Comparisons Between Laparoscopy Only Versus In Vitro Fertilization in Combination With Laparoscopy for Increasing Probability of Pregnancy in Patients with Endometriosis Associated Infertility

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Recommended Citation
Comparisons Between Laparoscopy Only Versus In Vitro Fertilization in Combination With Laparoscopy for Increasing Probability of Pregnancy in Patients with Endometriosis Associated Infertility

Abstract

Background: Endometriosis is the presence of endometrial tissue in extra-uterine areas that can lead to pain and peritoneal adhesions, and may interfere with fertility. Endometriosis and endometrial cysts called endometriomata are common among infertile women (30-50%). For treatment and diagnosis of endometriosis and endometriomata, surgical laparoscopy has become the gold standard. Furthermore, in vitro fertilization (IVF) is another treatment option designed to produce pregnancy. The purpose of this paper was to assess whether surgery alone, in comparison to IVF in combination with surgery, can significantly increase the overall pregnancy rate in patients with endometriosis associated infertility.

Method: An exhaustive search of available medical literature was conducted using Medline through OVID, ISI Web of Science, and CINAHL databases. The following search terms used were endometriosis, infertility, laparoscopy, and in vitro fertilization. Inclusion and exclusion criteria were applied. Strength of evidence was evaluated using the GRADE tool.

Results: Three cohort studies, consisting of one prospective and two retrospective observational studies, were found regarding the use of IVF therapy in combination with surgery versus surgery alone for the treatment of endometriosis associated infertility.

Conclusion: Despite few randomized control trials performed on this topic, the lack of information on risks and costs of treatments, and the overall low GRADE outcome from these observational reports, the overall finding was that IVF therapy in addition to surgery increased the overall fecundity rate in patients with endometriosis associated infertility. More specifically, infertile patients with endometriosis would benefit from the surgical approach as the primary option. Those who do not become pregnant after surgery could pursue an IVF program. Though IVF could be considered a primary treatment option when there are multiple infertility factors or contraindication to surgery. Nevertheless, the combination of surgery and IVF offers the best chance of pregnancy for these patients.

Keywords: endometriosis, infertility, laparoscopy, in vitro fertilization

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Subject Categories
Medicine and Health Sciences

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Comparisons Between Laparoscopy Only Versus In Vitro Fertilization in Combination With Laparoscopy for Increasing Probability of Pregnancy in Patients with Endometriosis Associated Infertility

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR

For the Masters of Science Degree
August, 2012

Faculty Advisor: Dr. Mary Von
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Biography

[Information redacted for privacy]
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List of Abbreviations

ART.............................................................. Assisted Reproductive Technology
ASRM.......................................................... American Society of Reproductive Medicine
IVF................................................................. In Vitro Fertilization
r-AFS............................................................. revised-American Fertility Society
RCTs............................................................. Randomized Controlled Trials
Comparisons Between Laparoscopy Only Versus In Vitro Fertilization in Combination With Laparoscopy for Increasing Probability of Pregnancy in Patients with Endometriosis Associated Infertility

BACKGROUND

Endometriosis is the presence of endometrial tissue outside of the uterine cavity, most commonly surrounding the ovaries and fallopian tubes. Endometriomata are forms of endometriosis within the ovaries that arises out of deposits of endometrial cells derived from the uterus. John Sampson was the first to describe it as chocolate cysts in 1921. Their presence in extra-uterine areas can initiate immune and inflammatory responses that lead to pain and peritoneal adhesions, and may interfere with fertility. The exact mechanism of infertility associated with endometriosis is still controversial but likely depend on the stage of the disease. Endometriosis is surgical staged using the American Society of Reproductive Medicine (ASRM) staging system.1

An estimate of about 10% of women of childbearing age may be affected by endometriosis, and this percentage rises to above 40% among patients with symptoms of dysmenorrhea, dyspareunia and inter-menstrual bleeding.2-3 According to UpToDate, the average age range for women diagnosed with endometriosis is 20 to 45 years of age, with the highest incidence found in women between 40 and 44 years of age. Nevertheless, prevalence is difficult to determine because symptoms are diverse and nonspecific, and some women are asymptomatic.

Endometriosis impairs fecundity but it does not completely prevent pregnancy. The treatment of infertility in women with endometriosis involves a combination of expectant management (“wait and see”), medical interventions involving induction of
ovulation with hormones plus intrauterine insemination, surgical resection of endometriosis and endometriomata, and assisted reproduction technologies (ARTs) such as in vitro fertilization (IVF). A flow chart was recreated from *UpToDate* to illustrate an step-wise algorithm for management of endometriosis associated infertility that can generally be used, except in cases where there are multiple infertility factors such as male factors, decreased ovarian reserve or ovulation disorders, since these additional factors have negative effects on conservative therapy (Figure I).

