FERTILITY AND STERILITY®
VOL. 78, NO. 4, OCTOBER 2002

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization–embryo transfer in patients with endometriosis

Eric S. Surrey, M.D.,[a] *Kaylen M. Silverberg, M.D.,*[b] *Mark W. Surrey, M.D.,*[c] *and William B. Schoolcraft, M.D.*[a]

Colorado Center for Reproductive Medicine, Englewood, Colorado; Texas Fertility Center, Austin, Texas; and Reproductive Medicine and Surgery Associates, Beverly Hills, California

Objective: To evaluate the effect of a 3-month course of GnRH agonist administered immediately before IVF-ET in infertile patients with endometriosis.

Design: Prospective, randomized trial.

Setting: Three tertiary care assisted reproductive technology programs.

Patient(s): IVF-ET candidates with surgically confirmed endometriosis.

Intervention(s): Twenty-five patients received three courses of a long-acting GnRH agonist, 3.75 mg i.m. every 28 days, followed by standard controlled ovarian hyperstimulation. Twenty-six patients received standard controlled ovarian hyperstimulation with mid–luteal phase GnRH agonist down-regulation or microdose flare regimens.

Main Outcome Measure(s): Response to controlled ovarian hyperstimulation, ongoing pregnancy rates per cycle, group implantation rates, and implantation rate per embryo transfer procedure.

Result(s): The extent of surgically confirmed endometriosis was greater in patients who received the long-acting GnRH regimen for 3 months before IVF-ET. The groups did not differ significantly in terms of dose or duration of gonadotropin stimulation, number of oocytes retrieved, fertilization rate, or number of embryos transferred. Patients who received the long-acting GnRH regimen had significantly higher ongoing pregnancy rates (80% vs. 53.85%) and a trend toward higher implantation rates (42.68% vs. 30.38%).

Conclusion(s): Prolonged use of GnRH agonist before IVF-ET in patients with endometriosis resulted in significantly higher ongoing pregnancy rates than did standard controlled ovarian hyperstimulation regimens. No deleterious effect on ovarian response was observed. (Fertil Steril® 2002;78:699–704. ©2002 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, infertility, in vitro fertilization-embryo transfer, GnRH agonist

Received December 17, 2001; revised and accepted March 8, 2002.

Supported by a grant from TAP Pharmaceuticals, Inc., Waukegan, Illinois.

Presented in part at the 57th Annual Meeting of the American Society for Reproductive Medicine, Orlando, Florida, October 20–25, 2001.

Reprint requests: Eric S. Surrey, M.D., 799 East Hampden Avenue, No. 300, Englewood, Colorado 80110 (FAX: 303-788-8310; E-mail: esurrey@colocrm.com).

[a] Colorado Center for Reproductive Medicine.

[b] Texas Fertility Center.

[c] Reproductive Medicine and Surgery Associates.

0015-0282/02/$22.00
PII S0015-0282(02)03373-3

The benefits of IVF-ET in the treatment of endometriosis-related infertility are well established (1, 2). In the absence of mechanical distortion, IVF-ET may be accomplished in part by removing gametes and zygotes from an immunologically hostile peritoneal environment (3, 4).

Gonadotropin-releasing hormone agonists are effective in treating symptomatic endometriosis (5–8). These agents appear to suppress serum and peritoneal cytokine levels and may enhance return of endometrial markers of implantation (9–11). Despite such potentially beneficial effects, these agents have little effect in terms of increasing spontaneous pregnancy rates in patients with endometriosis (12). It is possible that by the time ovarian function returns and these patients could spontaneously conceive, a process that may take months given natural fecundity rates, the inhibitory effects of the disease process return even though the patients remain asymptomatic.

Any potential benefits of GnRH agonists in infertile patients with endometriosis may be best realized during maximal disease suppression. The circumstance that might best achieve this aim would be to perform IVF-ET immediately after prolonged GnRH agonist therapy.

