

Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation–intrauterine insemination or in vitro fertilization–embryo transfer

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Objective: To compare controlled ovarian hyperstimulation–intrauterine insemination (COH-IUI) or IVF-ET pregnancy rates per cycle (PR) and cycle and cumulative fecundity (f and cf) with COH-IUI or IVF-ET in endometriosis.

Design: Retrospective analysis.

Setting: Endometriosis research institute.

Patient(s): Women with endometriosis and infertility (n = 313) who underwent consecutive COH-IUI (202 patients, 648 cycles), IVF-ET (111 patients, 139 cycles), or IVF-ET after failed COH-IUI (56 patients, 68 cycles).

Intervention(s): None.

Main Outcome Measure(s): Crude PR and life table–estimated f and cf.

Result(s): With COH-IUI, 69 patients conceived; 65 conceived with IVF-ET; and 30 conceived with IVF-ET after COH-IUI (PR 11%, 47%, and 44%). With COH-IUI, six-cycle cf was 41%, and f for cycles 1–6 was 15%, 12%, 8%, 7%, 7%, and 0. With IVF-ET, three-cycle cf was 73%, whereas f for cycles 1–3 was 47%, 27%, and 33%. First-cycle f with IVF-ET was significantly higher than cf of six COH-IUI cycles. When the data were stratified according to the stage of endometriosis and women's age, the benefit of IVF over COH was even more pronounced. Prior COH-IUI failure did not adversely affect IVF-ET outcome.

Conclusion(s): In endometriosis, PR, f, and cf are significantly higher with IVF-ET than COH-IUI, especially in stage IV and in women >38 years of age. Considering adverse effects of prolonged ovarian stimulation on endometriosis, IVF-ET should be the first-line approach in the management of infertility in this disease. If COH-IUI is attempted, it should not exceed three to four cycles. (*Fertil Steril*® 2002;78:750–6. ©2002 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, infertility, fecundity, pregnancy, COH-IUI, IVF-ET

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The effect of endometriosis on fertility and the mechanisms involved are unclear and frequently questioned. It is generally accepted that fertility in stage III–IV endometriosis is impaired, but not necessarily so in stages I and II. Several comparative studies in women undergoing donor insemination for male-factor infertility indicate that cycle-specific fecundity rates in stage I or II endometriosis are between 2% and 6.5%, much lower than the corresponding fecundity rates of 11% to 14% for controls (1, 2). In another report, spontaneous monthly

fecundity rate in stage I–II endometriosis was 2.52% (3). Furthermore, in a cohort follow-up study of 312 couples with untreated endometriosis of different stages, spontaneous live births per 100 months were 0.68 for stage I and II, 0.10 for stage III and IV, and 0.52 overall (4).

After laparoscopic resection and ablation of stage I–II endometriosis, monthly fecundity rate in a randomized control trial was 4.7%, as compared with 2.4% for women who underwent only a diagnostic procedure (5). The in-

MATERIALS AND METHODS

crease in fecundity rates after medical treatment of stage I–II endometriosis appears to be comparable. Although life table analysis was not used, the average monthly pregnancy rate after medical treatment of stage I–II disease can be estimated as ranging between 2.3% and 6.3% (6). Altogether, these studies clearly indicate impaired fertility in women with endometriosis regardless of stage. They also suggest that resection or suppression of endometriosis only partially improves fertility.

During the past 2 decades, numerous studies have reported alterations in the peritoneal environment in women with endometriosis and suggested that these changes may have an adverse effect on fertility (7). It has been proposed that secretory products of the ectopic endometrial and/or immune cells interfere with ovulation, endocrine function, gamete and embryo transport, oocyte fertilization, and embryo development and implantation (8). Substances implicated as having an antifertility effect have been variously identified as cytokines, growth factors, prostaglandins, reactive oxygen species, autoantibodies, and so on. It is clear that some of these putative mechanisms of infertility in endometriosis may be corrected by controlled ovarian hyperstimulation (COH)–IUI, but others may require replacement of the adverse *in vivo* peritoneal environment by a presumably better controlled *in vitro* environment of the laboratory.