Laparoscopy is considered the first line diagnostic option for treatment of endometriosis and endometriomata.\(^1\) It is accepted that surgery should be the primary therapeutic option because of its efficacy\(^4-10\) and also for its safety.\(^11\) Moderate and severe endometriosis may lead to anatomic distortion and interfere with fecundity. The aim of surgical interventions is to restore the normal anatomy of the ovaries and re-establish normal pelvic conditions. Surgical restoration of the tubo-ovarian anatomy can be essential to improving the rate of conception and thus can improve IVF outcomes.\(^12\)

The benefit of surgical intervention for endometriosis was suggested by some authors to reduce risks of caesarean section, preterm birth, ante-partum hemorrhage, placental complications, and pre-eclampsia.\(^13-14\) An additional advantage of surgical treatment is that this method can differentiate endometrial lesions from a neoplasm of the ovary. Endometriosis can increase the risk for certain types of cancer. There are studies that suggest that endometriosis is a risk factor for ovarian cancer.\(^15-16\) On the other hand, risks associated with surgical resection of endometriosis and endometriomata are serious complications, post-surgical infection, iatrogenic damage to adjacent pelvic organs, and resultant loss of follicles adjacent to the cyst wall leading to reduced ovarian reserve or
ovulation frequency. Consequently the overall effect is reduced response to hormonal stimulation during medical interventions as well as poorer success rates from IVF outcomes. Other factors against the surgical option are that it requires general anesthesia, and that it is a resource intensive step.

Another approach to treating infertile women with endometriosis is in vitro fertilization. The first pregnancy from an in vitro-fertilized embryo was reported more than three decades ago.¹⁷-¹⁸ Though IVF is the most resource-intensive step of infertility therapy, it is also the treatment associated with the highest per cycle pregnancy rate. Based on data from 1993, cost of IVF per live birth was in the range of 22000 to 43000 dollars.¹⁹ Although ART such as IVF is costly and involves much of patients’ time and effort, it now accounts for 1-3% of live births in the United States and Europe.²⁰ Success rates of IVF have increase and costs per live birth have decreased since 1993.²¹

Clinical decisions, in the management of infertility associated with endometriosis, are still controversial because few randomized controlled trials (RCTs) have been carried out to evaluate the real effectiveness of different treatments, such as laparoscopy and IVF. There are reasons that contribute to the lack of RCTs available on this issue such as ethical and social concerns on how to appropriately design such studies. Other than effectiveness of treatment, other factors such as time involved in seeking treatments, psychosocial implications especially in cases of miscarriages and ectopic pregnancies, financial costs of treatments, and treatment risks play a major role for patients in their determination of which treatment modality to pursue. These qualitative factors can determine which treatment routes patients might decide on so it would be worthwhile for researchers to further investigate the effect these factors have for patients seeking
treatments for endometriosis related infertility. This would be a patient relevant issue for future studies to look into.

Laparoscopy is the first line treatment option\(^1\) while IVF, though costly, has the highest per cycle pregnancy rate for infertile women with endometriosis\(^20\). The purpose of this paper is to perform a systematic review of the literature to observe the combined effect of IVF integrated with laparoscopic surgery versus laparoscopy alone on pregnancy rates in the treatment of endometriosis-associated infertility.

**METHODS**

An extensive literature search was performed using Medline through OVID, ISI Web of Science, and CINAHL. These databases were accessed through the Pacific University Library system. The following keywords were searched individually and in combination: “endometriosis”, “infertility”, “laparoscopy”, and “in vitro fertilization”. The search was limited to human subjects and to the English language. A total of 48 articles were identified in the original search. Relevant articles were selected and cross-referenced for additional materials. Duplicated and unrelated articles were eliminated. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, developed by the GRADE working group\(^22\) was used to measure the strength of recommendation (Table I).

