Infertility treatment by in vitro fertilization in patients with minimal or mild endometriosis

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Summary

Purpose: To estimate the clinical effectiveness of in vitro fertilization treatment in patients with minimal or mild endometriosis (stages I and II) in comparison to the patients with tubal infertility in terms of fertilization, pregnancy and livebirth rates.

Methods: Retrospective analysis of the outcome of IVF-ET in 612 cycles of the patients with endometriosis (389 stimulated with HMG/HCG and 223 co-treated with GnRH-a) and in 7,339 cycles of the patients with tubal infertility (5,520 stimulated with HMG/HCG and 1,819 co-treated with GnRH-a).

Results: Regardless of the type of ovarian stimulation, the fertilization rate per treated cycle was practically the same in both groups (endometriosis 81.4% vs tubal infertility 84.2%; p=0.07). However, in the endometriosis group the pregnancy rate was higher (25.3% vs 18.9%; p=0.000), and so was the livebirth rate (19.0% vs 14.2%; p=0.003).

Considering the type of ovarian stimulation, the fertilization rate in the endometriosis group was almost the same in the HMG/HCG (81.2%) and in the GnRH-a co-treated cycles (81.6%), and did not differ from that in the tubal infertility group (83.6% in the HMG/HCG vs 85.9% in the GnRH-a cycles). In the GnRH-a co-treated cycles the pregnancy rate and the livebirth rate were not significantly higher in the endometriosis group than in the tubal infertility group (27% and 20.2% vs 22.2% and 17.5%). In the HMG/HCG stimulated cycles the pregnancy rate was significantly higher in the endometriosis than in the tubal infertility group (24.3% vs 17.7%; p=0.004), and so was the livebirth rate (18.4% vs 13.0%; p=0.008).

Conclusion: In patients with minimal or mild endometriosis the IVF-ET procedure is at least as effective as in patients with tubal infertility.

Key words: Minimal endometriosis; Mild endometriosis; IVF-ET outcome

Introduction

In women with severe endometriosis the presence of structural changes and of ovarian and tubal adhesions prevents oocyte release and transport, and leads to mechanical disruption and infertility. In cases of minimal or mild endometriosis and no apparent structural damage, the etiologic basis for infertility is unclear. Various factors have been proposed: endocrine, immunologic and inflammatory, and the treatment has been adjusted accordingly. When after an adequate treatment period conception does not occur, the IVF-ET procedure is considered.

In order to estimate the clinical effectiveness of the IVF-ET procedure in patients with minimal and in those with mild endometriosis we analyzed the clinical data and results of treatment and compared them to those obtained in the patients undergoing IVF-ET for pure tubal infertility.

Materials and Methods

Retrospectively we analyzed the effectiveness of IVF-ET treatment in patients with endometriosis stages I and II and in those with tubal infertility in cycles performed in the period 1990-1999.

The inclusion criteria for the endometriosis group were laparoscopically confirmed endometriosis stage I or II according to the American Fertility Society classification [1], regular menstrual cycle, partner's normal sperm count, and normal levels of prolactin, FSH and LH.

The inclusion criteria for the tubal infertility group were incurably damaged or removed fallopian tubes, partner's normal sperm count, and normal levels of prolactin, FSH and LH.

The clinical effectiveness of the IVF-ET procedure was additionally analyzed according to the type of ovarian stimulation - the human menopausal gonadotropin (HMG) and human chorionic gonadotropin (HCG) stimulation protocol versus the GnRH-analogue (GnRH-a) co-treatment long protocol.

In both groups the indication for the GnRH-a co-treatment was at least one unsuccessful ovarian stimulation for IVF-ET.

The patients treated by the HMG protocol were administered a standard dose of HMG (Pergonal, Laboratoires Serono S.A., Aubonne, Switzerland) three ampoules per day for the first three days of the treatment cycle, followed by individually adjusted doses according to day-to-day changes in estradiol (E2) concentration and ultrasound follicular and endometrial appearance. HCG (Primogonyl, Schering AG, Berlin, Germany) 10,000 IU was administered when the dominant follicle reached a mean diameter of >17 mm, endometrial thickness of > 7 mm, and the E_2 level of at least 0.40 nmol/l.

The GnRH-a long protocol was started on day 22 of the cycle when Suprefact (Hoechst AG, Frankfurt/Main, Germany), in a daily dose of 0.6 ml s.c., was applied for 15 consecutive days. If serum E_2 levels decreased to <0.05 nmol/l and follicles were ≤ 5 mm in diameter, ovarian stimulation with HMG was started and the same parameters were considered as in the conventional HMG protocol.

