

Minimal and mild endometriosis negatively impact on pregnancy outcome

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SUMMARY

Endometriosis, a highly prevalent gynecological disease, can lead to infertility in moderate to severe cases. Whether minimal stages are associated with infertility is still unclear. The purpose of this systematic review is to present studies regarding the association between pregnancy rates and the presence of early stages of endometriosis. Studies regarding infertility, minimal (stage I, American Society of Reproductive Medicine [ASRM]) and mild (stage II, ASRM) endometriosis were identified by searching on the MEDLINE database from 1985 to September 2011 using the following MESH terms: endometriosis; infertility; minimal; mild endometriosis; pregnancy rate. 1188 articles published between January of 1985 and November of 2011 were retrieved; based on their titles, 1038 citations were excluded. Finally, after inclusion and exclusion criteria, 16 articles were selected to be part of this systematic review. Several reasons have been discussed in the literature to explain the impact of minimal endometriosis on fertility outcome, such as: ovulatory dysfunction, impaired folliculogenesis, defective implantation, decrease embryo quality, abnormal immunological peritoneal environment, and luteal phase problems. Despite the controversy involving the topic, the largest randomized control trial, published by Marcoux et al. in 1997 found a statistically different pregnancy rate after resection of superficial endometrial lesions. Earlier stages of endometriosis play a critical role in infertility, and most likely negatively impact pregnancy outcomes. Further studies into stage I endometriosis, especially randomized controlled trials, still need to be conducted.

Keywords: Endometriosis; infertility; minimal endometriosis; stage I/II endometriosis; pregnancy outcome; systematic review.

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RESUMO

Endometriose mínima e leve e seu impacto negativo sobre a gravidez

O objetivo desta revisão sistemática é apresentar estudos sobre a associação entre as taxas de gravidez e a presença de fases iniciais de endometriose. Estudos relacionados com a infertilidade e estágios mínimos e leves (estágios I,II, American Society of Reproductive Medicine [ASRM]) foram identificados por busca na base de dados MEDLINE, de 1985 a setembro de 2011. Os seguintes termos foram usados como palavras-chave: endometriose, infertilidade, taxa de gravidez; estágio mínimo; estágio leve de endometriose. Entre janeiro de 1985 e novembro de 2011, 1188 artigos foram recuperados; com base no título, 1038 citações foram excluídas e, finalmente, depois de critérios de inclusão e exclusão, 18 artigos foram selecionados para fazer parte desta revisão sistemática. Várias razões têm sido discutidas na literatura na tentativa de explicar o impacto da endometriose mínima no resultado da fertilidade, tais como: disfunção ovulatória, foliculogênese alterada prejudicada, defeito na implantação, baixa qualidade embrionária, ambiente peritoneal inflamatório e hostil e problemas da fase lútea. Apesar de toda polêmica envolvendo o tópico, o maior ensaio clínico randomizado foi publicado por Marcoux *et al.* Os autores encontraram uma taxa de gravidez estatisticamente significativa após a ressecção de lesões superficiais de endometriose. Estágios iniciais de endometriose desempenham um papel crítico relacionado à infertilidade e, provavelmente proporcionam um impacto negativo nas taxas de gravidez em pacientes com endometriose. Outros estudos envolvendo estágios iniciais de endometriose, especialmente ensaios clínicos randomizados, ainda precisam ser realizados.

Unitermos: Endometriose; infertilidade; endometriose mínima; endometriose leve; revisão sistemática; estágio I endometrioses; estágio II endometrioses; ASRM.

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INTRODUCTION

Endometriosis, a highly prevalent gynecological disease, can lead to infertility in moderate to severe cases¹. Whether minimal stages are associated with infertility is still unclear. The relationship between infertility and endometriosis, though clinically recognized, is not clear². In moderate to severe disease (stages III to IV, as outlined by the American Society of Reproductive Medicine [ASRM]), the association between infertility and endometriosis has been widely connected to severe pelvic adhesions. These adhesions can cause a variety of anatomical abnormalities such as cul-de-sac obliteration and large ovarian cysts, which can hinder ovum capture and transport³⁻⁶. The presence of these severely ectopic endometrial lesions is also known to decrease implantation rates⁷, decrease oocyte retrieval rates, and decrease pregnancy rates when assisted reproductive technologies (ART) such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are used⁸.

