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Laparoscopic surgery improves pregnancy outcomes in women with suspected endometriosis with or without pathological confirmation

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Summary

Purpose of the investigation: To verify whether histologic confirmation of endometriosis impacts fertility outcomes. *Materials and Methods:* Women with unexplained infertility (UI) underwent laparoscopic excision or ablation with CO_2 laser or electrocautery of all suspected endometriotic lesions, followed by clinical treatment between January 2007 and December 2013; pregnancy (> 12 weeks) within 12 months of monitored cycles was the main outcome measured. *Results:* Women with histological confirmation (n=74) did not differ from those not confirmed (n=29) with age, body mass index, gravidity, parity, ovulation induction protocol, and past duration of infertility. Pregnancy outcome was similar in both groups (39/74 *vs.* 15/29 - $p = 0.9$ – *Chi*-square) and there was no statistical difference in time to conceive/deliver ($p = 0.7$) between groups. *Conclusions:* There is no difference in fertility outcomes in women with UI, whether or not suspected endometriosis is confirmed pathologically.

Key words: Laparoscopy; Endometriosis; Pregnancy outcome.

Introduction

The 2002 National Survey of Family Growth stated that 2.1 million (7.4%) household women between the ages of 15 to 44 were infertile [1]. The diagnostic evaluation of infertile couples typically addresses five basic problems: the assessment of the male partner, documentation of ovulatory function, demonstration of patency of at least one fallopian tube, assessment of cervical and/or uterine disease, and assessment of intraperitoneal disease. The diagnosis of "unexplained infertility" (UI) is frequently applied to infertile couples where the male partner has normal sperm analysis and the female partner is ovulatory with at least one patent fallopian tube with a normal uterine cavity. The diagnosis of unexplained infertility occurs in up to 30% of couples [2]. Evaluation of peritoneal factors, such as pelvic adhesive disease or endometriosis, requires laparoscopic examination, a step that is increasingly delayed or omitted from the infertility workup, in favor of empirical treatment with *in vitro* fertilization (IVF), even though the utility of IVF for UI is not supported by evidence-based medicine [3]. The current European Society of Human Reproduction and Embryology (ESHRE) Endometriosis Consensus guidelines support the use of laparoscopy for minimal or mild disease, which is often the stage found in women with UI [4-10]. Others authors disagree with laparoscopy [11]. Badawy *et al.*, in a large randomized clinical trial, concluded that laparoscopy could be postponed in unexplained infertility, until ovarian stimulation and timed intercourse were unsuccessful in achieving pregnancy [12]. In support of laparoscopy, Drake *et al.* reported that endometriosis was the dominant finding in patients with unexplained infertility [4] and endometriosis is associated with reduced fertility [13], even in its mildest forms [14, 15]. More recently, Littman *et al.* demonstrated an advantage to diagnostic laparoscopy for unexplained IVF failure patients, showing that most were able to conceive without IVF once endometriosis was identified and treated [16]. Phillips *et al.*, evaluating cost effectiveness of surgery versus IVF for mild endometriosis, found that surgery was cost-effective compared to two cycles of IVF [17].

Surgeons treating infertility face a dilemma when their diagnosis of pelvic endometriosis is not confirmed by histological findings. Marchino *et al.*, in a prospective clinical study, concluded that histological confirmation was necessary to validate the diagnosis of endometriosis, but they were unsure about the clinical impact of such findings [18]. Studies in the United States have implied that endometriosis is only diagnosed if lesions are confirmed by the pathologist [19], while a recent consensus by the ESHRE group on the diagnosis of endometriosis felt visual inspection was

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sufficient [10]. Based on the present authors' experience at a tertiary care fertility center in the southeastern United States, they find that a majority of couples with UI have minimal or mild endometriosis at the time of laparoscopy and many do not get histological confirmation because of the nature of ablation techniques or because minimal disease goes undocumented by the busy pathologist. Nevertheless, in the present authors' hands, complete removal or ablation of any and all subtle lesions of endometriosis appears to be beneficial in terms of pregnancy outcomes. Therefore, they chose to study this question further and to compare the pregnancy rates over time in a group of women with unexplained infertility that underwent laparoscopy with resection or ablation of endometriosis to determine whether histologic confirmation of endometriosis has a clinical impact on fertility rates in these women.

