

Pregnancy Outcome following Active Management of Endometriosis after Laparoscopy in Infertile Women – A Prospective Cohort Study

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ABSTRACT

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Endometriosis is an important etiological factor in female infertility worldwide. Endometriosis is a disease that deteriorates the reproductive potential of women of child bearing age. The aim of this study was to assess the prevalence of endometriosis in women attending our centre, reproductive outcome following treatment and predictors for improving outcome.

A prospective cohort study was carried on infertile women who underwent laparoscopy for endometriosis.

Keywords: Endometriosis, Infertility

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INTRODUCTION

Endometriosis is an important etiological factor in female infertility worldwide. Endometriosis is defined as presence of endometrial glands and stroma outside the uterus mainly in pelvis. The prevalence of endometriosis in infertile women ranges from 25 to 50 % compared to 5 % in fertile women. Endometriosis is a disease that deteriorates the reproductive potential of women of child bearing age (Momoeda et al, 2002). Hence methods to improve reproductive outcome carries great significance.

Laparoscopy has revolutionized the management of all stages of endometriosis. However with the advent of assisted reproductive techniques, the role of laparoscopic evaluation has come down. This study projects laparoscopy as an accepted and integral part of infertility evaluation.

The role of active management after laparoscopy in endometriosis is controversial. The results of COH with CC/gonadotrophins combined with IUI are promising in endometriosis. These treatment options can increase overall fecundity but do not cause regression of endometriotic lesions (Olive DL, 2001). In early stages of endometriosis CC-IUI gives a fecundity rate of 6 to 8% per cycle and with gonadotrophins 12 to 20% per cycle. But randomized controlled trials are lacking in moderate or severe endometriosis. Among the ART, IVF has replaced IUI. Despite high pregnancy rates

with IVF, it is expensive and time consuming. Therefore it is reasonable to consider simple and inexpensive therapies such as COH with IUI in conditions like endometriosis. (van Voorhis BJ et al 1997).

Although conservative surgery at laparoscopy is nowadays considered the treatment of choice for stage 3 and 4 endometriosis. But this approach does not seem to be so effective in preventing the recurrence as well as improving the pregnancy rates (Bussaca et al 2001). The role of GnRH analogues comes here. The aim of GnRH analogues is to accomplish complete resection of lesions that could not be surgically removed, to treat microscopic foci and to increase pregnancy rates. Two studies emphasized the role of short term therapy with GnRH analogues after surgery (Vercellini et al, 1999)² while others failed to observe any improvements (Bianchi et al 1999). In the present study we have evaluated the effectiveness of post operative regimen of GnRH analogues for stage 3 and 4 endometriosis.

The aim of this study was to assess the prevalence of endometriosis in women attending our centre, reproductive outcome following treatment and predictors for improving outcome.

MATERIALS AND METHODS

A prospective cohort study was carried on infertile women who underwent laparoscopy for endome-

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triosis. These cases of endometriosis confirmed by laparoscopy were followed up in a fertility research centre between June 2003 and June 2008 over a period of 5 years. For this study we collected data from patient records and telephonic interview with the patients when required. The demographic data obtained included age at interview, date of birth, ethnicity, education, menstrual cycle history, gravidity, parity and type of infertility. All these women went through preliminary hormonal assays including FSH, TSH, prolactin and transvaginal sonography. Laparoscopy was performed under general anesthesia in the follicular phase of menstrual cycle. Staging of endometriosis was done on the basis of Revised American Fertility Society classification 1985. Thorough laparoscopic evaluation and appropriate treatment done in each case. Cystectomy was done in those with endometriomas of more than 2.5 cm diameter. All cases had histopathological confirmation. These infertile women were advised to try naturally for a period of 6 months after laparoscopy. After this six months period, these patients underwent further treatment as follows. Those with good tubo-ovarian relations were advised controlled ovarian stimulation combined with intrauterine insemination for three cycles. Others were managed with only controlled ovarian stimulation. Ovarian stimulation with clomiphene citrate 100 mg daily or aromatase inhibitors (Letrazole) 2.5 mg twice daily from second to sixth day of menstrual cycle was the treatment regime. Patients were followed for follicular growth. A few patients were given parenteral gonadotrophins. This included human menopausal gonadotrophin, recombinant FSH preparations and urinary FSH preparations at dosed of 75 IU. Those patients with poor tubo ovarian relationships received post operative GnRH analogues for three months. Depot preparations of GnRH analogues 3.75 mg were used. All women were followed up for assessing the clinical pregnancy rates. Viable pregnancy was confirmed by the detection of fetal heart by transvaginal sonography.

STATISTICAL METHODS

Variables entered in SPSS11. Difference between groups was tested by Chi-square test for ordinal variables. Discrete variables analysed by Fischer's exact test

RESULTS

A total of 8135 infertility cases registered in our hospital between June 2003 and June 2008. Laparoscopic evaluation was done in 2004 cases. Endometriosis was detected in 412 cases (20.5%).