However, in minimal (stage I) endometriosis, the relationship between infertility and the disease is not as evident because pelvic adhesions are not severe enough to create damaging anatomical effects. There are, however, possible mechanisms that could cause infertility in patients with mild disease, including ovulatory dysfunction, impaired folliculogenesis, defective implantation, ectopic endometrium abnormalities, abnormal immunological peritoneal environment, and luteal phase problems⁸⁻¹³. Despite these suggested mechanisms, the question remains whether endometriosis negatively impacts fertility when no anatomic alterations exist¹⁴. In order to improve the chances of infertile patients with endometriosis to become pregnant, physicians have essentially two options: surgery and ART. There is a consensus for the indication of surgery when the patients have severe pain; however, there is no consensus regarding whether surgery or ART should be performed as the first line of treatment on oligosymptomatic infertile patients with endometriosis. There is increased evidence that surgery for advanced stage of endometriosis improves IVF outcome. The effect of surgery on stage I/II is still debatable^{15,16}. The purpose of this systematic review is to present the most up-to-date studies regarding the association between minimal to mild endometriosis and infertility. Specifically, studies that assess the association between pregnancy rates and the presence of stage I endometriosis in patients who had laparoscopic surgery or underwent various ARTs will be reviewed.

METHODS

Relevant studies were identified by searches of the MEDLINE database from 1985 to September 2011. Electronic searches were conducted, using the following MESH

terms: endometriosis; 69 infertility; minimal endometriosis; mild endometriosis; stage I and stage II ASRM. A manual search of references was performed for additional article retrieval. Review articles, editorials, and repeated manuscripts were excluded. Only manuscripts written in English were included. All included data were extracted independently by two different authors. The electronic search strategy of MEDLINE is available in the Appendix. The initial MEDLINE search using the search terms previously noted produced 1188 articles. Based on their titles, 1038 citations were excluded. Abstracts of the remaining studies (n = 150) were examined and, if relevant, were selected to be read in unabridged form. These studies were then reviewed using the final inclusion criteria, which included original articles published in English that measured pregnancy outcomes in endometriosis. Thirty-five articles were selected. Studies that did not include minimum to mild endometriosis were excluded. 16 articles were thus selected to be part of the review (Figure 1).

The following information was extracted from the 16 studies: (1) study design, (2) number of patients involved, (3) endometriosis stage, (4) control group, (5) ARTs employed, and (6) outcome/results with statistical significance (Table 1).

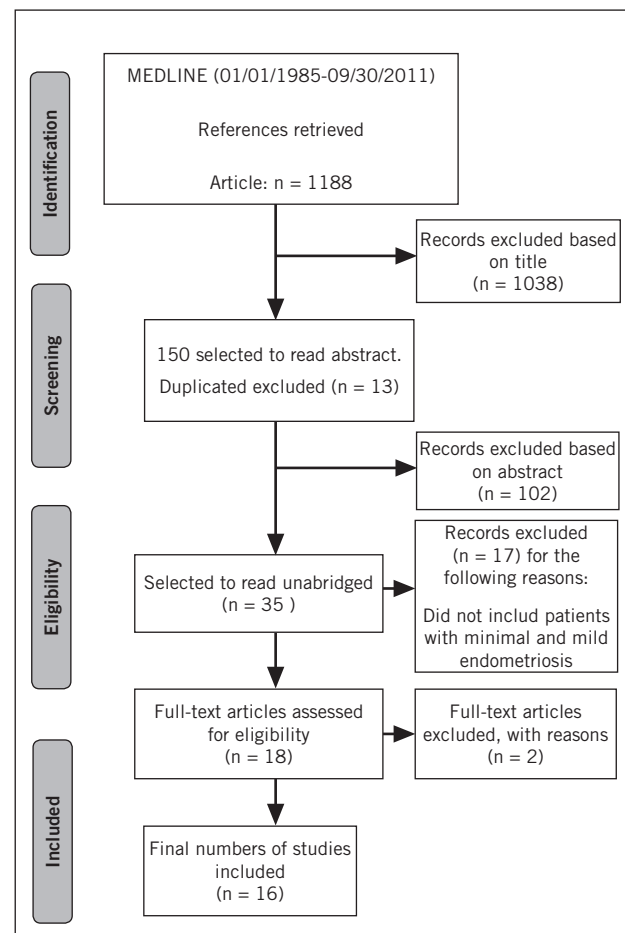


Figure 1 – Methods of systematic review.