The importance of this study is directly related to the expense of infertility treatment. Unexplained infertility patients that remain without a diagnosis of endometriosis due to a lack of histologic confirmation may be subject to more expensive and possibly ineffective therapies or undergo further unnecessary testing. As health insurance is not widely available to cover the cost of assisted reproductive techniques in most states in the United States, laparoscopic surgery for the diagnosis and treatment of endometriosis in unexplained infertility patients appears to remain an important alternative for this group of patients. Finally, failure to diagnose endometriosis pathologically, may have little if any impact on the surgical outcome, and therefore should be examined critically.

Materials and Methods

Patient selection and variables

This cohort study was approved by the Institutional Review Committee of the Greenville Health System (Pro00013235, from September 3, 2013). The electronic records of all women who presented between January 2007 and December 2013 with UI at the Fertility Center of the Carolinas were reviewed for this study. All subjects met the following inclusion criteria: age between 21 and $\leq$ 41 years old, at least one year of infertility (defined as failure to conceive after one year of regular intercourse without use of any contraceptive method), a male partner with at least one normal semen analysis based on the World Health Organization criteria [20], regular cyclic menses (24 to 35 day intervals), and at least one patent fallopian tube. Women with known intramural or submucosal uterine leiomyomata, past myomectomy or pelvic adhesive disease and those who underwent IVF or frozen embryo transfer (FET) were excluded from the study. Included patients were followed for up to one year (12 months) of monitored cycles at the Greenville Health System outpatient clinic. Data were collected from electronic records. Subjects were divided into two groups according to the pathology report confirming or not the presence of endometriosis found during laparoscopy. All surgeries were performed at Greenville Health System by one of four reproductive endocrinologists, each with subspecialty fellowship training. Every case was documented by video photography. The surgeon assigned suspicious endometriotic lesions based on visual inspection according to the American Society of Reproductive Medicine (ASRM) criteria [21]. Briefly, endometriosis was suspected if clear, red, white, nodular, vesicular, powder burn or atypical lesions were observed. Allen Masters windows were considered to be a positive sign of endometriosis only if internal peritoneal lesions were visually identified. All visible and/or suspected endometriotic lesions were excised or ablated using CO_2 laser energy or electrocautery. Any adhesions present were similarly lysed to restore pelvic anatomy. After surgery, all patients began clinical treatment in the next menstrual cycle.

Surgical groups

Subjects with visual evidence of endometriosis were further analyzed into two groups: those with or without histological confirmation of endometriosis. A board certified pathologist analyzed the biopsies and diagnosed endometriosis using standard histologic criteria [22]. Briefly, endometriosis was defined by the presence of endometrial glands and/or stroma with or without hemorrhage outside the uterine cavity. In some cases, pathological diagnosis was not obtained due to the paucity of disease, possible sampling error or due to cautery effect.

Outcomes

The primary outcome was crude viable pregnancy rate with up to one year of monitored cycles, in both groups. Viable pregnancy was verified by ultrasound and defined by the presence of an intrauterine gestation(s) with fetal heartbeat in a gestation exceeding 12 weeks. Chemical pregnancy (presence of positive plasma or urine hCG, without ultrasonographic evidence of an embryo with heartbeat after five weeks of follow-up), and spontaneous abortion at $\leq$ 12 weeks were considered to be non-viable pregnancies. Cycle fecundity was calculated by dividing the number of viable pregnancies by the number of total cycles. In order to reduce bias, monitored cycle in the surgical group prior to surgery were excluded.

Sample size and statistical analysis

Sample size was calculated according to the data published by Nowroozi *et al.* [23] and Aanesen *et al.* [24], where pregnancy success after laparoscopic removal of endometriosis was 60%, and unexplained infertility treated with intrauterine insemination was 15%. With these figures and using an alpha error of 2.5% and a power of 95%, it would be required to have at least 28 patients in each group to have a 95% chance of detecting, as significant at the 2.5% level, an increase in pregnancy rates from 15% in the group of women without confirmation of endometriosis by pathology to 60% in those with pathological confirmation. Categorical variables, group and pregnancy outcome within 12 months, were compared by using the Log-rank (Mantel-Cox) Test. Demographic characteristics such as age, body mass index (BMI), gravidity, parity, and duration of infertility were compared by Student's t test, if data had a Gaussian distribution, or Mann-Whitney analysis, if data did not have a Gaussian distribution. Normal distribution was calculated using D'Agostino & Pearson omnibus normality test.