**RESULTS**

**Pregnancy Rates**

A total 48 studies were screened, and only three remained after application of eligibility criteria. The first study reviewed was performed by Barri et al.\(^23\) This prospective observational cohort study compared reproductive outcomes between
laparoscopy treatment alone versus IVF treatments after laparoscopy in women with endometriosis associated infertility. The study included 825 patients with endometriosis associated infertility with mean age of 35.3 +/-3.1 years (age range between 20 and 40 years), mean infertility duration 3.2+/-2.3 years, and these patients were diagnosed stage III to IV cystic endometriosis with endometriomata. Of the 825 women, 483 had surgery as a primary option, and 262 subsequently became pregnant (54.2%). Among the patients who did not become pregnant, 144 underwent IVF cycles and 56 additional pregnancies were achieved (38.9%). Barri et al\textsuperscript{23} concluded that, infertile patients with endometriosis should undergo surgical treatment as the primary option. Those who do not become pregnant after surgery should be treated with IVF. The combination of surgery and IVF offers the best chance of pregnancy for patients.\textsuperscript{23}

The next study reviewed was a retrospective cohort study performed by Coccia et al.\textsuperscript{24} This observational study included 107 infertile women who underwent laparoscopic surgery for endometriosis. Among those patients, 40 women had spontaneous pregnancies after the surgery. Sixty-seven women who did not become pregnant after the surgery subsequently underwent IVF that resulted in 20 pregnancies. The mean age of the women in this study was 33 or 34 years and the age range was 29 to 38 years. The women had stage I to IV endometriosis, and had had endometriosis related infertility for at least one year. This study\textsuperscript{24} concluded that, pregnancy rate achieved after the integrated laparoscopy-IVF approach was significantly higher than the pregnancy rate after surgery alone (P <0.05).

The final study reviewed was Nakagawa et al\textsuperscript{25} which evaluated 33 infertile women with ovarian endometriomata who received laparoscopic removal of endometrial
cysts. Of the 33 women, 10 pursued IVF after laparoscopy (IVF subgroup). The remaining 23 women pursued conventional infertility treatment after the surgery (non-IVF subgroup). The mean age for the non-IVF subgroup and the IVF subgroup was 32.9 +/-3.6 and 35.2 +/-2.8, respectively and the duration of infertility was 5.2 +/-3.9 for both groups. The pregnancy rates in the group with laparoscopic removal of endometriomata (non-IVF subgroup) and in the group with IVF subsequent to surgery (IVF subgroup) were 60.9% and 50%, respectively. The Nakagawa et al study\textsuperscript{25} concluded that, the removal of ovarian endometrioma might improve the fecundity of infertile patients.\textsuperscript{25}

**Additional Study Information**

In the Barri et al\textsuperscript{23} study, 61.6% of patients less than 35 years old became pregnant during a mean time of 12.5 months (1-66 months) in the group where surgery was the primary option, while only 29.7% of patients aged 35 years or older became pregnant (P<0.05) within the same group, in a mean time of 6.6 months (1-14 months). Likewise, in the group with IVF as the primary option, patients aged less than 35 years had a pregnancy rate of 35.7% which was significantly higher than the 25% obtained in the patients aged 35 years or above (P<0.05).

Similarly, results according to the Coccia et al study\textsuperscript{24} showed pregnancy rate significantly reduced in women greater than 35 years old in comparison to those younger (23.2% versus 54.1%). Additionally, the cumulative pregnancy rate in the immediate post-surgery period was more favorable for conception. Greater fecundity was observed during the first 6 months after surgery in both IVF with surgery and surgery only groups. The fecundity at 6 months after laparoscopy (25%) was significantly higher (P<0.005) than in the later preceding intervals according to this Coccia et al study.\textsuperscript{24} Pregnancy rate
was significantly higher in stage I and II (70.2%) than in the more severe disease (45%).
In women with stage I and II endometriosis, fecundity rate remained high in the first year after surgery. In the more severe cases, fecundity in the first 6 months (23.1%) was significantly greater than the following 6 months (P<0.05).24

**DISCUSSION**

Based on the studies reviewed, the overall findings were that the combined approach of IVF in addition to surgery resulted in higher pregnancy rates than with surgery alone for treatment of endometriosis associated infertility. Two studies23-24 reviewed showed a significant improvement in pregnancy rates when laparoscopy was combined with IVF, while one smaller study25 showed no significant difference. The findings of these studies are summarized in Table II. Even though confidence interval was not provided in this study, the statistical significance of the P value was less than 5% therefore the results of the studies signified that these findings were likely due to the treatment effect not chance.