Table 1 – Summary of all manuscript included in the systematic review

Author & year	Study design	Main group (n)	Comparison group (n)	Treatment	Main outcome	Significance $p < 0.005$
Rodriguez-Escudero et al. 1988 ¹⁴	Cohort	Stage I endometriosis with azoospermic or severely oligospermic partner, uses AID (n = 21)	Stage I endometriosis with normal partner semen analysis and no medical treatment (n = 40)	ART (AID)	Cumulative pregnancy rate	Yes
Arumugam and Urquhart 1991 ¹⁷	Prospective, controlled, non-randomized cohort	Laparoscopic electrocoagulation of stage I and II endometriosis (n = 17)	Diagnostic laparoscopy of stage I and II endometriosis only (n = 20)	Surgery	Cumulative pregnancy rates	No
Tanbo et al. 1995 ³³	Retrospective analysis	Stage I endometriosis (n = 265)	Unexplained infertility (n = 359)	ART (IVF)	Pregnancies per transfer	No
Guzick et al. 1997 ²⁰	Retrospective analysis	Stage I and II endometriosis (n = 274)	Stage III and IV endometriosis (n = 195)	Surgery and/or medication	Cumulative pregnancy rate	No
Isaksson and Tiitinen 1997 ²⁷	Retrospective analysis	Stage I endometriosis (n = 23)	Unexplained infertility (n = 47)	ART (IUI, DIPI, or TI)	Pregnancy rate	No
Marcoux S et al. 1997 ²²	Randomized, controlled trial	Laparoscopic surgery of stage I and II endometriosis (n = 172)	Diagnostic laparoscopy of stage I and II endometriosis only (n = 169)	Surgery	Cumulative pregnancy rate probability	Yes
Berube S et al. 1998 ¹⁹	Prospective cohort	Laparoscopic treatment of stage I and II endometriosis (n = 168)	Diagnostic laparoscopy of stage I and II endometriosis only (n = 263)	Surgery	Cumulative pregnancy rate probability	No
Omland et al. 1998 ³⁰	Prospective cohort	Stage I and II endometriosis (n = 49)	Unexplained infertility (n = 119)	ART (AIH)	Pregnancy rate	Yes
Parazzini 1999 ¹⁸	Randomized control trial	Resection or ablation of visible stage I and II endometriosis (n = 51)	Diagnostic laparoscopy of stage I and II endometriosis only (n = 45)	Surgery	Pregnancyrate	No
Milingos S et al. 2002 ²⁴	Clinical cohort	Diagnostic laparoscopy of stage I – II endometriosis with medication (n = 59)	Diagnostic laparoscopy of stage I – II endometriosis only (n = 43)	Surgery and/or medication	Pregnancy rate	Yes
Akande V et al. 2004 ²⁶	Retrospective	Stage I and II endometriosis (n = 75)	Unexplained infertility (n = 117)	Surgery	Estimated probability of pregnancy	Yes
Omland et al. 2006 ³⁴	Retrospective cohort	Stage I endometriosis (n = 43)	Unexplained infertility (n = 48)	ART (ICSI)	Pregnancy rate	No
Werbrouck E et al. 2006 ²⁸	Retrospective, controlled cohort study	Stage I endometriosis (n = 41)	Unexplained infertility (n = 49)	ART (COH, IUI)	Pregnancy rate	No
Vercellini et al. 2006 ²¹	Cohort	Stage I and II endometriosis (n = 124)	Stage III and IV endometriosis (n = 98)	Surgery	Pregnancy rate	No
Matorras R et al. 2010 ²⁹	Prospective, double blinded study	Stage I endometriosis (n = 24)	Healthy with no endometriosis (n = 51)	ART (AID, IUI)	Pregnancy rate	No
Opoien et al. 2011 ³⁵	Retrospective cohort	Laparoscopic surgery of stage I and II endometriosis (n = 399)	Diagnostic laparoscopy of stage I and II endometriosis only (n = 262)	Surgery/ ART (IVF, ICSI)	Pregnancy rate	Yes

AID, artificial insemination donor; ART, assisted reproduction techniques; IVF, in vitro fertilization; IUI, intrauterine insemination; DIPI, direct intraperitoneal insemination; TI, timed intercourse; AIH, artificial insemination husband; ICSI, intracytoplasmic sperm injection; COH, controlled ovarian hyperstimulation.