Clinical treatments between groups were compared using *Chi* Square for trend analysis. Subgroup analysis was performed in subjects that had endometriosis under visual inspection. This group was subdivided into two groups: those who had confirmation by pathology report (pathology confirmed group), and those where endometriosis was not found (pathology not confirmed group). Fisher's exact test was used in 2x2 tables. The Log-rank (Mantel-Cox) test was used to compare pregnancy outcome within 12 months between these groups. Cases where visually suspected endometriotic lesions were not sent to pathology were considered in the pathology not confirmed group. Statistical calculation was performed with GraphPad Prism 6.0 software.

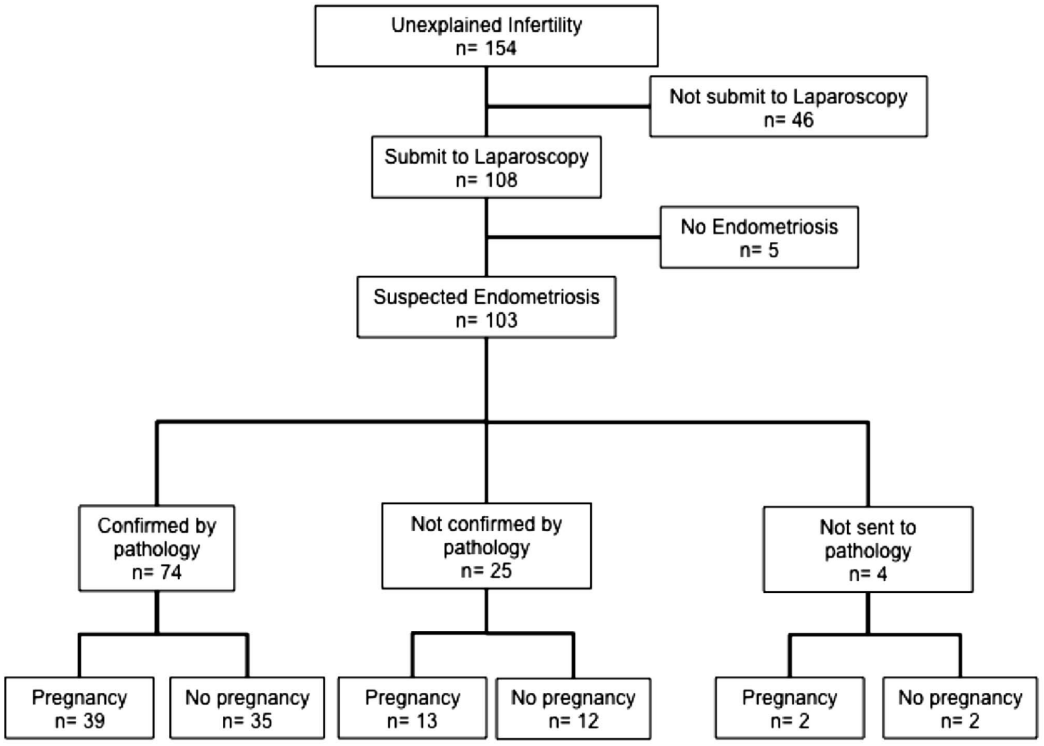

Figure 1. — Flow chart of the patients in the study.

Table 1. — *Demographics of the studied population.*

Characteristic	Confirmed (n = 74)	Not confirmed (n=29)	*p* value
Age (yrs)	32.4 ± 3.6	31.6 ± 4	0.3[a]
BMI	23.5 (20.4 to 25.7)	23.2 (20.6 to 25.9)	0.8[b]
Gravidity	1 (0 to 1)	1 (0.5 to 1)	0.1[b]
Parity	0 (0 to 1)	0 (0 to 0)	0.2[b]
Months of Infertility	18 (12 to 30)	14 (12 to 24)	0.1[b]
Endometriosis stage n (%)			
I	6 (8)	11 (38)	0.0007[c]
II	43 (58)	15 (52)	
III	18 (24)	2 (7)	
IV	7 (9)	1 (3)	

[a] Student *t* test – values are mean ± standard deviation;
[b] Mann-Whitney test – numbers are median (25% and 75% percentile);
[c] *Chi*-squared test for trend.