The only difference between the two protocols was in a higher initial dose administered in GnRH-a co-treated cycles, i.e. four ampoules per day for the first three days of therapy.

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The monitoring of follicular and endometrial development was performed by vaginal ultrasound (Bruel and Kjaer, Gentofte, Denmark).

Concentrations of E_2 were determined with radioimmunoassay commercial kits (Sorin, Biomedica, Sallugia, Italy). Normal values for serum E_2 are 0.09-0.37 nmol/l in the follicular phase and 0.18-1.65 nmol/l in the preovulatory peak.

In the endometriosis group a total of 612 cycles were analyzed: 389 cycles were stimulated with the HMG/HCG protocol, and 223 cycles with GnRH-a co-treatment.

In the tubal infertility group 7,339 cycles were analyzed, of which 5,520 were stimulated with HMG/HCG, and in 1,819 cycles GnRH-a co-treatment was applied.

The comparison of the effectiveness of the IVF-ET procedure between the two groups was calculated considering the number of oocytes retrieved and fertilized, number of embryos transferred, pregnancy and livebirth rates.

Statistical analysis of the data for testing the significance of differences between the mean values was performed using the t-test and Chi-square test (Statistic package SPSS), and Mann-Whitney U test.

Results

The mean patient age did not differ between the groups (p=0.07).

The E_2 level before HCG administration did not differ between the groups, whereas the number of HMG vials used was higher in the endometriosis group.

Regardless of the type of ovarian stimulation, the fertilization rate per treated cycle was practically the same in both groups (p=0.07). However, in the endometriosis group the pregnancy rate was higher (p=0.000), and so was the livebirth rate (p=0.003) (Table 1).

Table 1. — *Clinical data and results of the IVF-ET procedure in patients with endometriosis and tubal infertility regardless of the type of ovarian stimulation.*

	Endometriosis	Tubal infertility	Difference (p)
Age (years)	33.9±4.1	33.5±4.1	0.069
No. of cycles	612	7339	
No. of HMG vials	22.2±9.7	20.2±9.0	0.000
Mean E_2 level (nmol/l)	4.22±3.35	4.25±3.31	0.951
No. of oocytes	5.0±3.6	4.9±3.4	0.617
No. of fertilized oocytes	2.6±2.3	2.7±2.2	0.041
No. of embryos	1.8±1.4	2.1±1.5	0.000
Fertilization rate/cycle	81.4%	84.2%	0.0740
Pregnancy rate/ET	25.3%	18.9%	0.0006
Livebirth rate/ET	19.0%	14.2%	0.0030
Ectopic rate/ET	0.41%	0.66%	0.514
Miscarriage rate/ET	5.80%	4.05%	0.045

Considering the type of ovarian stimulation, the fertilization rate in the endometriosis group was almost the same in the HMG/HCG (81.2%) and in the GnRH-a co-treated cycles (81.6%), and did not differ from that in the tubal infertility group (83.6% in the HMG/HCG vs 85.9% in the GnRH-a cycles).

The pregnancy rate and the livebirth rate in the GnRH-a co-treated cycles were almost the same in the two groups. The pregnancy rate in the HMG/HCG cycles, however, was significantly higher in the endometriosis than in the tubal infertility group (0.004), and so was the livebirth rate (p=0.008) (Tables 2 and 3).

Table 2. — *Clinical data and results of the IVF-ET procedure in patients with endometriosis and tubal infertility co-treated with GnRH-analogues.*

	Endometriosis	Tubal infertility	Difference (p)
Age (years)	34.8±4.2	35.1±4.1	0.233
No. of cycles	223	1819	
No. of HMG vials	4.91±4.14	5.40±4.39	0.293
Mean E_2 level (nmol/l)	31.6±9.6	30.1±10.1	0.009
No. of oocytes	5.4±4.0	5.5±3.7	0.447
No. of fertilized oocytes	2.9±2.6	3.1±2.5	0.116
No. of embryos	1.9±1.6	2.1±1.4	0.031
Fertilization rate/cycle	81.6%	85.9%	0.0890
Pregnancy rate/ET	27.0%	22.2%	0.155
Livebirth rate/ET	20.2%	17.5%	0.372
Ectopic rate/ET	0	0.59%	0.304
Miscarriage rate/ET	6.7%	4.1%	0.109

Table 3. — *Clinical data and results of the IVF-ET procedure in patients with endometriosis and tubal infertility treated with HMG+HCG.*