DISCUSSION

The standard diagnostic procedure for endometriosis is laparoscopic surgery⁵. Laparoscopy can be used not only for diagnosis, but also for treatment. The most common treatment approach is to remove all visible endometrial lesions¹⁷, which theoretically should restore natural fertility. When conducting the present literature review, several studies that assessed the association between minimal endometriosis and infertility in patients who had undergone laparoscopic surgery were retrieved.

The results are conflicting: some of the studies found no association whereas others did. Among those that did not find any association is a cohort study by Arumugam and Urquhart¹⁷, which compared pregnancy rates of women with stage I and II endometriosis who had undergone laparoscopic electrocoagulation of all visible lesions ($n = 17$) with those of women with stage I and II endometriosis who had diagnostic laparoscopy only ($n = 20$).

The authors found no statistically significant difference in pregnancy rates between the two groups ($p > 0.5$) and concluded that the presence of minimal endometrial lesions does not damage the pelvic anatomy to such an extent that it interferes with normal fertility¹⁷.

Parazzini¹⁸ conducted a study similar to that of Arumugam and Urquhart from 1991¹⁷, in which women with stage I and II endometriosis were separated into one of two groups: those who underwent laparoscopic ablation of all endometrial lesions and those who underwent diagnostic laparoscopy only. In this randomized controlled study, 12 of the 51 (24%) women who underwent ablation became pregnant, while 13 of 45 (29%) women conceived following diagnostic laparoscopy only, a difference that was not statistically significant ($p > 0.05$). These authors suggested that laparoscopic ablation does not help improve fertility in women with minimal endometriotic disease¹⁸.

In a prospective cohort study, Bérubé et al. compared cumulative pregnancy rate; the probability of becoming pregnant in the first 36 weeks after laparoscopy and of carrying the pregnancy for ≥ 20 weeks in infertile women with stage I and II endometriosis. One group received therapeutic laparoscopy while the comparison group received only diagnostic laparoscopy. These results demonstrated that women with minimal and mild endometriosis, who had all lesions removed, had a significantly higher pregnancy rate than the comparison group¹⁹.

A retrospective analysis by Guzick et al. found no significant difference in pregnancy rates among the four stages of endometriosis in women who had undergone medical and/or surgical treatment. Although these results also suggest that stage I endometriosis does not have a significant negative effect on fertility, the study's design was retrospective. Furthermore, the study did not contain a control group of women with unexplained infertility. This

makes the comparison of this study with studies that had control groups difficult. More importantly, it is difficult to draw any strong conclusions from the data without a control group and thus, this study cannot clearly support one view over another²⁰.

Among the studies that found a connection between mild disease and infertility is that by Vercellini et al. who conducted a cohort study to assess fertility in cases of endometriosis via pregnancy rates. This study consisted of 537 women who were diagnosed in all four stages of the disease, in whom no other cause of infertility could be identified. All visible endometrial lesions were removed through laparoscopy in all 133 patients. The crude pregnancy rates were 42% in stage I, 40% in stage II, 57% in stage III, and 52% in stage IV. No statistically significant difference was found between any pairing of the groups ($p = 0.68$)²¹.

These results are not as strong as those of the previously mentioned studies, which found no association, as this study did not contain a control group of women without endometriosis. The other limitation was that the main objective was to assess the predictive value of the current classification of endometriosis in terms of response to surgical treatment; it was not specifically designed to study the connection between mild disease and infertility. Due to these limitations, no firm conclusion can be made^{17,18}. Several other studies have found that laparoscopy improved fertility in patients with minimal to mild endometrial lesions. Marcoux et al., in 1997, conducted a randomized controlled trial comparing women with stage I and II endometriosis who underwent laparoscopic ablation of all visible endometrial lesions ($n = 172$) with women who underwent diagnostic laparoscopy only ($n = 169$). All women were followed postoperatively for 36 weeks. The cumulative pregnancy probability rate for the laparoscopic surgery group was 30.7% versus 17.7% for the diagnostic laparoscopy-only group ($p = 0.006$). This statistically significant difference suggests that the presence of stage I endometriosis is associated with infertility²².

