. It has been recommended that controls with documented fertility lend validity to epidemiological studies on endometriosis (Holt and Weiss, 2000).

Effects of ovarian endometrioma on fertility

Many distinct and plausible causes have been reported as the reason for subfertility associated with endometriosis. These factors include tubal distortion, impaired folliculogenesis, fertilization/implantation defects, toxic/inflammatory factors in the peritoneal cavity and poor embryo quality. Compromised follicular development has been reported in patients with endometriosis (Pellicer et al., 1998) as well as decreased fertilization rates as a result of a reduction in oocyte quality. Impaired ovarian function, pituitary ovarian dysfunction, granulosa cell impairment and uterine function impact on oocyte quality and embryo quality, resulting in ovariolytic, fertilization and implantation disorders (Wardle et al., 1985; Yovich et al., 1985; Dmowski et al., 1986; Garrido et al., 2002; Hughes et al., 2004). It has also been reported that endometriomas may affect the hormonal response to ovarian stimulation regimens with a trend towards fewer oocytes retrieved and a significant reduction in the number of pre-ovulatory follicles (Diugi et al., 1989; Nakahara et al., 1998; Yanushpolsky et al., 1998; Al-Azemi et al., 2000) and the present meta-analysis validated these reports.

Many other studies have reported that ovarian cystectomy does not negatively affect ovarian response and reserve (Canis et al., 2001; Marconi et al., 2002; Wong et al., 2004).

Additional research has found that the proportion of apoptotic bodies in the membrana granulosa cells and the cumulus cells from patients with chocolate cysts is significantly higher than that in patients without chocolate cysts. Nakahara et al. also reported a significant negative correlation between the proportion of apoptotic bodies and oocyte quality. Patients with chocolate cysts had significantly reduced numbers of follicles, retrieved oocytes and mature oocytes ($P < 0.05$) (Nakahara et al., 1998). The ovarian endometrioma per se or surgical removal of endometrioma can cause reduced ovarian reserve and responsiveness to ovarian stimulation. Conservative management of ovarian endometrioma has been recommended by some of the authors to preserve ovarian reserve.

Fertility after laparoscopic surgery for ovarian endometrioma

Patients with infertility caused by ovarian endometriomas may benefit from surgery. However surgery may compromise the ovarian reserve because of loss of normal ovarian tissue and follicles and ovarian volume following surgery. The objective of surgery is removal of the ovarian endometriomas to enhance fertility outcomes. There are multiple treatment options available for managing ovarian endometrioma such as expectant management, ultrasound-guided aspiration, drainage of the endometriotic cyst and vaporization of the cyst wall with laser, ovarian fenestration with bipolar electrocoagulation and laparoscopic cystectomy (Canis et al., 2001; Yoshida et al., 2002; Benassi et al., 2003). However, there is a lack of consensus regarding the ideal surgical technique and also on the benefits and drawbacks of surgery. Some studies have found that surgery adversely affects fertility whereas other studies have reported no effect on fertility outcomes. Meticulous surgical techniques should be utilized to minimize damage to healthy ovarian tissue and avoid compromising the blood supply.

In addition to the specific surgical technique, multiple other factors are related to reproductive outcomes such as the age of the patient, size of the endometriotic cyst, and the amount of normal ovarian tissue conserved during surgery. The mean follicular response in post-cystectomy ovaries was significantly lower than that of normal ovaries in unstimulated cycles ($P = 0.046$) and also with clomiphene-stimulated cycles ($P = 0.011$) (Loh et al., 1999). The reduction in the responsiveness of post-cystectomy ovaries can be overcome with gonadotrophin stimulation. The size of the ovarian endometrioma prior to surgery was reported to have no impact on ovarian responsiveness.

In a prospective follow-up study, Wong and Simon divided patients into two groups: one with endometriomas at the time of IVF–embryo transfer and the other group with no endometrioma (Wong and Simon, 2004). A subgroup of patients with past or present ovarian endometriomas had lower pregnancy rates than a control group of patients with endometriosis only, but the difference did not reach statistical significance. Women with persistent or recurrent endometriomas also had lower pregnancy rates than women who had endometrioma removed.
by cystectomy, but again, the difference was not statistically significant. However, the study by Wong et al. (2004) contained a small number of patients in each of the subgroups, which might have led to the study being inadequately powered. Surgical removal of endometriomas was not reported to significantly improve pregnancy and implantation rates by other authors.