COH-IUI improves endocrine environment, corrects ovulatory dysfunction, and facilitates sperm transport. It has been used routinely in the management of infertility in women with endometriosis. A meta-analysis of 962 cycles of COH-IUI in endometriosis demonstrated a monthly fecundity rate of 13% in stage I–II and 8% in stage II–IV (9), much higher than the rates reported after medical or surgical treatment of the disease. Tummon et al. (10) in a randomized controlled trial compared the effect of COH-IUI against no treatment in women with stage I–II endometriosis. Live birth rate was 11% per cycle for COH-IUI as compared with 2% for controls.

A more complex IVF-ET procedure corrects not only the endocrine and ovulatory dysfunctions but also replaces abnormal ovum pickup and gamete transport mechanisms, compensates for abnormal fertilization, and eliminates potentially adverse effects of the intraperitoneal environment on fertility. In agreement with the concept that it is the adverse intraperitoneal environment that impairs fertility, the results of IVF-ET have been comparable in women with and without endometriosis (11).

The objective of this study was to compare crude pregnancy rates and life table–estimated cumulative and cycle-specific fecundity rates in women with endometriosis undergoing COH-IUI or IVF-ET at our institute. The effect of women's age and stage of endometriosis and of embryo cryopreservation and male factor were also considered in the analysis.

The subjects in this study included 313 women of reproductive age with endometriosis and infertility who underwent consecutive COH-IUI or IVF-ET cycles between January 1997 and November 2001 at our facilities. The data were obtained from the medical records, and the only patients excluded from the study were those using donor gametes. There were 202 women who underwent 648 COH-IUI cycles and 111 women who underwent 139 IVF-ET cycles. Included in these numbers were 56 women who failed COH-IUI and underwent 68 IVF-ET cycles. Patient characteristics are listed in Table 1. There were no significant differences in any of the characteristics between the groups, except for the E₂ level at the time of hCG administration and the distribution of stages II and IV endometriosis.

Estradiol levels at the time of hCG were significantly higher in the IVF than COH groups. Stage II endometriosis was more frequent in COH and stage IV in the IVF group ($P < .05$). There was no difference in age distribution according to the stage of the disease between the groups. Endometriosis was diagnosed and staged at our facility or by the referring physicians according to the revised American Society for Reproductive Medicine classification (12). Last surgical and/or medical treatment and staging of endometriosis had been performed between 3 months and 5 years before the study.

Complete resection of endometriosis and adhesions was attempted in all cases. If resection was incomplete, and especially if residual adhesive disease was present, IVF-ET rather than COH-IUI was performed. At the time of the study, all patients had recurrent symptoms and/or findings clinically suggestive of active endometriosis. Endometriomas were either resected laparoscopically before the ovarian stimulation or, in two cases, were aspirated using a transvaginal ultrasound-guided approach. Ovarian stimulation for COH-IUI and IVF-ET was performed according to the standard protocols (9, 13).

In both COH-IUI and IVF-ET cycles, couples with male factor were included. However, severe male factor was one of the indications for IVF-ET as a primary approach. These couples underwent intracytoplasmic sperm injection (ICSI) during the IVF-ET cycle. COH-IUI was typically performed as the initial treatment in women who had hysterosalpingographic evidence of tubal patency unless the couple had previously failed repeated COH-IUI attempts; the female had severe endometriosis, extensive adhesive disease, or tubal changes; or severe male factor existed. Pregnancy was defined as an elevated β -hCG with a gestational sac on transvaginal sonography. All pregnancies minus spontaneous abortions were live births, with the exception of 5 in COH and 11 in the IVF group that were 20+ weeks at the time of this report and are ongoing.

Statistical analysis was performed with the *t* test for

TABLE 1

Patient characteristics.

