Superovulation and Intrauterine Insemination in Cases of Treated Mild Pelvic Disease

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Purpose: *Our purpose was to examine the effect of treated mild pelvic disease on the outcome of superovulation with intrauterine insemination (SO/IUI).*
Methods: *Three hundred cycles of SO/IUI were retrospectively reviewed for 118 women with laparoscopically treated minimal/mild endometriosis and 67 cycles for 28 women with minimal/mild distal tubal disease/adnexal adhesions and compared with 265 cycles in 111 couples with idiopathic infertility.*
Results: *The monthly fecundity rate (MFR) of 6.8% and live birth rate (LBR) of 6% in the endometriosis group were significantly lower ($P = 0.002$) than those in the idiopathic infertility group (MFR = 13.5%, LBR = 12.1%). The 10.9% MFR and 7.5% LBR in the minimal/mild tubal/adnexal disease were not significantly different from those in the other two groups.*
Conclusions: *MFR and LBR were higher after SO/IUI in idiopathic infertility compared to those for treated mild/minimal endometriosis or mild/minimal tubal/adnexal adhesions. However, SO/IUI still remains a reasonable option for both these groups prior to IVF-ET.*

KEY WORDS: Adnexal disease; intrauterine insemination; minimal/mild endometriosis; superovulation.

INTRODUCTION

The mechanism(s) of reduced fecundity in minimal to mild endometriosis, distal tubal disease, or adnexal adhesions is (are) unknown. The incidence of mild endometriosis in asymptomatic women of reproductive age varies between 0.7 and 20% and their 36-month cumulative live birth rate (LBR) without any therapeutic intervention has been reported to be 20% (1). Superovulation and intrauterine insemination (SO/IUI) have been advocated as further management of these patients. Randomized studies reported significantly higher success rates with SO/IUI versus nontreated controls (2,3). However, most patients in these series did not undergo prior corrective surgery. A randomized study of surgical treatment versus no treatment at the time of diagnostic laparoscopy noted a significant three fold increase in the treated group (4).

We have previously observed significantly lower success rates with SO/IUI among patients having undergone any surgical treatment of pelvic disease (5.3%) compared to those without pelvic pathology at diagnostic laparoscopy (12.4%) (5). In vitro fertilization is associated with higher success but is more expensive. Alternatives such as SO/IUI may be more cost-effective as an early option. The aim of the present study was to assess the efficacy of SO/IUI in patients with minimal to mild endometriosis, as well as patients with minimal to mild distal tubal disease and/or adnexal adhesions who had undergone prior laparoscopic treatment. The efficacy of SO/IUI in these patients was compared to that in patients with idiopathic infertility.

MATERIALS AND METHODS

A retrospective chart review was performed on all patients who underwent SO/IUI between January

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1993 and December 1995. The study groups consisted of women who had laparoscopic surgery for stage 1–2 endometriosis ($n = 118$) or minimal to mild adnexal disease ($n = 28$) prior to attempting SO/IUI. Two hundred sixty-five SO/IUI cycles for idiopathic infertility in 111 couples during the same period served as the control group. All patients underwent IUI with their partner's sperm. Patients with an associated male-factor diagnosis were excluded from analysis. This study was approved by the institutional review board.

All couples had at least 1 year of primary or secondary infertility with their current partner. All couples had a normal basic infertility evaluation that included one or more semen analyses, a hysterosalpingogram, and luteal-phase assessment. All women had regular menstrual cycles with midluteal progesterone >10 ng/ml and/or an in-phase endometrial biopsy. The control group had a diagnostic laparoscopy with no pelvic pathology. Staging of endometriosis was performed at the time of surgery using the revised American Fertility Society scoring system (6). Distal tubal disease and adnexal adhesions were retrospectively graded from the operative reports according to the American Fertility Society classification (7). Patients with minimal and mild tubal disease and adnexal adhesions were combined into the mild adnexal disease group. All pelvic pathology was treated laparoscopically at the time of diagnosis.

SO was achieved with intramuscular (im) injections of human menopausal gonadotropin (hMG) beginning with 150 IU for 4 days initiated on day 3, 4, or 5 of the menstrual cycle after a normal baseline ultrasonogram. The subsequent dose was individualized based on transvaginal ultrasonography and serum E_2 levels. Human chorionic gonadotropin, 10,000 IU, was administered by im injection when at least one follicle measured 18 mm in mean diameter. A single IUI was performed approximately 36 hr later. Semen was collected by masturbation after 2–3 days of sexual abstinence and a semen analysis was performed both before and after washing by centrifugation through a Percoll (Irvine Scientific, Santa Ana, CA) density gradient. The supernatant was removed and the pellet resuspended in 0.4 ml of human tubal fluid medium (Irvine Scientific). Clinical pregnancies were defined by visualization of fetal cardiac activity on vaginal ultrasonography. Live birth outcome was determined by interview. The main study outcomes were the monthly fecundity rate (MFR) and live birth rate (LBR) per cycle.

Statistical Analysis

Pelvic surgery and nonpelvic surgery patients were compared using Wilcoxon rank-sum test for continuous variables, such as postwash sperm motility and female age, which have previously been found to be significant IUI risk factors. Logistic regression, which was adjusted for the fact that some women attempted more than one cycle by using GEE methods, was used to determine which IUI risk factors were significant within this group. Significant risk factors were included in subsequent analyses to assess the significance of each pelvic disease and its severity. Data were analyzed for differences in MFR and LBR among different groups by repeated-measures GEE logistic regression. Summary statistics are presented as mean ± standard error, and SAS version 7 (SAS Institute Inc., Cary, NC) was used for all calculations. A P value < 0.05 was considered statistically significant.

