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Effect of the Short Follicular Phase on Subsequent Conception

Key Words

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Follicle maturation
Pregnancy rates

Abstract

The present study was designed to evaluate whether there is a lower pregnancy rate in women with short follicular phases, as defined by attaining the peak estradiol level before day 11 of the cycle. Thirty-two early ovulators with mature follicles were matched with 32 women being treated for similar infertility problems, who ovulated between days 12-20. Pregnancies were achieved by 9 (28.1%) of the early ovulators compared to 19 (59.4%) of the controls. The mean number of cycles required to achieve a pregnancy was 8.6 in the early ovulators compared to 6.4 in the controls. Using the clinical life table method, the 12-month pregnancy rate was estimated to be 31.4% for early ovulators as compared to 66.3% for controls. Whether lengthening the follicular phase by drug treatment will improve pregnancy rates remains to be seen.

Introduction

Treatment of infertile women with documented luteal phase deficiencies (LPD) using exogenous progesterone (P) therapy has been shown to increase pregnancy rates as long as the dominant follicle is mature [1, 2]. Since follicular maturation appears to be an important factor in enhancing conception, we were interested in further studying the follicular maturation process in infertile women. Specifically, we questioned whether the length of time required to achieve follicular maturation effects pregnancy rates when all other known infertility factors remain constant, and the LPD has been corrected with P therapy.

Previous studies involving the menstrual cycle have demonstrated the adverse effect of long follicular phase [3] and luteal phase on pregnancy rates [4]. The present study was focused on the effect of a short follicular phase

on pregnancy. The pregnancy rates in women who attain follicular maturation before day 11 of their cycle, and who were considered to be early ovulators, were compared to the rates in women who have demonstrated mature follicles after day 11 of their cycle.

Materials and Methods

All patients included in this study were selected from a group of 1,000 consecutive patients registering for infertility therapy in one treatment center. Patients demonstrating an LPD (i.e. the results of two endometrial biopsies were out of phase by more than 2 days in two consecutive cycles) as one of their infertility factors were monitored to ascertain the pattern of their follicular maturation phase. Maturation of the follicle was defined as having attained on ultrasound an average diameter of at least 18 mm with a peak serum estradiol level of at least 200 pg/ml [2]. Women who demonstrated peak follicular maturation (highest follicular phase E₂ level) before day 11 in two consecutive menstrual cycles (with or without a follicle-matur-

ing drug, FMD) were identified as early ovulators and considered for inclusion in the study. Women who demonstrated peak follicular maturation after day 11 but before day 20 in two consecutive menstrual cycles were identified as 'normal' and considered for inclusion in the study as controls.

Patients were eliminated from the study if subsequent evaluation found evidence of tubal occlusion, extensive pelvic adhesions, stage 3 or more endometriosis or severe male factor (as defined by $< 5 \times 10^6$ /ml progressively motile sperm) unless therapeutic donor insemination was employed. Those requiring FMDs, e.g. clomiphene citrate, human menopausal gonadotropins or bromocriptine (used for hyperprolactinemia which was defined as the serum prolactin over 25 ng/ml), were eliminated if they formed more than one mature follicle in either of the first two cycles of evaluation.

The experimental design required that each early ovulator meeting the selection criteria for the study be matched with an eligible control on the basis of age, infertility factors, length of infertility, therapy administered and time of treatment in the center. Thus, each early ovulator and matching control differed only in the length of follicular phase and each had demonstrated maximum follicular maturation in two consecutive cycles.

From the 1,000 patients monitored, only 32 early ovulators meeting the selection criteria were identified. Each early ovulator was matched with a control, for a total of 64 patients who were monitored during the study. The patients were followed for ten additional cycles (after the first two with successful follicular maturation) unless they became pregnant or requested termination of therapy. Women with LPD were treated with exogenous P; some were also taking FMDs. Sonographic evaluation of follicular maturation was continued throughout the study to assure that the timing of follicular maturation for each patient remained constant during the course of the study.