Parameter	Treatment cycle		
	COH-IUI	IVF-ET	IVF after COH
Patients/cycles	202/648	111/139	56/98
Mean age (range)	34 (21–43)	33 (23–43)	34 (23–43)
Years of infertility (mean)	3.3	4.3	4
Months since first diagnosis (mean)	46	38	30
Months since last surgery (mean)	43	38	46
% Stage distribution at last surgery (%)			
Stage I	19	21	25
Stage II	54	44 ^a	56
Stage III	19	15	8
Stage IV	8	20 ^a	11
Months since last medical treatment (mean)	25	24	20
No. nullipara (%)	80 (40)	49 (44)	27 (48)
No. patients without significant male factor	172	85	36
Mean E ₂ @ HCG (pg/mL)	644	1,499 ^a	1,585 ^a

^a Significant difference at $P < .05$ as compared with COH-IUI group.

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parametric data or χ^2 test for categorical data. Cycle and cumulative fecundity rates were calculated using Cramer's life table analysis (14). The starting point for life table analysis was the beginning of the stimulation cycle, and the end point was pregnancy. Statistical significance was set at $P < .05$.

RESULTS

The overall results are demonstrated in Table 2. Crude pregnancy rates per cycle were significantly higher in all IVF-ET groups than COH-IUI groups. There was no difference between the groups in the frequency of spontaneous abortions. The frequency of twins was higher in the IVF

group (12 of 65 vs. 3 of 69). There were four triplet and one quadruplet gestations (resulting from a split embryo) in the IVF and three triplet and one quadruplet gestations in the COH group.

We transferred between two and three embryos during IVF-ET cycles, and implantation rates per embryo are listed in Table 2. Embryo implantation rates were significantly higher ($P < .05$) than per-cycle COH-IUI pregnancy rates. If embryo cryopreservation and subsequent transfers are considered, per-cycle IVF-ET pregnancy rate was 51%. When couples with a significant male factor were excluded, there was no change in COH-IUI pregnancy rates (11%), but IVF-ET pregnancy rates increased to 51%.

TABLE 2

Pregnancy rates and outcome according to treatment.

Treatment group	No. patients	No. cycles	No. (%) pregnant	No. embryos transferred (mean)	Implantation rate (%)	% Multiple gestation	No. SAB (%)
COH-IUI	202	648	69 (11)	N/A	N/A	10	18 (26)
IVF-ET	111	139	65 (47) ^a	2.9	27 ^a	26	13 (20)
IVF after COH	56	68	30 (44) ^a	3.1	23 ^a	27	5 (17)
IVF-ET + FUET	111	139	71 (51) ^a	2.8	23 ^a	25	13 (18)
Excluding significant male factor							
COH-IUI	172	534	58 (11)	N/A	N/A	8	10 (17)
IVF-ET	85	94	48 (51) ^a	2.8	29 ^a	26	7 (14)

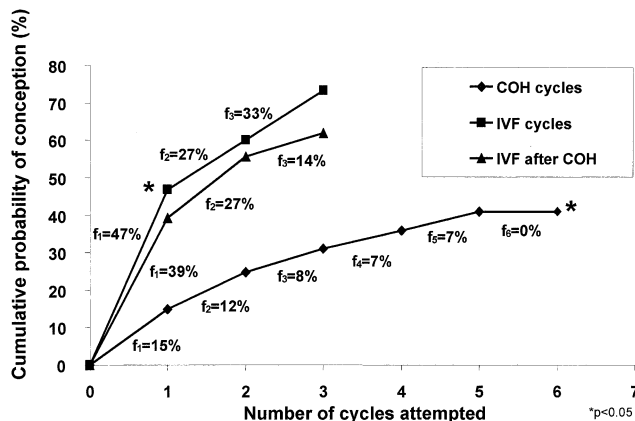
^a Significantly different than the corresponding COH-IUI group at $P < .05$.

SAB = spontaneous abortions; FUET = cryopreserved embryo transfer.

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FIGURE 1

Cycle and cumulative fecundity in women with endometriosis undergoing COH-IUI, IVF-ET, or IVF-ET after failed COH-IUI.



