OBJECTIVE: To investigate the association of endometriosis on assisted reproductive technology (ART) outcomes and to review if surgical treatment of endometriosis before ART affects the outcomes.

DATA SOURCES: We searched studies published between 1980 and 2014 on endometriosis and ART outcome. We searched MEDLINE, PubMed, ClinicalTrials.gov, and Cochrane databases and performed a manual search.

METHODS OF STUDY SELECTION: A total of 1,346 articles were identified, and 36 studies were eligible to be included for data synthesis. We included published cohort studies and randomized controlled trials.

TABULATION, INTEGRATION, AND RESULTS: Compared with women without endometriosis, women with endometriosis undertaking in vitro fertilization and intracytoplasmic sperm injection have a similar live birth rate per woman (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.84–1.06, 13 studies, 12,682 patients, I²=35%), a lower clinical pregnancy rate per woman (OR 0.78, 95% CI 0.65–0.94, 24 studies, 20,757 patients, I²=66%), a lower mean number of oocyte retrieved per cycle (mean difference –1.98, 95% CI –2.87 to –1.09, 17 studies, 17,593 cycles, I²=97%), and a similar miscarriage rate per woman (OR 1.26, 95% CI (0.92–1.70, nine studies, 1,259 patients, I²=0%). Women with more severe disease (American Society for Reproductive Medicine III–IV) have a lower live birth rate, clinical pregnancy rate, and mean number of oocytes retrieved when compared with women with no endometriosis.

CONCLUSION: Women with and without endometriosis have comparable ART outcomes in terms of live births, whereas those with severe endometriosis have inferior outcomes. There is insufficient evidence to recommend surgery routinely before undergoing ART.

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Endometriosis is associated with subfertility, and up to 50% of women with endometriosis have difficulty conceiving naturally. The cause and effect of endometriosis on subfertility remains controversial although it is known that without intervention, women with more severe disease are less likely to conceive. There are conflicting results regarding the reproductive outcomes associated with subfertile women with varying severity of endometriosis undergoing assisted reproductive technology (ART). Many clinicians will recommend surgical treatment to improve subfertility in women with mild and moderate endometriosis albeit that this recommendation is based on moderate evidence from two randomized controlled trials (n=382). One further randomized controlled trial not included in the meta-analysis by Duffy et al reported conflicting results.

There is currently no consensus as to whether surgical treatment should be offered to women undergoing ART to improve their reproductive outcome. A meta-analysis performed more than 10 years ago indicated that the pregnancy rate is halved in women with endometriosis undergoing ART treatment. A more recent meta-analysis reported on the detrimental effect of endometriosis on...
implantation and clinical pregnancy rates but did not examine the effect of surgery on the reproductive outcome of ART in women with endometriosis. Guidelines from national authorities appear conflicting and based on scarce evidence.

Surgical intervention is generally thought to be beneficial although the drawbacks of surgical complications can be significant. Hence, surgical treatment of endometriosis before fertility treatment may improve the outcome although it may potentially cause harm.

The objectives of this systematic review and meta-analysis are to investigate the association of endometriosis on the reproductive outcomes of women undergoing ART and to evaluate the association of surgery before the ART treatment on reproductive outcomes.

**SOURCES**

Published studies (nonrandomized and randomized studies) were eligible for inclusion. Studies were only included once if they had overlapping data. For the purpose of this review, we excluded publications that only included patients with endometrioma(s) during the course of treatment.

We included studies comparing the ART (this is defined as in vitro fertilization with or without intra-cytoplasmic sperm injection) outcomes of women with endometriosis with women with no endometriosis. Studies were excluded if the participants received any known nonsurgical treatment (medical management, alternative treatment), were involved with donor or recipient oocyte treatment, or if the study did not have any available nonendometriosis control group. The revised American Fertility Society staging of the endometriosis was used to grade the disease severity. Studies that specified “surgical treatment” on women with endometriosis were categorized as “surgical treatment specified” and others were categorized as “surgical treatment not specified.”