The strength of the Coccia et al study24 was that they had a very long follow-up period during which 31.2% of patients were observed for more than 5 years, with an average length of 6 years (range 1-11 years). This showed reliable data about the final pregnancy outcomes and live birth chances in infertile women with endometriosis after laparoscopic surgery. Additionally, Coccia et al24 depicted the cumulative pregnancy curve during the immediate post-operative period to be particularly favorable for conception. Considering that endometriosis is a progressive disease, this time-dependent diminution of fecundity may be related to a detrimental effect of the disease on fertility.24

The Nakagawa et al study25 conveyed that endometrial cysts greater than 3 cm in
diameter or the presence of endometriosis should be operatively treated prior to ART treatments in order to increase pregnancy chances. Furthermore, this study addressed the risk of surgical intervention on diminishing the ovarian reserve by damaging the ovarian cortex during dissection of the cyst wall. This risk was also addressed in the Barri et al study. This was an important complication to address because patients should be aware that there are iatrogenic outcomes that can reduce future fertility results. However, the issue of laparoscopy having a detrimental effect on the ovarian reserve and consequently yielding poorer ART outcome is currently controversial between several past studies.

There are limitations to the studies examined for this paper. The results of these observational cohort studies do not meet the level of rigor found in randomized control trials (RCTs). The power of the Coccia et al study and Nakagawa et al studies were limited by its retrospective analyses. Unfortunately, there are few RCTs to examine the relative benefit of surgery compared to ARTs in infertile patients with endometriosis. As addressed earlier, there are ethical, social and technical difficulties in designing RCTs involving randomization and allocation of treatments between study groups.

A possible weakness of the Nakagawa et al study was that their study groups differ from the other two studies examined. The laparoscopic surgery group was divided into IVF and non-IVF subgroups. The non-IVF subgroup had conventional infertility treatment in addition to surgery which makes it difficult to directly compare this study group to the surgery only groups of the other studies. The added conventional infertility therapy in the non-IVF subgroup is a confounder in this study that most likely obscured the direct effect of surgery alone on pregnancy rate. The study did not specify what kind of conventional infertility treatment patients had in the non-IVF subgroup. However, the
benefit of this study was that the results indicated that presence of endometriomata resulted in endometriosis associated infertility by altering the normal pelvic condition. As a result, surgery will improve fertility rates though to what extent, it is unknown.

Cost is a very important factor to address in how patients choose treatment modalities. The cost of therapy could create treatment discrepancy in patients with lower income or who lack medical insurance coverage. Patients as well as clinicians are limited in the treatment decisions that they can make due to this factor. It is important to note that the treatment that patients select might not be the optimal choice based on evidence based medicine. Similarly, psychosocial effects from failing to conceive during infertility treatments of surgery and/or IVF cycles would also serve as important factors for patients to consider in their disease management decisions. More research should focus on these issues to examine the implications of these factors on treatment decisions.

CONCLUSION

The main purpose of this systematic review was to evaluate whether the combined approach of IVF with surgery was better than surgery alone in promoting fecundity in patients with endometriosis associated infertility. The primary outcome examined in the three cohort studies was reproductive outcome. Secondary factors, affecting the primary outcome of pregnancy, that were looked at in these studies were age of patients, stage of endometriosis as determined by the ASRM, and time after surgery affecting the fecundity rate.

The overall findings from these studies found that the probability of conception in women with endometriosis associated infertility was much higher after an integrated laparoscopy and IVF approach than surgery alone (Table II). The overall
recommendations for clinical practice after analyzing these cohort studies are that infertile patients with endometriosis should seek operative treatment as the first line of therapy in order to give patients the best chance of conceiving naturally. Patients should be advised to start trying to conceive naturally soon after laparoscopic surgery. IVF is indicated as a second line of treatment. When pregnancy does not occur within 9-12 months, they should move to an IVF program. On the other hand, Barri et al\textsuperscript{23} proposed that IVF be considered a primary treatment option in cases where there are additional fertility factors or when there is some contraindication to surgery. Nevertheless, the combined approach of surgery and IVF may offer higher chances of pregnancy to infertile women with endometriosis.