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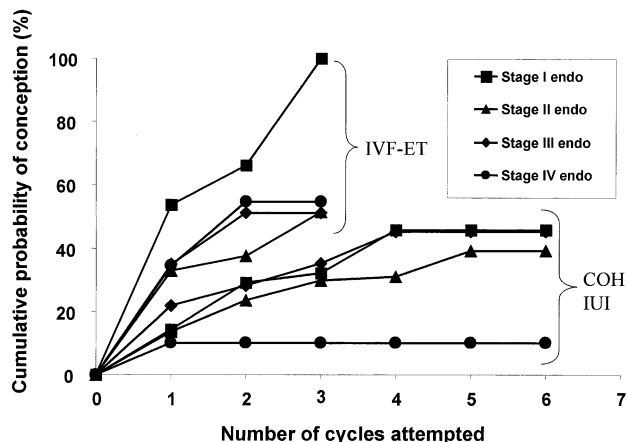
Life table—estimated cycle and cumulative fecundity rates for the main three groups are illustrated in Figure 1. Cycle 1–6 fecundity in the COH-IUI group was 15%, 12%, 8%, 7%, 7%, and 0, respectively, with six-cycle cumulative fecundity of 41%. There was a plateau effect after five cycles, and there were no pregnancies during the sixth cycle. Cycle 1–3 fecundity in the IVF-ET group was 47%, 27%, and 33%, respectively, with three-cycle cumulative fecundity of 73%. There was no evidence of a plateau. First-cycle fecundity with IVF-ET (47%) was significantly greater ($P < .05$) than was the cumulative fecundity after six COH-IUI cycles (41%). In patients who underwent IVF-ET after failed COH-IUI, cycle 1–3 fecundity was 39%, 27%, and 14%, respectively, with three-cycle cumulative fecundity of 62%. There was no significant difference between this group and the primary IVF-ET group, but the cycle and cumulative fecundity rates were higher than in the COH-IUI group.

When pregnancies with cryopreserved embryos were considered and when couples with a significant male factor were excluded, both cycle and cumulative fecundity rates were higher. For IVF-ET including cryopreserved embryos, cycle 1–3 fecundity was 50%, 30%, and 33%, respectively, with the three-cycle cumulative fecundity of 77%. For the IVF-ET group without male factor, the numbers were 46%, 31%, 50%, and 81%, respectively.

Cumulative fecundity rates in the COH and IVF groups, analyzed according to the stage of endometriosis, are demonstrated in Figure 2 and according to the age of the female in Figure 3. First-cycle fecundity in stage IV endometriosis was 10% with COH-IUI, and there were no conceptions during subsequent cycles (Fig. 2). With IVF-ET, stage IV fecundity during three cycles of observation was comparable to that of stages II and III. Cycle and cumulative fecundity in

FIGURE 2

Effect of COH-IUI or IVF-ET on fecundity according to the stage of endometriosis.



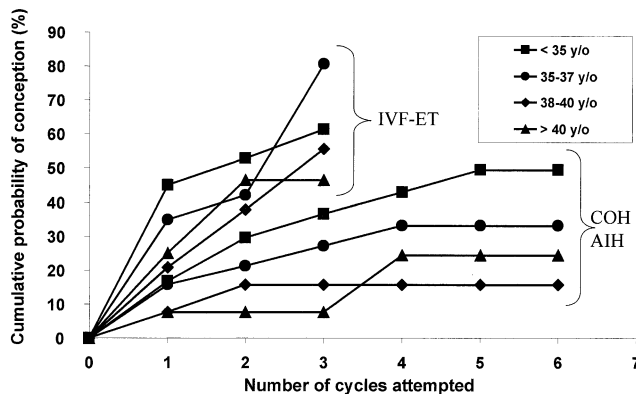
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women >38 years of age were below that of other age groups with COH-IUI (Fig. 3). With IVF-ET, there were no significant differences.