Table 2. — *Cycle characteristics and therapies used by the study group.*

Treatment Parameters	Confirmed (n = 74)	Not confirmed (n=29)	*p* value
Number of cycles/patient (n)	206/74	73/29	
Pregnancies (n)	39	15	
% per patients	52.7	51.7	0.9[a]
% per cycle	18.9	20.5	0.7[a]
Type of treatment (n)			
Combined	93	22	0.07[b]
Natural	2	7	
Oral	75	28	
Superovulation	34	16	

[a] Fisher's exact test; [b] *Chi*-square test for trend.

Results

A total of 154 subjects were identified with UI between 2007 and 2013. From these, 108 met the inclusion criteria and were followed (Figure 1). Age, BMI, gravidity, parity, and duration of infertility were not different between groups (Table 1). Endometriosis was visually identified in 103 women and confirmed by histological examination in 74 cases (71.8 – 95%CI: 62.4 to 79.6). From all subjects with suspected endometriosis, 72.8% were assigned to rASRM Stage I or II (Table 1). Only four cases of suspected endometriosis did not have a biopsy sent to histological analysis (Figure 1). The average follow-up was three months and total was 12 months (range one to 12 months). Within 12 months of follow-up, successful pregnancy occurred in 39 of 74 of the confirmed group (52.7%, 95%CI 41.4 to 63.6), while in the group without pathological confirmation, successful pregnancy occurred in 15 of 29 (51.7%, 95%CI 34.4 to 68.6). There was no difference in the treatment types for ovulation induction between groups ($p = 0.07$; Chi-square for trend). There were no serious surgical complications reported in the laparoscopy group.

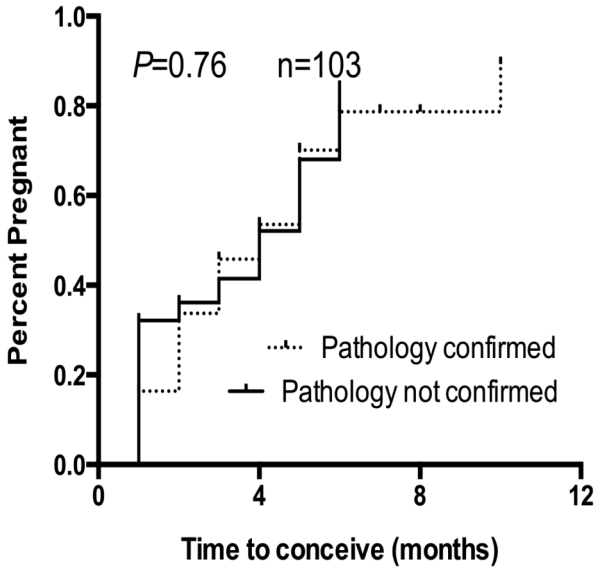

Figure 2. — Life table analysis (Log-rank Mantel-Cox) comparing overall time to pregnancy in women with UI who underwent laparoscopy and did or did not have histological confirmation of endometriosis.

Pregnancy outcomes were monitored in 279 cycles (206 cycles in confirmed group and 73 cycles in not confirmed group) (Table 2). Cycle fecundity in confirmed group was 18.9% (95%CI: 14.1 to 24.8%), while in the not confirmed group cycle fecundity it was 20.5% (95%CI: 12.8 to 31.1%). Using the Log-rank (Mantel-Cox) Test, the comparison between groups with or without pathological confirmation of suspicious lesions of endometriosis was not significantly different (Figure 2).

Discussion

There have been conflicting data between the ASRM and ESHRE guidelines on the impact of laparoscopy in patients with minimal and mild disease, as well as the need for confirmation of histological findings for the diagnosis of endometriosis. Since a lack of pathological diagnosis can occur for a variety of reasons unrelated to the pathophysiology of the disease or the impact of surgery, the present authors questioned whether confirmation should be required. In this study, they found that laparoscopic excision or ablation of suspected lesions of endometriosis yielded a 52% pregnancy rates after laparoscopy whether or not suspected endometriosis was confirmed pathologically.