It has been suggested that surgery may diminish the ovarian reserve. In a follow-up study with age-matched tubal factor infertility controls, prior surgery for stage IV endometriosis did not improve IVF outcomes (Aboulghar et al., 2003). In addition, reduced responsiveness to ovarian stimulation after surgery (ovarian cystectomy) has been observed in many retrospective studies (Pagidas et al., 1996; Tinkanen and Kujansuu, 2000). Donnez et al. (2001) reported that endometrioma surgery with internal wall vaporization did not impair IVF outcomes. Large endometriomas (>3 cm, corresponding to a RFS score of 16) can be safely and effectively treated with laparoscopic surgery, increasing the likelihood of pregnancy in infertile patients over a relatively short post-operative period (Milingos et al., 2002). In a study on 64 infertile patients with large ovarian endometriomas, 53% of the patients became pregnant in the first 2 years after surgery. This study concluded that laparoscopic surgery could safely and effectively treat severe endometriosis and large endometriomas. A randomized controlled trial by Beretta et al. reported better fertility outcomes in patients with laparoscopic ovarian cystectomy than with aspiration and bipolar electrocoagulation (Beretta et al., 1998). The laparoscopic approach has been proposed to be a valuable procedure for ovarian endometriomas greater than 3 cm in diameter. In a randomized controlled trial, Muzii et al. reported that the technique of the excision of endometrioma may not significantly affect the quality of resected ovarian tissue or the complication rate (Muzii et al., 2005). In this randomized controlled trial the patients were randomised to either the stripping technique or the bipolar coagulation and cutting technique. The results with both the techniques were comparable and are safe options for treatment of endometriomas. These findings were in contrast to those of Beretta et al. (1998).

There are strikingly different views amongst authors regarding the role of surgery prior to IVF. While many studies have investigated whether surgery improves IVF outcomes in patients with moderate to severe endometriosis or in patients with ovarian endometrioma, there is no consensus. The lack of consensus can be due to multiple confounding factors in these studies, such as the age of patient, unilateral or bilateral disease, associated disease, and the difference in protocols of different IVF centres.

Effects of ovarian endometrioma on IVF

Assisted reproduction is widely used to manage infertility associated with endometriosis. IVF may enhance the low fecundity associated with advanced endometriosis. Various studies have evaluated the success of IVF in patients with endometrioma, and some studies have reported beneficial effects (Tinkanen and Kujansuu, 2000; Suganuma et al., 2002) while others have reported poor outcomes (Dlugi et al., 1989; Yanushpolsky et al., 1998; Geber et al., 2002). There is a lack of consensus in the reported literature on outcomes of assisted reproduction in patients with ovarian endometriomas. There are no studies that have evaluated the effects of endometriomas per se on IVF outcomes. All of the studies in the literature have investigated IVF outcomes in patients with resected endometriomas or aspirated endometriomas. Many confounding factors can affect pregnancy outcomes such as the size of the endometrioma, previous medical therapy, prior surgical therapy, the type of surgical procedure, interval between therapy and IVF–embryo transfer, and the experience of the surgeon. In addition, the techniques used for IVF–embryo transfer and for the treatment of endometriomas have changed, making it difficult to compare studies over time. For example, in earlier studies, laparoscopic aspiration was used to retrieve oocytes whereas later studies used ultrasound guidance for oocyte retrieval.

In a meta-analysis of 22 studies, Barnhart et al. reported that the odds of pregnancy in patients with endometriosis-associated infertility undergoing IVF–embryo transfer was 50% compared with women with infertility related to other causes (Barnhart et al., 2002). Cumulative live birth rates (CLBR) of 63.2% have been reported in patients with endometriosis treated with IVF and ICSI in a cohort study (Witsenburg et al., 2005). The CLBR of endometriosis patients did not differ from those of patients undergoing IVF/ICSI for other indications. CLBR are a better indicator of assisted reproduction outcomes than the cumulative pregnancy rates estimated by life table analysis, which frequently are an overestimation. The findings of the cohort study by Witsenburg et al. (2005) are in contrast to those from the meta-analysis by Barnhart et al. (2002). Based on the Centers for Disease Control (CDC) data, similar pregnancy and live birth rates have been reported when comparing couples with diagnosis of tubal factor infertility, ovulatory dysfunction, endometriosis, male factor infertility or unexplained infertility (Van Voorhis, 2006). The CDC data and recent studies do not support the results of the earlier meta-analysis by Barnhart et al. that the odds of pregnancy are significantly reduced in patients with endometriosis undergoing IVF. The meta-analysis confirms that the reduction in follicle numbers and oocytes aspirated in patients with ovarian endometriomas does not impair pregnancy outcomes with IVF-embryo transfer (Figures 3–6). The results of the present meta-analysis are also consistent with the results of a recent prospective randomized trial reported by Demirol et al., 2005. In this trial patients were randomized to either ICSI directly or ovarian surgery followed by ICSI. Patients in the second group had longer stimulation and lower oocyte numbers but the fertilization, implantation and pregnancy rates did not differ between the two groups (Demirol, 2005).