TABLE 1

Baseline clinical data.

Group	No. of patients	Depot GnRH agonist	Age (y)	Day 3 level		Time between surgery and IVF-ET cycle (mo.)	Revised ASRM score[a]	Stage I and II endometriosis	Stage III and IV endometriosis
				FSH (mIU/mL)	Estradiol (pg/mL)				
1	25	Yes	33.12 ± 0.67 (range: 28–39)	6.17 ± 0.54	30.26 ± 5.37	14.52 ± 2.45	31.56 ± 3.05	4	21
2	26	No	32.58 ± 0.56 (range: 27–39)	7.32 ± 0.32	30.23 ± 4.84	17.85 ± 2.4	22.44 ± 3.38	11[b]	15[b]

Note: Results are expressed as the mean (±SE) unless otherwise indicated.

[a] According to the American Society for Reproductive Medicine Revised Endometriosis Score and Staging System (17).

[b] $P<.05$.

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Earlier investigations at single centers with varying control groups and stimulation protocols have suggested that such an approach is effective (13–15).

We sought to determine whether IVF-ET immediately after prolonged GnRH agonist therapy has benefit in patients with endometriosis.

MATERIALS AND METHODS

This prospective, randomized trial was performed at three tertiary care assisted reproductive technology programs. Candidates were infertile patients with endometriosis documented at laparoscopy or laparotomy within 60 months of cycle initiation (range, 2–55 months). All patients had regular menses (every 26–33 days) and were candidates for autologous IVF-ET undergoing fresh embryo transfer only.

Patients with early follicular phase serum FSH levels greater than 12 mIU/mL and evidence of ovarian endometriomata were excluded. No patients had received prolonged GnRH agonist therapy as treatment for endometriosis within 12 months of study entry. Informed consent as approved by the institutional review board at each center was obtained.

Patients were randomized into two groups by using a computer-generated random number table. Group 1 consisted of 25 patients who received a depot preparation of the GnRH agonist leuprolide acetate (Lupron Depot; TAP Pharmaceuticals, Waukegan, IL), 3.75 mg i.m. every 28 days for three injections. The first injection was administered during the early follicular phase. Controlled ovarian hyperstimulation as described below was initiated within 45 days of the last leuprolide acetate injection.

Group 2 consisted of 26 controls with endometriosis who did not receive the long-acting GnRH agonist but instead underwent standard controlled ovarian hyperstimulation regimens.

Controlled ovarian hyperstimulation consisted of standard GnRH agonist down-regulation using leuprolide acetate (TAP Pharmaceuticals), 0.5 to 1.0 mg/d s.c. for 7 to 10 days, initiated 30 to 45 days after the third leuprolide acetate depot injection (group 1) or in the mid-luteal phase (group 2). Once gonadotropin suppression was confirmed, the dose was reduced to 0.25 to 0.5 mg/d s.c., and exogenous gonadotropin stimulation was initiated. Other patients received a microdose flare regimen as described elsewhere (16).

The specific regimen and gonadotropin dose to be used was determined before randomization and based on the standard protocols of each institution. Human chorionic gonadotropin was administered when at least one follicle achieved a mean diameter of 19 mm and the participant's serum estradiol level was at least 500 pg/mL. Techniques and indications for oocyte aspiration, oocyte and embryo culture, insemination, ICSI, assisted hatching, and embryo transfer were based on the protocols specific to each center.

Ongoing pregnancy rates were defined as the presence of sonographically visualized cardiac activity per cycle initiated. Implantation rates were defined as the number of sonographically visualized fetal poles with cardiac activity per number of embryos transferred. A biochemical pregnancy was defined as a serum hCG level greater than 5 mIU/mL measured 14 days after oocyte retrieval, with no subsequent sonographic evidence of a fetal pole with cardiac activity.