	Endometriosis	Tubal infertility	Difference (p)
Age (years)	33.4±3.9	33.0±3.9	0.122
No. of cycles	389	5520	
No. of HMG vials	16.8±4.0	17.0±5.6	0.774
Mean E_2 level (nmol/l)	3.80±2.70	3.84±2.72	0.831
No. of oocytes	4.8±3.3	4.7±3.3	0.625
No. of fertilized oocytes	2.4±2.1	2.6±2.1	0.044
No. of embryos	1.8±1.3	2.1±1.6	0.002
Fertilization rate/cycle	81.2%	83.6%	0.338
Pregnancy rate/ET	24.3%	17.7%	0.004
Livebirth rate/ET	18.4%	13.0%	0.008
Ectopic rate/ET	0.66%	0.68%	0.952
Miscarriage rate/ET	5.2%	4.0%	0.297

Discussion

In women with minimal or mild endometriosis the precise relationship between endometriosis and infertility remains unclear. Some authors have proposed impaired folliculogenesis and ovulation [2,3] or luteinized unruptured follicle syndrome [4] and luteal phase defect [5] as a potential cause of infertility. While in some cases induction of ovulation resolves the problems of infertility, there remains a group of patients who do not respond to the therapy. The observation of inflammatory changes in the peritoneal fluid, an increase of macrophage number and activity, higher levels of cytokines and prostanoids are considered as antigenic stimuli, impairing fertility by a direct cytotoxic effect on the oocyte, spermatozoa and embryo. Following medical treatment of endometriosis no improvement in fecundability has been registered [3].

In cases refractory to the conventional infertility treatment, the IVF-ET procedure enables controlled ovarian hyperstimulation, thus surpassing ovulation impairment as a possible cause of infertility since in vitro fertilization

avoids hostile peritoneal and/or tubal environment, while luteal supplementation avoids luteal phase defects.

Our results obtained from the patients with minimal or mild endometriosis confirm the idea of an inadequate tubal environment present in endometriotic patients. Considering the fact that all patients with endometriosis had normal results of previous ovulatory cycles it seems that changes in the tubal or peritoneal environment could contribute to infertility.

In HMG/HCG treated patients the fertilization rate per cycle was comparable between the two groups (endometriosis 81.2% vs 83.6% tubal infertility). Moreover, the pregnancy rate and the livebirth rate were higher in the endometriosis group. In the GnRH-a co-treated patients the fertilization rate was the same in both groups, and so were the pregnancy and livebirth rates.

Our results are in agreement with those of Ledger [6] who found that both in vitro fertilization and intrauterine insemination improve fertility in mild and moderate endometriosis.

In our study we evaluated the outcome of treatment in patients with normal ovarian response. Patients with endometriosis or tubal infertility, without other pathologic findings, are usually considered as normal responders. However, pure tubal infertility may often involve patients with subclinical forms of polycystic ovaries (PCO). These patients represent a diagnostic and therapeutic problem due to no evident hormonal or menstrual disorders. Ovarian overreaction becomes evident only during ovarian stimulation. According to Jacobs, PCO may be asymptomatic in healthy women, but if the reproductive axis is stressed, the clinical expression of the condition may become clinically evident [7]. In one of our previous studies we confirmed the existence of subclinical PCO, manifested as exaggerated E_2 concentrations and multiple follicle development, only after the introduction of ovarian stimulation [8]. By taking this issue into consideration, we can explain a higher fertilization rate, although not significantly higher, achieved in the patients with tubal infertility following the GnRH-a stimulation protocol.

The situation is different in the patients with endometriosis stages III and IV. Azem *et al.* [9] compared the outcome of the IVF-ET procedure between the patients with endometriosis stages III and IV and those with tubal infertility and found that the former had a poorer IVF outcome in terms of fertilization rate (40% vs 70%), pregnancy rate (10.6% vs 22.4%) and livebirth rate per cycle (6.7% vs 16.6%).

In ovarian endometriosis Al Azemi *et al.* [10] registered a significantly poorer ovarian response than in women with tubal infertility undergoing the IVF procedure. However, the cumulative pregnancy and livebirth rates were similar in both groups, thus confirming that ovarian endometriosis does not decrease the chances of successful IVF treatment.

The results of this study show that in patients with minimal or mild endometriosis the fertilization rate does not differ significantly from that in patients with tubal infertility. Once the oocyte is fertilized and cleaved, the possibility of implantation and the normal development of the embryo is the same as in the patients with tubal infertility. Therefore, we may conclude that patients with minimal or mild endometriosis undergoing the IVF-ET procedure have approximately the same chance of a successful outcome of treatment as patients with tubal infertility.

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