Primary outcome measure is live birth rate per woman defined as the number of deliveries that resulted in at least one liveborn neonate expressed per 100 patients.

Secondary outcome measures are 1) clinical pregnancy rate per woman (defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy) and was expressed per 100 patients; 2) miscarriage rate defined as any loss of pregnancy before 24 weeks of gestation; and 3) mean number of oocytes retrieved per cycle.

**STUDY SELECTION**

We searched studies published between 1980 and 2014 on endometriosis and ART outcome without language restriction. Electronic databases, trial registers, and web sites including MEDLINE, EMBASE, Cochrane Central register of Controlled Trials, ClinicalTrial.gov, and Web of Science were searched based on keywords, medical subject heading terminology, or both. The reference lists of all known primary and review articles were examined to identify cited articles and abstracts not captured by electronic search.

Two review authors (M.H., Y.C.) independently examined these full-text articles for compliance with the inclusion criteria, select studies eligible for inclusion in the review, and the methodologic quality of the studies and extracted relevant data. The quality of individual studies was assessed in accordance to the Meta-analysis Of Observational Studies in Epidemiology criteria and the Newcastle Ottawa Scale. Study investigators were contacted if clarification was needed for study eligibility. The process is documented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart (Fig. 1).

Where data are available, we analyzed the association of 1) the different stages of endometriosis (American Society for Reproductive Medicine I–II and American Society for Reproductive Medicine III–IV) and 2) surgical treatment on the outcome measures specified.

Methodologic and clinical heterogeneity among included studies was assessed by measuring the $I^2$ value; heterogeneity was also explored by means of sensitivity analysis. Dichotomous data (eg, clinical pregnancy rate) and continuous data were analyzed using Mantel-Hansel odds ratio and the mean difference between treatments groups, respectively.

**RESULTS**

From our search strategy (Fig. 1), 36 retrospective observational studies (n=29,454) were included (Table 1). The majority of the included studies had a quality score of more than 7 and eight studies scored the highest possible score of 9 (Table 2). A total of 4,852 women had endometriosis. The majority of control groups (23/36) had tubal factor. Most of the included studies stated the stage of the disease (n=22). Almost all of the included studies reported clinical pregnancy rate (33/36) as the primary outcome, with 13 (13/36) reporting a live birth rate. Twelve studies from this meta-analysis included participants who received surgical treatment for endometriosis, whereas the others did not specify. None of
these studies provided the duration from the surgical procedure to the ART. Eight studies included patients with endometrioma, of which three studies presented data pertaining to women with endometriomas separately that we were able to use. All the studies except one specified that they have excluded participants who have had any medical treatment before the ART.\textsuperscript{46} The study characteristics are depicted in Table 1.

The overall live birth rate was not statistically different between women with endometriosis and women with no endometriosis (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.84–1.06, 13 studies, 12,682 patients, $I^2=35\%$) (Appendix 1, available online at http://links.lww.com/AOG/A581). Compared with women with no endometriosis, women with endometriosis had a lower clinical pregnancy rate (OR 0.78, 95% CI 0.65–0.94, 24 studies, 20,757 patients, $I^2=66\%$) (Appendix 1, http://links.lww.com/AOG/A581), a lower mean number of oocytes retrieved per cycle (mean difference $-1.98$, 95% CI $-2.87$ to $-1.09$, 17 studies, 17,593 cycles, $I^2=97\%$) (Appendix 1, http://links.lww.com/AOG/A581) and no difference in the miscarriage rate (OR 1.26, 95% CI 0.92–1.70, nine studies, 1,259 patients, $I^2=0\%$) (Appendix 1, http://links.lww.com/AOG/A581).