Data were evaluated by using the Student group *t*-test and χ^2 analyses, with correction factors where appropriate. Unless otherwise indicated, the results are expressed as the mean (±SE). $P<.05$ was considered statistically significant.

RESULTS

Table 1 shows baseline clinical data on all patients. Groups 1 and 2 did not differ significantly in terms of age, early follicular phase serum FSH or estradiol level, interval between the most recent surgical intervention and cycle onset, surgical technique used, or endometriosis score. However, a significantly greater proportion of group 1 patients

TABLE 2

Outcome of controlled ovarian hyperstimulation.

Group	Gonadotropin dose (75-IU ampules)	Duration (d)	No. of oocytes retrieved	Fertilization rate (%)	No. of embryos transferred
1	42.4 ± 3.21	10.12 ± 0.43	14.84 ± 1.5	63.34 ± 3.79	3.28 ± 0.19
2	43.2 ± 2.5	10.08 ± 0.21	15.23 ± 1.56	61.85 ± 4.42	3.04 ± 0.2

Note: Results are expressed as the mean (±SE) unless otherwise indicated.

Surrey. GnRH agonist, endometriosis, and IVF-ET. Fertil Steril 2002.

than group 2 patients had stages III or IV endometriosis according to revised American Society for Reproductive Medicine scoring ($P<.05$) (17).

Table 2 shows outcomes of controlled ovarian hyperstimulation. The groups did not differ with regard to total gonadotropin dose or days of administration, stimulation regimen, number of oocytes obtained, fertilization rate, or number of embryos transferred. The proportions of patients undergoing standard down-regulation or microdose flare controlled ovarian hyperstimulation, ICSI, assisted hatching, or day 3 vs. 5 embryo transfer were similar between the groups.

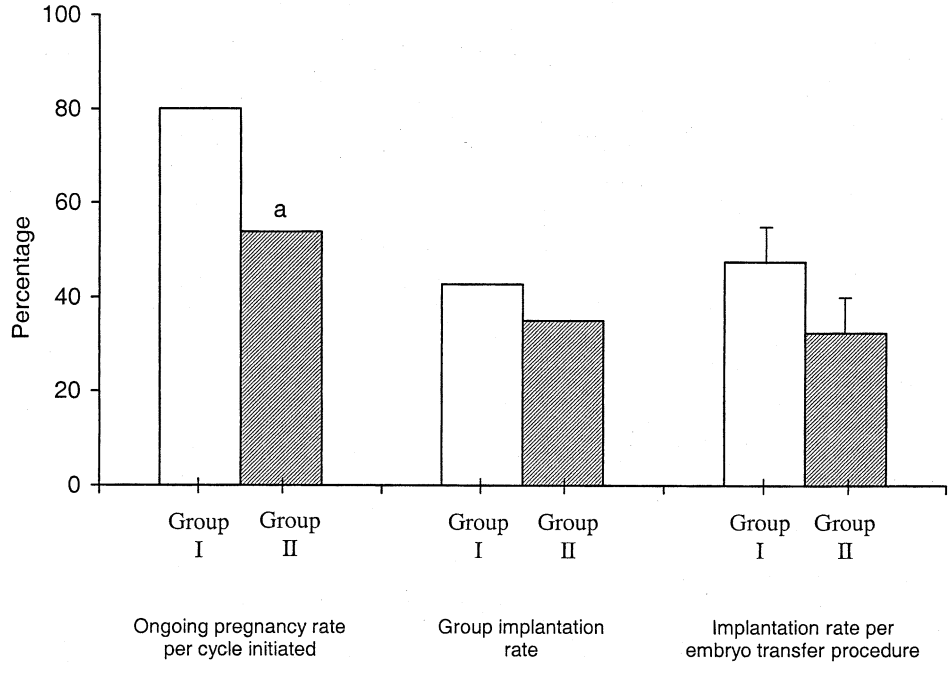
Figure 1 shows results of ET. Patients in group 1 had a significantly higher ongoing pregnancy rate. Trends toward higher group implantation rates and implantation rates per embryo transfer procedure were not statistically significant. The percentage of patients with positive pregnancy tests who had biochemical pregnancies only did not significantly differ between group 1 and group 2 (12.5% vs. 7.6%).