RESULTS

This study included 118 patients with stage 1–2 endometriosis and 28 patients with mild adnexal adhesions. To serve as controls, 111 couples diagnosed as idiopathic infertility were included in the study. Overall they underwent 300, 67, and 265 cycles of SO + IUI, respectively. The women's age and the postwash sperm motility used for IUI procedure were comparable between the groups.

Logistic regression of LBR and MFR revealed an overall statistically significant difference of 0.04 and 0.005, respectively. Further analysis demonstrated a significant difference only for endometriosis and idiopathic infertility (Table I).

DISCUSSION

We assessed the pregnancy rates of patients with surgically corrected mild pelvic diseases comprising of minimal/mild endometriosis and mild adnexal diseases that were treated with SO/IUI. Patients with idiopathic infertility served as control group. There is no control group of untreated mild pelvic diseases, which is a shortcoming of our study.

The mechanism by which mild pelvic disease exerts its influence on fertility remains elusive. Laparoscopic surgery for minimal and mild endometriosis has been shown to increase the monthly fecundity

Table I. Overall Patient Characteristics*

	No. of patients	No. of cycles	Age of woman (mean ± SE)	Postwash sperm motility (mean ± SE)	MFR per cycle (%)	LBR per cycle (%)
Idiopathic infertility	111	265	37.7 ± 0.4	76.4 ± 1.5	13.5	12.1
Mild adnexal disease	28	67	38.1 ± 0.7	72.2 ± 3.7	10.9	7.5
Endometriosis 1–2	118	300	37.2 ± 0.3	78.5 ± 1.3	6.8	6.0

* $P = 0.002$ and 0.02 for MFR and LBR, respectively, between idiopathic and endometriosis groups. All other differences were not statistically significant.

rate in infertile women from 3.2 to 6% in a randomized controlled trial (4). Another randomized study compared SO/IUI with expectant management among women with minimal/mild endometriosis and showed that the addition of SO/IUI significantly increased the LBR from 2 to 11% (2). However, only 47% of patients in that study had corrective surgery at the time of diagnostic laparoscopy. Analysis of a subset of women with surgically corrected endometriosis studied by Nulsen *et al.* in a randomized trial showed significantly higher MFRs with SO/IUI compared to IUI alone (8). They reported monthly fecundity rates with SO/IUI of 11.8 and 19.3% for treated endometriosis and idiopathic infertility, respectively. Fedele *et al.*, in their randomized controlled trial, found no difference in cumulative pregnancy rates but a better cycle fecundity rate between three cycles of superovulation and 6 months of expectant management in infertile patients with minimal/mild endometriosis (3).

In our study, treated minimal/mild endometriosis patients with SO/IUI had a significantly lower MFR compared to the idiopathic infertility group (6.8 versus 13.5% per cycle; $P = 0.002$). Overall it appears that our result of 6.8% MFR in treated minimal/mild endometriosis is somewhat lower than that in other studies. It may be because our patients were older than in the other studies. The age (mean ± SE) of patients included in our study was 37.4 ± 0.3 years.

For individuals with a diagnosis of mild adnexal adhesions, SO/IUI therapy appeared to be effective. They had lower values of MFR in comparison to the idiopathic infertility patients (10.9 versus 13.5%) but the difference was not statistically significant. Dodson and Haney also reported a cycle fecundity rate in stimulated cycles of 10%, which is comparable to our result (9). The difference in the MFR between the mild adnexal adhesion and the endometriosis groups after SO/IUI was not found to be statistically significant.

A combined analysis of the literature on idiopathic infertility done by Guzick *et al.* yielded an estimated pregnancy rate of 18% per cycle for SO/IUI cycles, which is somewhat higher in comparison to that in our study (10). The most likely explanation may be the higher age of patients included in our study. Agarwell and Buyalos found a decrease in pregnancy rate after SO and IUI at 35 years of age (11). In another study it was reported that women above 40 years of age had a pregnancy rate per cycle significantly lower than that of their younger counterparts (12).

No clear hypothesis has been formulated to explain infertility associated with mild pelvic diseases. The reason for the increased fecundity seen with treatment remains unknown. Correction of minor ovulatory dysfunction is thought to be the mechanism by which fecundity improves with SO in women with surgically corrected endometriosis (2). Although the fecundity achieved after treatment in mild pelvic diseases is significantly improved over baseline, it does not reach that seen in the normal population (13). At some centers, SO/IUI pregnancy rates may be comparable with those seen with IVF (14,15). Therefore the choice of initiating IVF or SO/IUI will depend on a variety of factors such as cost and the success rate of the available IVF program. A cost–benefit analysis done by Peterson *et al.* found that four cycles of SO/IUI were less expensive than IVF and also alleviated the need for invasive oocyte retrieval and extracorporeal fertilization (16).

CONCLUSION

In summary, we have shown in this retrospective study that in surgically treated mild pelvic diseases such as endometriosis and adnexal diseases, SO/IUI yielded a cycle fecundity which is lower than that in idiopathic infertility but higher than the baseline. SO/

IUI is an effective, relatively low-risk alternative treatment for these groups of patients prior to IVF-ET.

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