The findings from the study by Marcoux et al. are further supported by data from a meta-analysis published by Jacobson et al. that compared the results of this study with those from Parazzini. The conclusions of these studies suggest that when ectopic endometrial tissue is no longer present, the peritoneal environment becomes more favorable for pregnancy, allowing for a possible linkage between stage I endometriosis and infertility. These studies have shortcomings, as the meta-analysis was based only on two studies. However, the two studies included are the only randomized controlled trials that, to date, have been performed on this particular subject^{18,23}. Several other studies that were not randomized controlled trials have also been conducted. These found a significant difference in pregnancy rates between women with stage I-II endometriosis

who underwent complete ablation and those who underwent diagnostic laparoscopy only. Milingos et al. performed a study similar to Marcoux et al., in which they compared the cumulative probability of pregnancy among women with stage I and II endometriosis who underwent operative laparoscopic treatment with that of women who underwent diagnostic laparoscopy only²⁴.

The study by Milingos et al. was different, since it focused on women who had diagnostic laparoscopy followed by six months of medical therapy using GnRH agonists, which help control the toxic microenvironment created from the presence of increased immunological cellular systems formed in response to chronic inflammation^{24,25}.

Medical treatment also suppresses the growth of endometrial lesions in affected sites, creating areas that are free of disease, thus it is somewhat similar to surgically removing the ectopic endometrial tissues. Results from the study by Milingos et al. showed that the cumulative probability of pregnancy after laparoscopic ablation (30.6%) was significantly higher than that in the diagnostic laparoscopy only (16.2%) ($p = 0.0001$)²⁴.

These authors also observed that the cumulative probability of pregnancy was significantly higher in women undergoing medical treatment (25.4%) than in women who underwent diagnostic laparoscopy only (16.2%) ($p = 0.014$). These results suggest that stage I endometriosis affects fertility, and therefore the endometrial tissue is the original cause for infertility²⁴.

Akande et al. suggest that the presence of endometrial tissue significantly decreases the probability of pregnancy in women with minimal to mild endometriosis. In this study, the women's ability to conceive naturally was compared between those with stages I and II endometriosis expectantly managed with only diagnostic laparoscopy and women with unexplained infertility. The findings indicated that women with unexplained infertility had a significantly higher probability of pregnancy over a three-year period than the women with stage I and II endometriosis ($p = 0.048$)²⁶.

These results are in agreement with those of Marcoux et al. and Milingos et al. because they suggest that the presence of minimal ectopic endometrial tissues hinders fertility. However, the study by Akande et al. had limitations due to its selective and retrospective nature. The author also noted that the sample population was dissimilar to other studies as it contained women with levels of subfertility instead of total infertility^{22,24,26}. Another form of assessing whether stage I endometriosis affects fertility is by analyzing studies that used various forms of ART as the treatment option. Pregnancy rates were used as the main outcome measure in most of the studies examined^{27,28}.

Intrauterine insemination (IUI) increases monthly fecundity in couples with unexplained infertility, thus it can

also be seen as a potential technique to help women with endometriosis. Due to this, investigators have chosen to use IUI as a means to test the association between minimal endometriosis and infertility^{27,28}.

Isaksson and Tiitinen conducted a retrospective analysis in which they compared three techniques (IUI, direct intraperitoneal insemination [DIPI], and timed intercourse [TI]) between women with untreated minimal endometriosis and those with unexplained infertility. While the couples with unexplained infertility using IUI, DIPI, and TI had a higher pregnancy rate (27.7%) than the women with minimal endometriosis using the same ART techniques (17.4%), this difference was not statistically significant ($p > 0.05$)²⁷. Because the pregnancy rates were similar between the two groups, the results suggest that stage I endometriosis does not have a significant effect on fertility. However, it should be noted that this was a retrospective analysis and thus may have had some elements of bias. Another group of authors compared pregnancy rates between women with minimal disease undergoing controlled ovarian hyperstimulation (COH) and IUI in whom all visible lesions were removed by previous laparoscopic surgery and patients with unexplained infertility. The clinical pregnancy rates per cycle were 21% and 20.5%, respectively ($p > 0.05$)²⁸. They concluded that the pregnancy rates were similar between the two groups. However, from this conclusion, it can also be deduced that stage I endometriosis has an effect on infertility. This is because Werbrouck et al. suggested that surgically correcting stage I endometriosis improves infertility, indicating that the presence of the stage I endometriosis initially had a negative impact²⁸.