Median age group of the study population was 30 years (range 19 to 43). 353 patients presented with primary infertility (85.6%) and 59 patients with secondary infertility (14.3%). Staging of endometriosis was according to the revised AFS criteria on laparoscopy (Table 1).

Table 1. Laparoscopic stage wise incidence of disease

Staging of disease	No of cases (n=412)	Percentage
Minimal endometriosis	79	19.1 %
Mild endometriosis	102	24.7 %
Moderate endometriosis	128	31.06%
Severe endometriosis	103	25%

Cystectomy was done for endometriomas in 181 cases, salpingoovariolysis and bowel adhesiolysis was performed in 152 cases, thereby restoring tubo-ovarian anatomy. Coagulation of endometriotic deposits was performed in 79 cases (Figure1).

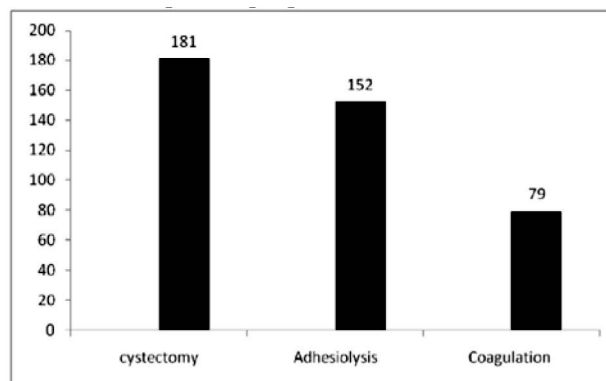


Figure 1. Laparoscopic procedures for endometriosis

In the study group, 31.06 % of patients were in stage 3, 25% in stage 4, 24.7% of in stage 2 and 19% in stage 1 (Table 1). During the follow up period, 157 (38.1%) patients conceived. Out of this 122 patients conceived within 1 year after laparoscopy.

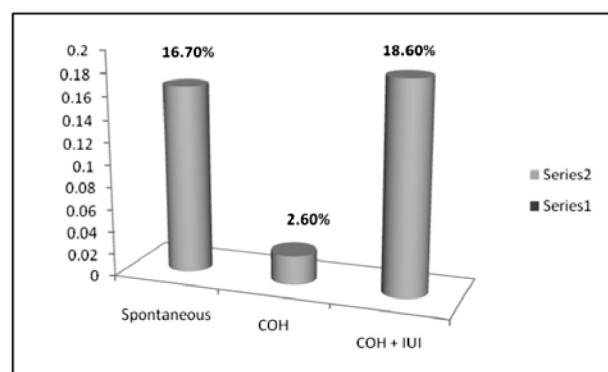


Figure 2. Mode of conception

‡Spontaneous — Spontaneous conception
 §COH — Controlled ovarian hyperstimulation
 || COH+IUI— Controlled ovarian hyperstimulation combined with intrauterine insemination

In the study group, 69/412 patients (16.74%) conceived spontaneously, 11/412 patients (2.6%) conceived with controlled ovarian hyperstimulation and 77/412 (18.6%) conceived following controlled ovarian hyperstimulation combined with intrauterine insemination (Figure 2).

In the study group, we found that in stage 1 and 2 endometriosis 2.2% of patients conceived following ovarian stimulation whereas 27.8% of patients conceived following ovarian stimulation combined with intrauterine insemination. In stage 3 and 4 endometriosis 3 % of study group patients conceived following ovarian stimulation and 12.1% of patients conceived following ovarian stimulation combined with intrauterine insemination (Table 2).

Stage of disease	Spontaneous conception	COH only	COH +IUI	Tt (mcg)
Minimal (n=79)	24 (30.3%)	1 (1.2%)	30 (37.9%)	100
Mild (n=102)	18 (17.6%)	3 (2.9%)	19 (18.6%)	200
Moderate (n=128)	21 (16.4%)	6 (4.6%)	20 (15.6%)	300
Severe (n=103)	6 (5.8%)	1 (0.9%)	8 (7.7%)	400

*COH Controlled ovarian hyperstimulation
 † COH + IUI Controlled ovarian hyperstimulation combined intrauterine insemination

In the study, it was found that once severity of disease increased, the conception rate was sharply decreased. Analysis of linear trends in proportions applied for the same and found to be statistically significant. Chi square test for trend =51.827, p value=0.0001, which was found to be statistically significant (Table 3).

Stage of disease	Number of cases (n=157)	Percentage
Minimal Endometriosis	55	69.62%(55/79)
Mild Endometriosis	40	39.2% (40/102)
Moderate Endometriosis	47	36.71% (47/128)
Severe Endometriosis	15	14.56% (15/103)

In stage 1 and 2 endometriosis 52.4 % patients conceived and 26.8% patients conceived in stage 3 and 4 endometriosis.

In the GnRH received group, 9 patients conceived whereas in GnRH not received group only 3 conceptions. Fischer's exact test applied, value came as -0.008. p value <0.05, hence the results were statistically significant (Table 4). 77% of conceptions were within one year after laparoscopy.