We performed a subgroup analysis in accordance to American Society of Reproductive Medicine stages (I–II and III–IV). In women with less severe disease (American Society of Reproductive Medicine I–II), all of the outcomes were comparable to women with no endometriosis; this included live birth rate (OR 0.96, 95% CI 0.82–1.12, eight studies, 4,157 patients, $I^2=6\%$) (Appendix 2, available online at http://links.lww.com/AOG/A581).
online at http://links.lww.com/AOG/A582, clinical pregnancy rate (OR 0.84, 95% CI 0.69–1.03, 15 studies, 9,692 patients, $I^2=37\%$) (Appendix 2, http://links.lww.com/AOG/A582), and mean number of oocytes retrieved per cycle (mean difference $-0.58$, 95% CI $-1.16$ to $0.01$, 11 studies, $I^2=70\%$) (Appendix 2, http://links.lww.com/AOG/A582).

In contrast, women with more severe disease (American Society of Reproductive Medicine III–IV) had a lower live birth rate (OR 0.77, 95% CI 0.64–0.92, eight studies) [Appendix 2, http://links.lww.com/AOG/A582], 3,849 patients, $I^2=0\%$, lower clinical pregnancy rate (OR 0.60, 95% CI 0.44–0.81, 15 studies, 9,471 patients, $I^2=71\%$) (Appendix 2, http://links.lww.com/AOG/A582), and lower mean number of oocytes retrieved per cycle (mean difference $-1.76$, 95% CI $-2.73$ to $0.79$, 14 cycles, 9,172 patients, $I^2=92\%$) (Appendix 2, http://links.lww.com/AOG/A582) when compared with women with no endometriosis.

The effect of surgery would have been best assessed between women with endometriosis who had received surgical treatment and those who had not received the treatment. However, there was only one study$^{70}$ published with this comparison. The authors concluded that in women with less severe endometriosis (American Society of Reproductive Medicine stages I–II), a higher live birth rate (OR 1.47, 95% CI 1.01–2.13, 661 women) were recorded in women who had surgical treatment compared with those who had not.

### Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Dates</th>
<th>Patient Type, Stage(s)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Mekaru et al, 2013$^{34}$</td>
<td>Japan</td>
<td>Retrospective cohort</td>
<td>2004–2008</td>
<td>Endometriosis, stage I–II</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>May et al, 2012$^{57}$</td>
<td>U.K.</td>
<td>Retrospective cohort</td>
<td>2004–2005</td>
<td>Endometriosis, all stages</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Kim et al, 2011$^{48}$</td>
<td>China</td>
<td>Retrospective cohort</td>
<td>NA</td>
<td>Endometriosis, stage III–IV</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>Falconer et al, 2009$^{50}$</td>
<td>Sweden</td>
<td>Prospective cohort</td>
<td>NA</td>
<td>Endometriosis, stage I–II</td>
<td>34</td>
</tr>
<tr>
<td>11</td>
<td>Kuroda et al, 2009$^{41}$</td>
<td>Japan</td>
<td>Retrospective case-control</td>
<td>2006–2008</td>
<td>Endometriosis, all stages</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>Al-Fadhli et al, 2007$^{47}$</td>
<td>Canada</td>
<td>Retrospective case-control</td>
<td>1999–2003</td>
<td>Endometriosis, all stages</td>
<td>87</td>
</tr>
<tr>
<td>14</td>
<td>Loo et al, 2005$^{53}$</td>
<td>Taiwan</td>
<td>Retrospective cohort</td>
<td>2000–2002</td>
<td>Endometriosis, all stages</td>
<td>85</td>
</tr>
<tr>
<td>15</td>
<td>Aboulghar et al, 2003$^{54}$</td>
<td>Egypt</td>
<td>Retrospective case-control</td>
<td>1999–2001</td>
<td>Endometriosis, stage IV</td>
<td>85</td>
</tr>
<tr>
<td>18</td>
<td>Meden-Vrtovc 2000$^{57}$</td>
<td>Slovenia</td>
<td>Retrospective cohort</td>
<td>1990–1999</td>
<td>Endometriosis, stage I–II</td>
<td>612</td>
</tr>
<tr>
<td>21</td>
<td>Pellicer et al, 1998$^{60}$</td>
<td>Spain</td>
<td>Case-control study</td>
<td>NA</td>
<td>Endometriosis, all stages</td>
<td>12</td>
</tr>
<tr>
<td>22</td>
<td>Huang et al, 1997$^{61}$</td>
<td>Taiwan</td>
<td>Retrospective cohort</td>
<td>1993 (January–December)</td>
<td>Endometriosis, stage I–II, III–IV</td>
<td>75 (C)</td>
</tr>
<tr>
<td>25</td>
<td>Tanbo et al, 1995$^{64}$</td>
<td>Norway</td>
<td>Retrospective analysis</td>
<td>1986–1994</td>
<td>Endometriosis, stage I (mild)</td>
<td>265</td>
</tr>
<tr>
<td>31</td>
<td>Inoue et al, 1992$^{70}$</td>
<td>Japan</td>
<td>Retrospective study</td>
<td>Up to December 1988</td>
<td>Endometriosis, stage I–II, III–IV</td>
<td>309</td>
</tr>
<tr>
<td>32</td>
<td>Mahmood et al, 1991$^{71}$</td>
<td>Scotland</td>
<td>Prospective study</td>
<td>NA</td>
<td>Endometriosis, all stages</td>
<td>20</td>
</tr>
<tr>
<td>33</td>
<td>Frydman et al, 1987$^{72}$</td>
<td>France</td>
<td>Retrospective cohort</td>
<td>1984–1986</td>
<td>Endometriosis, all stages</td>
<td>34 (C)</td>
</tr>
<tr>
<td>34</td>
<td>Matson et al, 1986$^{73}$</td>
<td>Australia</td>
<td>Retrospective cohort</td>
<td>NA</td>
<td>Endometriosis, stage I, II, III, IV</td>
<td>96</td>
</tr>
<tr>
<td>35</td>
<td>Wardle et al, 1985$^{74}$</td>
<td>U.K.</td>
<td>Retrospective cohort</td>
<td>NA</td>
<td>Endometriosis, all stages</td>
<td>47</td>
</tr>
<tr>
<td>36</td>
<td>Mahadevan et al, 1983$^{75}$</td>
<td>Australia</td>
<td>Retrospective cohort</td>
<td>1981–1982</td>
<td>Endometriosis, all stages</td>
<td>14 (C)</td>
</tr>
</tbody>
</table>
We evaluated the effect of surgery by analyzing studies that specified that their participants had surgical treatment before ART and those that did not specify surgical treatment separately. There was no difference in the live birth rate (OR 0.88, 95% CI 0.76–1.02, four studies, 3,492 patients, \( I^2 = 55\% \)) (Appendix 3, available online at http://links.lww.com/AOG/A583), a lower clinical pregnancy rate (OR 0.69, 95% CI 0.50–0.96, nine studies, 4,888 patients, \( I^2 = 79\% \)) (Appendix 3, available online at http://links.lww.com/AOG/A583), and mean number of oocytes retrieved per cycle (mean difference \(-2.37\), 95% CI \(-3.55\) to \(-1.20\), 11 studies, 3,909 cycles, \( I^2 = 97\% \)) (Appendix 3, available online at http://links.lww.com/AOG/A583) in studies in which participants had prior surgical treatment. In studies in which women had prior surgical treatment, while there was no difference in ART outcomes in those with American Society of Reproductive Medicine I–II live birth rate (OR 0.99, 95% CI 0.83–1.18, four studies, 2,796 patients, \( I^2 = 34\% \)) (Appendix 4, available online at http://links.lww.com/AOG/A584), clinical pregnancy rate (OR 0.87, 95% CI 0.61–1.23, five studies, 3,016 patients, \( I^2 = 54\% \)) (Appendix 4, available online at http://links.lww.com/AOG/A584), those with more severe disease (American Society of Reproductive Medicine III–IV) had a lower live birth rate (OR 0.78, 95% CI 0.65–0.95, three studies, 2,550 patients, \( I^2 = 43\% \)) (Appendix 5, available online at http://links.lww.com/AOG/A585), clinical pregnancy rate (OR 0.53, 95% CI 0.33–0.84, six studies, 3,470 patients, \( I^2 = 85\% \)) (Appendix 5,
and a lower mean number of oocytes retrieved per cycle
(mean difference $2.46$, $95\%$ CI $2.42$ to $1.51$,