The advantage of surgical intervention is prompt and accurate diagnosis of endometriosis and/or endometrioma with the added therapeutic benefit of restoring normal pelvic anatomy to help promote pregnancy outcomes in ART therapy. Prompt diagnosis via laparoscopy can also differentiate between endometrial lesions from neoplasm of the ovary since endometriosis is a risk factor for ovarian cancer,\textsuperscript{15-16} and can increase risk of certain neoplasm such as melanoma and thyroid cancer.\textsuperscript{16}

Assisted reproductive treatment should not be seen as competing with surgical treatment but as a complementary therapeutic strategy for treatment of endometriosis associated infertility. In treating infertile patients with endometriosis, clinicians should take into consideration stage of disease, age of patient, duration of infertility, timing post surgery to pursue other options such as IVF, costs, risks and benefits prior to making treatment decisions.
References


Table I. Characteristics and Quality Assessment (GRADE) ofReviewed Studies

<table>
<thead>
<tr>
<th>Design</th>
<th>Methodology</th>
<th>Results</th>
<th>Evidence</th>
<th>Precision</th>
<th>Bias</th>
<th>Grade of Evidence for Outcome</th>
<th>Overall GRADE of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barri et al(^{23}) study found pregnancy rate of combined strategy of surgery and subsequent IVF was significantly higher than with surgery alone (P&lt;0.0001)</td>
<td>Prospective Observational Study</td>
<td>No limitations</td>
<td>No inconsistency</td>
<td>No indirectness</td>
<td>No lack of precision</td>
<td>No publication bias</td>
<td>Low</td>
</tr>
<tr>
<td>Coccia et al(^{24}) found pregnancy rate achieved after integrated laparoscopy with IVF approach was significantly higher than surgery alone (P&lt;0.05).</td>
<td>Retrospective Observational Study</td>
<td>No limitations</td>
<td>No inconsistency</td>
<td>No indirectness</td>
<td>No lack of precision</td>
<td>No publication bias</td>
<td>Low</td>
</tr>
<tr>
<td>Nakagawa et al(^{25}) found no statistical difference between IVF and non-IVF group (P&lt;0.05).</td>
<td>Retrospective Observational Study</td>
<td>No limitations</td>
<td>No inconsistency</td>
<td>No indirectness</td>
<td>No lack of precision</td>
<td>No publication bias</td>
<td>Low</td>
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</table>
Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Participants</th>
<th>Total Patients</th>
<th>Stage of Endometriosis</th>
<th>Age range</th>
<th>Mean age</th>
<th>Duration of Infertility</th>
<th>Duration of study</th>
<th>Outcome measured</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barri et al: $^{2,3}$ RR=0.716 and NNT=6</td>
<td>825</td>
<td>III-IV with mean size endometriomata of 3.7-7.9 cm</td>
<td>20-40</td>
<td>32-38</td>
<td>0.9-5.0 years</td>
<td>7 years</td>
<td>Pregnancy rate</td>
<td>Pregnancy rate (surgery + IVF) significantly &gt;&gt; than surgery alone (P&lt;0.001)</td>
</tr>
<tr>
<td>Nakagawa et al: $^{2,5}$ RR= 0.82 and NNT=9</td>
<td>33</td>
<td>r-AFS scores statistically different among study groups</td>
<td>29-36</td>
<td>None given</td>
<td>1.3-9.1 years</td>
<td>4 years</td>
<td>Pregnancy rate</td>
<td>Pregnancy rate not statistically different b/w IVF &amp; non-IVF group P&lt;0.05</td>
</tr>
<tr>
<td>Coccia et al: $^{24}$ RR=0.797 and NNT=13</td>
<td>107</td>
<td>Surgery only Group: Stage I-II: 47 Stage III-IV: 60 Surgery &amp;IVF Group Stage I&amp;II: 24 Stage III- IV:43</td>
<td>29-38</td>
<td>33-34</td>
<td>1.3-5.7 years (average length of 6 years)</td>
<td>1-11 years</td>
<td>Pregnancy rate</td>
<td>Pregnancy rate (surgery + IVF) significantly &gt;&gt; (surgery alone) P&lt;0.05</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>Pregnancy rate</td>
<td>Preg rate in ♀&lt;35 y/o significantly &gt;&gt; ♀ &gt;35 y/o</td>
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<td>Preg rate w/in 6 mo post surgery significantly &gt;&gt; than later time intervals</td>
</tr>
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</table>

r-AFS: revised American Fertility Society
Figure I: Flow Chart for Management of Infertility in Women with Endometriosis

**LAPAROSCOPY**

- Complete resection

**Stage I +II**
- Expectant management x 6 months
  - ♀ > 35 years old
  - ♀ < 35 years old
  - Clomiphene +

**Stage III +IV**
- IVF
  - OR
  - Gonadotropin Injection +

**IVF** = in vitro fertilization
**IUI** = intrauterine insemination
*x6 months* = for six months
*stages refer to stages of endometriosis*
*Laparoscopy may be remote from time of attempting pregnancy.*

Chart was recreated from *UpToDate.com*