There is a lack of consensus amongst studies as to whether ovarian response is adequate or suboptimal in patients with ovarian endometriosis. Endometriosis is associated with ovulatory disorder, which has been reported to cause a 2-fold reduction in fertilization rates (Wardle et al., 1985). This significant reduction in fertilization rates may be due in part to defective folliculogenesis and a resultant impairment in oocyte quality. Some studies reported impaired ovarian responsiveness to ovarian stimulation in patients with ovarian endometriosis (Loh et al., 1999; Al-Azemi et al., 2000; Ho et al., 2002) and others reporting a lack of adverse effect (Canis et al., 2001; Marconi et al., 2002). Ovarian endometriomas have been reported to have adverse effects on oocyte and embryo quality and implantation rates (Simon et al., 1994; Ariët et al., 1996; Bergendal et al., 1998; Yanushpolsky et al., 1998; Azem et al., 1999). In a recent large study on 127 patients with endometriomas
who underwent laparoscopic ovarian cystectomy followed by IVF–embryo transfer, a significantly smaller number of oocytes were harvested per retrieval compared with the control group of 95 patients with tubal occlusion (Loo et al., 2005). The overall clinical pregnancy rates were not different, though the fertilization and the implantation rates were significantly lower in the operated endometrioma group, reflecting that the chances of pregnancy are not reduced in the exposed group.

In principle, IVF–embryo transfer circumvents the adverse effects that the peritoneal environment in patients with endometriosis can have on the gametes and on sperm–oocyte interaction and embryotoxic effects. Endometriosis has also been proposed to cause changes in sperm and endosalpingeal interactions. This is consistent with the evidence that extensive endometriosis plays a pivotal role in causing mechanical difficulties in oocyte aspiration and retrieval (Chilllik et al., 1985). Surgically removing large ovarian endometriomas may greatly facilitate greater access to the follicles.

Down-regulation with GnRH agonists for ovulation induction/assisted reproduction may be beneficial in patients with endometriomas, the mechanism of action is proposed as reduced cytokine concentrations. Gonadotrophin agonist treatment for causing pituitary desensitization may lead to reduced interleukin-6 production by the endometriotic cells (Iwabe et al., 2003). It was proposed that serum interleukin-6 could help monitor the ovarian endometriomas. Expression of secretory leukocyte protease inhibitor in tissue and peritoneal fluid of patients with endometriomas was reduced by GnRH agonist treatment (Suzumori et al., 2001). GnRH agonists may result in the partial involution of endometriomas, wherein the actions of GnRH analogues are mediated through modulating the concentrations of cytokines such as interleukin-6 or secretory leukocyte protease inhibitor.

Ultrasound-guided aspiration of ovarian endometrioma

Ultrasound-guided aspiration is an option for managing large ovarian endometriomas that are unlikely to respond to medical treatment (Mittal et al., 1999). The aspiration of the endometriomas was demonstrated to improve the ovarian response with an increase in number of oocytes available for retrieval and an increased number of embryos available for transfer (Dicker et al., 1991). Ultrasound-guided aspiration of the endometrioma either at the beginning of ovarian stimulation or at the time of oocyte retrieval was conducted in three of the studies included in the present meta-analysis (Yanuszpolsky et al., 1998; Pabuccu et al., 2004; Suzuki et al., 2005) (Table 1). In a well-designed study, where there were no differences amongst cases and controls in potential confounders such as age, body mass index and ovarian stimulation protocols, Suzuki et al. have reported depressive effects of endometriomas on oocyte development (Suzuki et al., 2005). Ultrasound-guided aspiration is a less invasive option; however, the high rates of recurrence following this procedure have led to restricted use. Acute abdominal pain and infectious complications have been reported following aspiration of endometriomas. The disadvantage is that sonographically guided therapeutic aspiration is associated with a high recurrence rate of 66.6% (Troiano and Taylor, 1998). Hormonal suppression therapy following aspiration may reduce the recurrence rates.

Conclusions

Ovarian endometriomas are a common and specific manifestation of the disease endometriosis. The meta-analysis was conducted to assess the impact of ovarian endometrioma on assisted reproduction outcomes. The results of the meta-analysis utilizing the random effects model indicate that ovarian endometrioma has adverse effects on follicle number and oocytes retrieved but not on embryo quality or pregnancy outcomes. The meta-analysis also indicates that patients with ovarian endometrioma benefit from IVF and ICSI due to pituitary down-regulation and women undergoing laparoscopic cystectomy can be counselled that surgery for ovarian endometrioma may result in a decrease in the number of retrieved oocytes, but that overall fertility outcomes are not affected. Future randomized controlled trials would be ideal wherein patients with endometriomas undergo assisted reproduction versus no assisted reproduction to assess whether the intervention improves the fertility outcomes. Prospective randomized controlled trials need to be designed for patients with ovarian endometrioma undergoing assisted reproduction cycles, to assess whether surgical treatment versus no surgical treatment improves pregnancy outcomes.

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