Table 4. Post operative GnRH analogue and conception rate

	Number(n)	Conception
GnRHa received	41	9
GnRHa not received	62	3

DISCUSSION

We undertook this study to find the prevalence of endometriosis in infertile women and the role of active treatment after laparoscopy. The general prevalence of endometriosis in reproductive age group women ranges from 2 to 50% worldwide (Missmer SA, Cramer DW 2003). Incidence of endometriosis in infertility ranges from 21 to 47 %. Unfortunately this number is widely disparate depending upon the study. Even though endometriosis is an important etiological factor in infertility, this disparity may be due to diagnostic selection bias. In the study group we have included only those cases where laparoscopy had either a diagnostic or therapeutic role. As per the study the prevalence of endometriosis in our centre was 20.5 %. Wheeler JM 1989 reported a prevalence of 20 %.

The median age in the study group was 30 years. Other studies had a mean age of diagnosis 25 to 29 years (Olive DL et al 1986). Staging of disease was done based on revised AFS criteria (Revised AFS classification of endometriosis, 1985). Revised AFS criteria is a scalar scoring system with arbitrary values assigned to each locus of disease with special emphasis on endometriotic invasion of adnexal tissue. Operative laparoscopy still remains the gold standard for endometriosis, since it can restore pelvic anatomy and produce regression of disease. This has been reflected in pregnancy rates after laparoscopy. In the study group we got 38.1% conception rates. Barnhart K et al, 2002 reported good pregnancy rates after laparoscopy. Surrey et al, 2003 and Alborzi S et al, 2004 reported 20 and 65% pregnancy rates respectively after laparoscopy. Pregnancy rate was high after laparoscopy according Parazzini F (1999). Marcoux et al reported a 30.7% pregnancy rate in the first 36 weeks after laparoscopy when compared to 17.7% in the diagnostic laparoscopy group. In that study the laparoscopic treatment increased the cumulative probability of conception by 73%. Study by Alborzi et al, 2004 supported this theory. Tanahuateo SJ et al, 2003 reported that laparoscopic evaluation avoided further assisted reproductive techniques in 25% of his patients.

In the study group, 69 patients conceived spontaneously, 11 patients conceived with ovarian stimulation and 77 patients conceived following controlled ovarian hyper stimulation combined with intrauterine insemination. We got 27.8% pregnancy rates following ovarian hyperstimulation combined with intrauterine insemination in stage 1 and 2 endometriosis and 12.1 % in stage 3 and 4 endometriosis. The results with intrauterine insemination were exceptionally good in early stages of endometriosis. Littman MD et al 2005 reported 76 % spontaneous conceptions and 24 % by assisted reproductive techniques in his study. No other randomized controlled trials comparing stage wise mode of conceptions was available. In the study, we got the maximum conception rates following ovarian hyper stimulation combined with intrauterine insemination cycles. This is in accordance with accepted literature. Olive DL, et al showed that ovulation induction combined with intrauterine insemination in women with endometriosis confers fertility benefit. Randomized controlled trials done by Chaffkin et al, Dodson WC et al and Fedele L et al showed that either GnRH agonists with FSH and LH, clomiphene citrate with intrauterine insemination or FSH combined with intrauterine insemination can increase pregnancy rates when compared to no treatment group.

Surgical ablation can increase pregnancy rates in early stages. Two randomized controlled trials showed increased fertility rates after ablation of minimal or mild diseases. (Olive DL et al 2001) Littman MD et al reported that complete and thorough microsurgical techniques can help infertile women to conceive without in vitro fertilization cycles and also help those going for IVF. The results in early stages of endometriosis is very much encouraging and in accordance with several published series. We got around 52.4% conceptions in stage 1 and 2 endometriosis together. In a prospective, multicentric, double blinded, controlled, randomized study by Marcoux and colleagues in a Canadian Collaborative trial named Endocan, surgical treatment by laparoscopy resulted in higher pregnancy rates (37.5% vs 22.5%, $p = 0.002$). This study also provides convincing evidence that surgery is beneficial in the treatment of minimal or mild endometriosis associated infertility. Ablation of endometriosis can increase the pregnancy rates in stage 1 and 2 endometriosis.

In the study, as the severity of disease increased, the conception rate also reduced. Only 26.8 % of our patients conceived in stage 3 and 4 endometriosis. Many observational studies showed increased fertility

rates in stage 3 and 4 endometriosis but there is lack of randomized controlled trials. M. Busaca et al, 2001 reported that use of post operative GnRH agonists can improve the pregnancy rates in advanced stages of endometriosis. In the present study GnRH received group had 9 conceptions when compared to non GnRH group. Further randomized controlled trials are needed to prove the efficacy of GnRH in severe endometriosis.

According to Barbieri RL 2002, majority of conceptions will be in the first 6 to 18 months after laparoscopy. In the study, 77% of patients conceived within one year after laparoscopy.

Laparoscopy is the gold standard for surgical treatment of endometriosis. Controlled ovarian hyper stimulation combined with intrauterine insemination following laparoscopy can give higher pregnancy rates in early stages of endometriosis. Post operative GnRH analogues had a definite role in severe endometriosis. The prevalence of endometriosis in our infertile population was 20.5%.

END NOTE

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