In an attempt to evaluate the effect of the time interval between the last medical or surgical treatment of endometriosis and COH-IUI or IVF-ET on the effectiveness of these procedures, we stratified our patients into the following groups: ≤ 6 months, 7–12 months, 13–18 months, 19–24 months, and >24 months from the last treatment. The data are demonstrated in Table 3. There were no significant differences in pregnancy rates according to different time

FIGURE 3

Effect of COH-IUI or IVF-ET on fecundity according to the age of the women with endometriosis.



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TABLE 3

The effects of time interval from last treatment on COH-IUI or IVF-ET success.

Endometriosis treatment	Interval to COH-IUI (mo)					Interval to IVF-ET (mo)				
	< 6	7–12	13–18	19–24	> 24	< 6	7–12	13–18	19–24	> 24
Surgical										
No. patients	76	44	25	24	33	15	32	16	12	36
No. cycles	261	152	89	45	101	16	36	20	19	48
No. pregnant	31	16	8	5	9	7	16	9	9	24
Pregnancy rate (%)	12	11	9	11	9	44	44	45	47	50
Medical										
No. patients	5	11	9	4	6	8	7	3	3	5
No. cycles	9	30	44	14	27	11	10	5	4	6
No. pregnant	1	2	0	1	1	5	5	2	1	4
Pregnancy rate (%)	11	7	0	7	4	45	50	40	25	67

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intervals between either the last medical or surgical treatment in either COH-IUI or IVF-ET groups.

DISCUSSION

The results of this study clearly indicate that the probability of conception in women with endometriosis and infertility is much greater with IVF-ET than during COH-IUI cycles. Our IVF-ET results were significantly better than those of COH-IUI regardless of whether crude pregnancy rates or life table cycle-specific or cumulative probability of conception were considered. Furthermore, both pregnancy rates and the estimated probability of conception during the first cycle of IVF-ET were significantly higher than those of six cycles of COH-IUI.

It can be argued that the presence of active endometriosis at the time of ovarian stimulation for COH-IUI or IVF-ET was not confirmed laparoscopically in our patients and that high IVF-ET success rates were actually a reflection of the absence of the active disease. However, the last surgical procedure performed was an average of 43 months before the study (range, 3–66 months), and last medical treatment was an average of 25 months (range, 2–49 months) before the study. At the time of COH-IUI or IVF-ET, all our patients had clinical evidence of endometriosis recurrence and were infertile. If active endometriosis were detrimental to the IVF-ET success, considering that endometriosis is a progressive disease, we would have seen a gradual decline in the IVF-ET success rates with an increasing time interval from the last endometriosis treatment. There was no adverse effect of time interval of ≤ 5 years (Table 3). There was also no detectable adverse effect in the COH-IUI group, although success rates were significantly lower in stage IV disease (Table 3; Fig. 3). Certainly, the increasing time interval from the last treatment in the COH-IUI group could have advanced the stage of the disease and moved some of the

patients to the IVF-ET group. Furthermore, although at the time of laparoscopic surgery an attempt was made to completely resect endometriosis in all patients, in some women, this resection was incomplete. There was also no apparent decrease in pregnancy rates in such cases.

We did not exclude from the analysis couples with a male factor. However, severe male factor was an indication for a primary IVF-ET approach with ICSI. If couples with a significant male factor are excluded from the analysis, the advantage of IVF-ET over COH-IUI becomes even more apparent, regardless of whether cycle-specific or cumulative fecundity or crude pregnancy rates are considered.

Most reports on IVF-ET success rates, including the annual Centers for Disease Control–Society for Assisted Reproductive Technology (SART) report (15), exclude from the analysis of fresh IVF cycles pregnancies achieved with embryos cryopreserved during that cycle and subsequently transferred. However, an argument can be made that these data should be considered in the analysis because embryo cryopreservation offers another chance for pregnancy to patients who either did not conceive during the fresh IVF cycle or want another pregnancy. In women with endometriosis, the advantage of cryopreserved embryo transfer is even more apparent because ovarian hyperstimulation, which may reactivate endometriosis, is not required. When cryopreserved–thawed embryo transfer was considered in our study, the cumulative probability of conception during three cycles of IVF-ET was 77%.