The studies by Isaksson and Tiitinen and Werbrouck et al. were similar in design (retrospective analysis) and population size ($n = 70$ vs. $n = 90$, respectively). Thus, the results of other studies that exam different types of ART must be reviewed in order to draw an overall conclusion^{27,28}.

The effects of IUI with artificial insemination donor (AID) or artificial insemination husband (AIH) in women with stage I endometriosis-related infertility was analyzed in several conflicting studies^{14,29,30}. In one study by Matorras et al.³⁰, pregnancy rates after using AID were compared between 24 women with untreated stage I endometriosis and 51 women with no endometriosis. The authors found that the per-cycle pregnancy rate of women with stage I endometriosis (8.6%) was statistically similar to that of the women with no endometriosis (13.3%) ($p > 0.05$). Considerable efforts to eliminate potential bias in the study were enforced by only using women with completely natural menstrual cycles and azoospermic partners. No ovarian intervention was used. Since pregnancy could only be achieved through AID, the frequency of intercourse was not a factor. However, it should be noted that the study had a relatively small sample population^{29,31}.

Two other studies used IUI with either AID or AIH as the treatment regimen. One study produced significantly higher pregnancy rates in women with minimal to mild endometriosis using IUI with AID compared to no medical treatment ($p < 0.05$)¹⁴. A second study revealed significantly higher pregnancy rates employing IUI with AIH in women with unexplained infertility compared to women using the same treatment with minimal endometriosis ($p < 0.05$)³⁰. These results indicate that the presence of endometriosis possibly creates a microenvironment that is hostile to sperm. However, the study by Rodriguez-Escudero et al. was limited by its small population size. When the results are combined with those of a similar study conducted by Omland et al., there are only 168 cases in total. Even the study by Matorras et al., whose sample consisted of 300 patients, was considered a relatively small sample size. Furthermore, the study by Matorras et al. was double-blinded, whereas Rodriguez-Escudero et al. did not indicate any bias-controlling measures^{14,29,30}.

The prevalence of endometriosis based on laparoscopic diagnosis was compared between infertile women and women with partners lacking viable sperm (azoospermic, human immunodeficiency virus [HIV]-infected) in a prospective study by Matorras et al. The results showed that the frequency of stage I endometriosis was not significantly different between the infertile women and the women not exposed to spermatozoa (19.6% vs. 26%). This similarity suggests that stage I endometriosis may not be a causal factor in infertility³¹.

Of all the ARTs, IVF has the highest pregnancy rates³². Due to this, women with endometriosis and infertility issues often look to IVF as a means of solving their fertility problems. Several studies have reported no significant differences in pregnancy rates between women with minimal endometriosis who undergo laparoscopic removal of all endometriotic tissues and those who only undergo diagnostic laparoscopy before IVF treatment^{18,19}.

In one retrospective analysis, pregnancy rates per retrieval and per transfer using IVF were compared between women with untreated stage I endometriosis and an unexplained infertility control group of 359 women. The pregnancy rates were comparable between the two groups ($p > 0.05$). This similar pregnancy rate therefore helps support the hypothesis that stage I endometriosis is not associated with infertility, as its presence did not significantly lower the chances for pregnancy in women using IVF³³.

The hypothesis that stage I endometriosis is not associated with infertility is also supported by studies that assessed ICSI. When IVF fails due to male factor infertility or oocyte dysfunction, women with minimal endometriosis can also choose to use ICSI with IVF to aid conception³⁴. This treatment may be used to determine the effects of stage I endometriosis on infertility. In a retrospective

cohort study, women with stage I endometriosis who had previously failed to become pregnant after IVF ($n = 43$) were compared with women with unexplained infertility who also used IVF and did not become pregnant ($n = 48$)³⁴. In this study, 13 of 40 women (32.5%) with stage I endometriosis and 15 of 44 (34.1%) women with unexplained infertility became pregnant after one cycle of IVF³⁴. As no statistical difference was found ($p > 0.05$), no difference was observed between the two groups, similar to the results found in earlier studies^{7,33}. However, a recent study by Opoien et al. came to a different conclusion³⁵.