DISCUSSION

In this randomized, multicenter trial, we found that administration of GnRH agonist for 3 months before controlled ovarian hyperstimulation in infertile patients with endometriosis resulted in significantly higher ongoing pregnancy

FIGURE 1

Ongoing pregnancy rates per cycle, group implantation rates, and mean (±SE) implantation rates per embryo transfer procedure in the two treatment groups. [a]$P\leq.05$ vs. group 1.



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rates after IVF-ET than did standard controlled ovarian hyperstimulation alone in similar patients. A trend toward increased implantation rates was also observed in the former group.

Despite prolonged gonadotropin suppression produced in group 1, the groups did not differ in terms of overall gonadotropin dose or days of controlled ovarian hyperstimulation. Of note, the average age in both groups was relatively young (33.12 ± 0.67 years [range, 28–39 years] in group 1 and 32.58 ± 0.56 years [range, 27–39 years] in group 2). Patients with endometriosis who have diminished ovarian reserve, those who were previous poor responders, and those older than 40 years of age may not respond as well to prolonged GnRH agonist therapy. Further investigation is needed.

The degree of surgically documented endometriosis was more extensive in group 1 than in group 2. The impact of this phenomenon as an independent variable affecting the outcome of IVF-ET is controversial. Several investigators have reported that the stage of endometriosis has no effect on pregnancy rates compared with controls with tubal disease (1, 2, 18). Others have reported that patients with stage III or IV endometriosis have a poorer outcome after assisted reproductive technology procedures than do matched controls (19, 20). The data presented in the current investigation suggest that even if this negative impact occurred, it could not be a contributing factor in the higher ongoing pregnancy rates reported in this patient group; rather, it would decrease pregnancy rates. We could not evaluate the question of whether prolonged GnRH agonist therapy may be more beneficial in patients with more extensive disease because our sample of patients with each stage of disease was small and pregnancy rates in all patients in group 1 were high.

Other investigators using diverse study designs and protocols have reported similarly beneficial outcomes with prolonged GnRH agonist therapy in patients with endometriosis (13–15, 21–23). Dicker et al. described 31 patients with stage III or IV endometriosis in whom IVF-ET had previously failed. These patients received a GnRH agonist for 6 months before a subsequent IVF-ET cycle, resulting in increased oocyte yield and a 30% pregnancy rate per cycle (13). In a nonrandomized trial, Nakamura et al. compared outcomes in patients who received a GnRH agonist for at least 60 days before ovarian stimulation. The investigators reported a need for greater gonadotropin doses but significantly higher pregnancy rates than in patients who received a standard mid-luteal GnRH agonist down-regulation protocol (14).

Curtis et al. noted that IVF-ET pregnancy rates in patients with endometriosis who were pretreated with a GnRH agonist for at least 6 weeks were similar to those in patients with tubal factor infertility (21). No control group of untreated patients with endometriosis was used in that study. In a semi-randomized study, Marcus and Edwards also reported significantly higher pregnancy rates at IVF-ET for 15 patients with endometriosis who received a GnRH agonist for 2 to 7 months compared with 69 controls (15). Success appeared to be greater with at least 4 months of agonist pretreatment, but the small number of patients evaluated for varying treatment intervals precludes definitive analysis.

Two prospective randomized trials have examined this topic. Remorgida et al. evaluated 60 patients with stage I or II endometriosis who were to undergo gamete intrafallopian transfer. Twenty patients pretreated with a GnRH agonist for 6 months demonstrated a nonsignificant trend toward higher pregnancy rates compared with two control groups of patients with endometriosis who underwent standard down-regulation or received no agonist (22).