Our pregnancy rates with IVF-ET in women with endometriosis and the probability of conception, both cycle specific and cumulative, are comparable to pregnancy rates with IVF-ET reported in this disease by the leading centers and not different from those seen in other diagnostic entities (11, 16, 17). We evaluated IVF-ET fecundity rates during three consecutive cycles, and there was no indication of the

plateau effect. However, a decrease in the pregnancy rates after the fourth IVF-ET cycle was previously reported by Meldrum et al. (17).

The COH-IUI pregnancy rates in women with endometriosis reported here are comparable to those reported with the same approach by other investigators (9, 10, 18). The benefit of COH-IUI in our study began to level off after three to four cycles of treatment and was negligible during the sixth cycle. This is consistent with the previous reports indicating a plateau effect after three to four cycles of COH-IUI (18). COH-IUI in our study was the most beneficial in women with early stages of endometriosis and was dismal in stage IV. COH-IUI results were also much lower in women >38 years of age than in those of younger age groups, regardless of the stage of disease. Therefore, if COH-IUI is to be attempted in women with endometriosis and infertility, it should preferably be limited to women <38 years of age, to those with early stages of the disease, and to no more than four cycles.

This study addressed exclusively the effectiveness of infertility management with two different approaches in women with endometriosis. The results were significantly better with IVF-ET than with COH-IUI, and with both approaches, the results were much better than those reported after medical or surgical treatment of endometriosis (5, 6). To our patients, even though they were symptomatic, the main objective was to conceive; the expectation was that pregnancy could have an ameliorating effect on endometriosis and its symptoms. There is no question that in women with symptomatic endometriosis in whom conception is not an issue, surgical resection or medical suppression of the disease is an appropriate treatment. Improved fertility after treatment in such cases would certainly provide an additional benefit. However, chances for spontaneous pregnancy would have to be weighed against the risk of endometriosis recurrence.

It is interesting to note that pregnancy rates in women with endometriosis undergoing COH-IUI or IVF-ET are much higher than those reported after surgical ablation or medical treatment of the disease. The above suggests that ovulatory dysfunction and, perhaps, abnormal sperm transport mechanisms corrected by the COH-IUI are significant infertility factors in endometriosis and that adverse effects of the peritoneal environment corrected by IVF-ET play an additional role. It could be argued that the increase in pregnancy rates with IVF-ET over COH-IUI is related to the fact that more than one embryo was transferred. However, when IVF-ET results are expressed as the implantation rate per embryo, the pregnancy rates remain significantly higher with IVF-ET than with COH-IUI. Moreover, a similar number of multiple pregnancies (other than twins) in the IVF and COH cycles indicate that it is not unusual, even with optimal monitoring, for more than one egg to be released during the COH-IUI cycles (19).

Serum E₂ levels at the time of hCG administration were significantly higher in the IVF-ET than COH-IUI cycles, and both were above the range of the preovulatory E₂ peak of spontaneous cycles. It has been suggested previously that peripheral E₂ concentrations, as well as the length of estrogen exposure, are directly related to the risk of endometriosis recurrence (20, 21). Ovarian stimulation therefore should be used judiciously in women with endometriosis. For this reason, the shortest course of ovarian stimulation, one that offers the highest probability of conception, would be most advantageous. There is no question that in this respect also, IVF-ET is superior to COH-IUI.

We conclude from our study that one cycle of IVF-ET offers a better probability of conception than do six COH-IUI cycles in women with endometriosis, regardless of the woman's age and stage of disease. In women >38 years of age or with stage III–IV endometriosis, in those with a significant adhesive or tubal disease, or in couples with a significant male factor, IVF-ET should be the first line of treatment. If an adverse effect of prolonged ovarian stimulation on the progression of endometriosis is considered and if there is an intent to limit the number of the stimulation cycles, this recommendation may be extended to all women with endometriosis and infertility. If COH-IUI is performed, the number of attempts should be limited to three or four.

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