In this retrospective cohort examining the effects of laparoscopy before IVF/ICSI treatment in women with stage I and II endometriosis, the pregnancy rates of 399 women who had complete removal of all visible endometriosis were compared with those of women who had diagnostic laparoscopy only. The patients were followed for more than 14 years (February 1995 to July 2009), and the pregnancy rate per oocyte retrieval in the women with complete ablation was 40.3% versus 29.4% in the women with diagnostic laparoscopy only. The difference in these pregnancy rates was significant ($p = 0.004$), suggesting that the presence of endometriosis may affect successful embryo implantation and pregnancy. The study also indicated that women who underwent complete diathermy of their endometriotic lesions conceived more quickly after IVF/ICSI treatment than women in whom endometriotic lesions were still intact. However, as the author states, limitations exist in these findings as fewer data were collected during the earlier portion of the study period when diagnostic laparoscopy only was more prevalent than complete diathermy. Therefore, this unequal distribution of patients over time allows for bias towards complete diathermy over diagnostic laparoscopy based purely on the number of samples available, possibly leading to overly significant data³⁵.

CONCLUSION

After a thorough analysis of 16 different studies analyzing patients of minimal to mild endometriosis with different control groups, the majority of studies indicate that stage I endometriosis is not associated with infertility. This conclusion was made after 11 of the 18 articles found no significant difference in pregnancy rates between groups with stage I endometriosis and control groups with no endometriosis present, either through unexplained infertility or ablation of all visible endometriotic tissues.

Furthermore, while not all of the articles used pregnancy rate as their outcome, no significant differences were found in the number of infertile women with stage I endometriosis in comparison to women with no endometriosis³¹, further suggesting that no connections actually exist between the minimal form of the disease and fertility issues.

However, when conducting more careful analysis of the two randomized controlled trials^{18,22}, this initial conclusion was found to be not true when comparing diagnostic *versus* therapeutic laparoscopic procedures in women with minimal to mild endometriosis compared to women with unexplained infertility. While this conclusion is only based on data from two studies, it is the strongest conclusion that can be drawn, since 14 of the 18 included studies have a retrospective design and thus, a great amount of bias is possible. In order to reach the conclusion with the least amount of potential bias, only randomized controlled trials should be considered (Box 1).

This review has other limitations. One major limitation is that most of the studies observed the connections between minimal endometriosis and infertility combined stage I and II endometriosis together as one study group^{7,17-19,22,24,26,30,35,36}, possibly because the study populations were small.

Unfortunately, doing so significantly impacted the ability to make a completely confident conclusion on the impact of stage I endometriosis on infertility. Data from stage II patients may have overshadowed that from stage I patients.

Another limitation results from the high subjectivity of the ASRM system for endometriosis scoring⁵. While the regulations set forth by the ASRM give clear instructions on how to score an area for endometriosis, it is based on the gynecologist's personal perspective. This allows for a possible lack of consistency and possible interobserver bias in scoring. Any subjective means of scoring leads to variants amongst gynecologists. It is difficult to completely avoid incorrectly including nonvisible or atypical ectopic endometrial implants in unexplained infertility groups instead of stage I endometriosis. While endometriosis is, generally speaking, easy to visually distinguish, a true indication of the presence of endometriotic tissue is not validated.

Another limitation is that this review only included papers in English. Although an extensive search was performed, some European journals and conference publications may have not been included.

Assessing the best evidence available in published literature, particularly the randomized controlled trials, it can be concluded that minimal to mild stages of endometriosis play a critical role related to infertility and negatively impact pregnancy outcomes. Further studies into stage I endometriosis, especially with the addition of more randomized controlled trials, are still necessary.

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Box 1 – Summary of study design of the manuscripts included in this systematic review

Retrospective analysis	Prospective cohort	Randomized controlled trial
Rodriguez-Escudero et al. 1988 ¹⁴	Arumugam and Urquhart 1991 ¹⁷	Marcoux et al. 1997 ²²
Tanbo et al. 1995 ³³	Berube et al. 1998 ¹⁹	Parazzini 1999 ¹⁸
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