**DISCUSSION**

This systematic review and meta-analysis shows that women with endometriosis undertaking ART have a similar live birth rate, a lower clinical pregnancy rate, and lower mean number of oocytes retrieved per cycle when compared with those without endometriosis. Although women with less severe disease (American Society of Reproductive Medicine I–II) have a similar reproductive outcomes compared with those with no endometriosis, women with more severe disease (American Society of Reproductive Medicine III–IV) had a $30\%$ lower live birth rate, $40\%$ lower clinical pregnancy rate, and lower mean number of oocytes retrieved when compared with women with no endometriosis.

With regard to the effect of surgery, one study showed some evidence of benefit for treating less severe endometriosis before ART (American Society of Reproductive Medicine I–II). Given that this is the only available study comparing groups of women who had surgical treatment with those who had no treatment, this result needs to be interpreted with caution. The nature of the study does not allow a high level of recommendation and does not imply laparoscopy.
should be performed in all asymptomatic patients before ART only to diagnose and treat less severe endometriosis to improve the result of the ART treatment.\textsuperscript{15} Our subgroup analysis, however, suggests that surgical treatment before ART in women with more severe endometriosis (American Society of Reproductive Medicine III–IV) is associated with a lower live birth rate, clinical pregnancy rate, and mean number of oocytes retrieved. However, there is insufficient evidence to recommend surgery routinely before ART.

The mechanisms accounting for a poorer reproductive outcome in women with endometriosis are largely unknown. The disease process, with a largely inflammatory component, can directly affect the oocyte quality, quantity, and the endometrial receptivity.\textsuperscript{71,72} Surgical removal of the disease just before ART, although beneficial for the reduction of symptoms\textsuperscript{73} and the reduction of the bulk of endometriotic disease, can damage ovarian tissue, diminish ovarian reserve, and induce adhesion formation and reformation.

Given the paucity of data currently available, the definitive evidence-based strategy for the management of moderate to severe endometriotic disease before ART is still unavailable.\textsuperscript{15} Surgical treatment of severe endometriosis is associated with significant surgical morbidity.\textsuperscript{74} Because women with more severe stages of endometriotic disease have a significantly lower mean egg yield per cycle, surgical intervention for them is to be contemplated only after careful consideration and appropriate counseling and discussion, especially in those who already may have limited ovarian reserve.\textsuperscript{17} Given that women with endometriosis have
the same live birth rate as those without endometriosis, and this is despite a lower mean oocyte yield per cycle, the question remains as to whether women with endometriosis may require more cycles of ART treatment to achieve a similar live birth rate per woman.

One of the drawbacks of this meta-analysis is the clinical heterogeneity in particular that relating to the variation in surgical skills, learning curve, techniques, and the lag time since the surgical intervention. Until the results of current ongoing randomized controlled trials are made, the assumption that the treatment efficacy of various surgical treatment modalities such as thermal compared with laser ablation or surgical techniques such as excision compared with ablation techniques are similar is a potential confounder of our meta-analysis. However, current available studies do not provide this level of details for analysis. Other clinical parameters, which can potentially contribute to the clinical heterogeneity of the data, included the lack of information on the patients’ ovarian reserve, variation in stimulation protocol, and the improvement in general of the ART success rate with time. To limit heterogeneity caused by the advancement in surgical equipment and assisted conception technology, we performed a sensitivity analysis to assess the outcomes on only studies published after 2000; the latter analysis did not alter our findings.

Our study was undertaken using extensive search strategies and stringent inclusion and exclusion criteria had enabled us to collate a comprehensive number of studies with a total number of participants of 29,454 women. The majority of studies were of moderate or high quality. Our study did not specifically address the effects of endometriomas or deep-infiltrating disease because these have been reviewed separately in previous review.

REFERENCES