Dicker et al. performed a similar study in 67 patients with stage II endometriosis who were undergoing IVF-ET (23). Thirty-five patients received a GnRH agonist for 6 months and achieved a significantly higher clinical pregnancy rate than did controls. However, the extraordinarily low pregnancy rates in the control group (3.9%) makes interpretation of the results difficult.

We chose to pretreat study patients with a long-acting GnRH agonist every 28 days for 3 months before initiation of controlled ovarian hyperstimulation to enhance patient compliance. One investigative team has also reported that initial pain relief scores were similar after 3 or 6 months of GnRH agonist treatment in patients with symptomatic endometriosis; however, that study did not examine fertility (24). In a retrospective study, Caruso et al. reported that pregnancy rates after IVF-ET or intrauterine insemination were similar in patients with endometriosis who were pretreated with a GnRH agonist for 10 to 90 days or greater than 90 days, but rates were significantly higher than those in patients treated for less than 10 days before gonadotropin stimulation (25). This finding suggests that treatment of IVF-ET patients for more than 90 days would not be advantageous. Whether a shorter treatment interval would be efficacious has not been studied.

The mechanism of action of GnRH agonist in our study can be hypothesized. Although GnRH agonists appear to have no direct effect on endometrial tissue (26), several investigative teams have demonstrated other beneficial effects that may increase fecundity in patients with endometriosis (9, 11, 27). Taketani et al. demonstrated that peritoneal fluid concentrations of interleukin-1 and tumor necrosis factor in patients with endometriosis who were treated with danazol or a GnRH agonist were suppressed to values less than those in untreated controls (9). The toxicity of this fluid on the mouse embryo noted in controls was virtually undetectable in the fluid of the treated patients. A beneficial effect of GnRH agonist therapy on natural killer cell activity has also been reported (27).

Sharpe-Timms et al. demonstrated that attenuated serum metalloproteinase-I concentrations in patients with endome-

triosis were restored after agonist administration (10). Imai et al. showed that the significant reduction in endometrial cell apoptosis in tissue obtained from patients with endometriosis was reduced by exposure to GnRH agonists (28). This may affect decreased endometrial cell survival. In a nonrandomized trial, Lessey et al. reported that administration of a GnRH agonist had a more beneficial effect on restoring endometrial $\alpha v\beta_3$ integrin expression, a purported marker of uterine receptivity, in patients with endometriosis compared with those managed expectantly or with laser ablation (11). This may explain the trend toward higher implantation rates in the pretreated group.

However, several well-designed studies have shown that traditional medical therapies for endometriosis do not improve spontaneous pregnancy rates in infertile women with endometriosis (12, 29, 30). It is possible that the aforementioned proposed benefits of prolonged GnRH agonist therapy have a limited duration. Once medication is discontinued, the pathologic processes associated with the disease may be reinitiated by the time ovulation resumes and natural conception could occur, even though the patient may remain asymptomatic. Performance of IVF-ET immediately after prolonged medical therapy, when endometriosis and the associated hostile peritoneal environment is maximally suppressed, may allow the patient the greatest chance of conception.

In conclusion, administration of a GnRH agonist for 3 months before IVF-ET in the infertile patients with endometriosis had no deleterious effect on ovarian response to exogenous gonadotropins. Although prolonged GnRH agonist therapy was administered to patients with more severe disease, significantly higher ongoing pregnancy rates and a trend toward higher implantation rates were observed. Given that pregnancy rates were also high in the control group, it is not clear which patients with endometriosis would consistently benefit from this approach. A larger sample is needed, and future studies should ideally be performed in conjunction with evaluation of the role of endometrial receptivity markers.

Acknowledgments: The authors thank the research, nursing and embryology staffs of the Colorado Center for Reproductive Medicine, Texas Fertility Center, and Reproductive Medicine and Surgery Associates for invaluable assistance and support and Ron Arzaga for typing the manuscript.

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