Early prospective studies reported that endometriosis is present in 25 to 40% of women with infertility [25-28], but much has changed in the past 20 years with improved equipment and better appreciation of clear or subtle endometriotic lesions. Meuleman *et al.* suggest that women with normal ovulatory cycles, patent fallopian tubes, and normal male sperm counts, consistent with the present unexplained infertility group, have endometriosis in nearly 50% of cases [29]. The prevalence of pathology confirmed endometriosis in the unexplained infertility group was 71.8% (95%CI: 62.4 to 79.6), which is comparable to the data found by others [9, 27, 28, 30, 31].

As pointed out by the recent ESHRE guidelines, a positive histology confirms the diagnosis of endometriosis while negative histology does not exclude it [32]. Indeed, it could be argued that the biological impact of endometriosis is more important than the present authors' ability to verify its presence histologically. There are a number of reasons why histological confirmation remains a poor indication of the true prevalence of endometriosis. Lesions may be ablated rather than sent to the pathologist. Cautery artifact may destroy the lesions before they can be read. Small lesions in the paraffin block section may not be included in a randomly selected cross-section. Microscopic disease including single cell layers may not be perceived as endometriosis by the pathologist. By monitoring pregnancy outcomes in women with endometriosis that did or did not have histological presence of disease, the present authors demonstrated that there was an increase in pregnancy rates, cycle fecundity, and time to pregnancy during laparoscopy that was not influenced by pathological confirmation.

In the present authors' practice, they aggressively excised or ablated all suspected lesions, including rASRM Stage I which can have atypical, diffuse or subtle appearance. Despite this tendency to ablate lesions, the authors were able to confirm 74 out of 103 suspected endometriotic lesions (71%; 95CI = 62.4 to 79.6). Stegmann *et al.* recently reported that only 65% of suspected endometriosis lesions were confirmed histologically [19] in a large NIH-based study. The possible explanations for the present findings of benefit in lieu of confirmation likely are related to the alteration of immunological or inflammatory milieu [33]. Of note, the majority of lesions that were not confirmed by pathology were Stage I and II (Table 1).

The present data showing improvement in pregnancy rates is in accordance with the literature, including the EndoCan trial that examined the role of laparoscopy for minimal and mild disease, showing that fertility improved after ablation of lesions at laparoscopy [34-36]. The Canadian study required powder burn lesions in the inclusion criteria, which could explain why the improvement in fecundity was more modest than the present results. Red or opaque lesions have been shown to be biologically more active than powder burn implants [37]. One reason the present pregnancy results exceed that of the EndoCan study might be related to the fact that the authors routinely excised or ablated all red, clear or opaque lesions. As a further extension of the EndoCan study, this study suggests that pathological confirmation should not be considered essential for the diagnosis of endometriosis over visual inspection alone.

Strengths of this study include the large number of cases and the fact that most included samples sent for pathology examination. There is a need for this type of study, as very few investigations have been performed regarding whether or not pathology is required in order to predict outcomes. The present study suggests that minimal or mild endometriosis does contribute to infertility and that pathological confirmation does not change the outcomes. A limitation of this study was that it was not designed to show equivalence, but superiority; lack of difference does not prove equivalence. It would require over 1,082 cases to exclude a difference of more than 10% between both groups. Nevertheless, the present results are similar to those found in randomized clinical trials [36, 38]. The high incidence of endometriosis in the present sample reflects a careful selection of subjects with prolonged unexplained infertility and signs and symptoms of endometriosis. Given today's diagnostic workup that includes semen analysis, hysterosalpingography and sonohysterography, endometriosis is a diagnosis of exclusion and is not an unexpected finding in this group of patients. The authors did not include monitored cycle prior to surgery, as this would have biased the data analysis, since 100% of these patients had failed to conceive prior to surgery.

Conclusion

Histological confirmation does not appear to be essential in order to demonstrate benefit of laparoscopic excision or ablation of suspected lesions of endometriosis. With better diagnostic tests that reliably predict the presence of endometriosis will likely facilitate future studies that seek to better define the relationship between minimal endometriosis and infertility.

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