Initial serum FSH levels were measured on days 2-3 of the follicular phase. Serum hormone levels (P, E₂, FSH and LH) were measured on the day of peak E₂ level. Serum E₂ and P levels were determined in all patients, but LH and FSH at midcycle and early follicular FSH levels were not obtained from some of the first patients included in the study.

Ultrasound examinations were performed by one of two experienced ultrasonographers using real-time ultrasound on an ATL ultra Mark 4 (Advanced Technology Laboratories, Bothell, Wash., USA) with a 3.5 MHZ abdominal transducer. Serum E₂ levels were measured by solid phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif., USA). Endometrial biopsies were performed utilizing the pipelle endometrial suction curette in the late luteal phase and were considered abnormal if the result was out of phase by more than 2 days in two consecutive cycles. The timing of ovulation was based on follicular maturation studies and serial serum LH levels. Ovulation was considered 12 h from the peak serum LH attained.

Serum P levels were measured using an immunoassay technique, based on enhanced luminescence (Amersham Corporation, Arlington Heights, Ill., USA), LH and FSH using a double antibody radioimmunoassay (Amersham) and chemiluminescence (Amersham Diagnostics, UK), respectively.

The clinical life table method was used to estimate the 12-month pregnancy rates for early ovulators and controls. These rates were compared by the log rank test using a probability level of 0.05. Average serum hormone levels between early ovulators and controls were compared using the paired t test with a probability level of 0.05.

Table 1. Distribution of infertility factors in 32 matched pairs

Infertility factors diagnosed	Pairs
<i>Primary infertility</i>	
LPD only	2
LPD and endometriosis	5
LPD and male factor	4
LPD and hyperprolactinemia	1
LPD, male factor, endometriosis	1
LPD, tubal cysts and/or adhesions	3
<i>Secondary infertility</i>	
LPD only	14
LPD and male factor	1
LPD and TDI	1

TDI = Therapeutic donor insemination.

Table 2. Description of therapy for study participants^a

Ovulation therapy ^a	Early ovulators (n = 32)		Controls (n = 32)	
	n	%	n	%
	P only	12	37.5	11
hMG	13	40.6	9	28.1
Clomiphene citrate	3	9.4	7	21.9
Combination	4	12.5	5	15.6
Patients with repeat biopsy after therapy	28	87.5	26	81.3
Corrected	13	46.4	15	57.7
Not corrected	15	53.6	11	42.3

^a Therapy used for at least 50% of cycles.

Results

The average follicular phase was 9.7 ± 0.65 days for the early ovulators as compared to 15.1 ± 2.52 days for the controls. All women in the study received exogenous P therapy with an average dosage of 79.8 ± 50.5 mg for the early ovulators and an average of 66.6 ± 38.4 mg for the controls. A summary of the infertility factors diagnosed and the therapy administered to the women in the study is presented in tables 1 and 2.

A comparison of the mean serum hormone levels between early ovulators and controls is presented in

table 3. There were no differences in mean hormone levels between early ovulators and controls (t test, paired). There was also no difference in the average age of the two groups: 34.3 ± 4.6 years for the early ovulators and 34.5 ± 3.5 years for the controls.

Pregnancies were achieved by 9 (28.1%) of the early ovulators and 19 (59.4%) of the controls. There were 6 pairs in which the early ovulators and the controls both became pregnant, and in 10 pairs there was no pregnancy. In 3 pairs, the early ovulators became pregnant, while the matched controls did not, and in 13 cases the controls became pregnant but the early ovulators did not. The 9 pregnant early ovulators required an average of 8.6 cycles to achieve pregnancy, while the average for the 19 controls was 6.4 cycles.

Table 3. Comparison of serum hormone levels

Serum hormone levels	Early ovulators (n = 32)	Controls (n = 32)
P ₃ , ng/ml	0.75 ± 0.30	0.75 ± 0.27
E ₂ , pg/ml	261.47 ± 75.71	282.78 ± 126.34
LH, mIU/ml	40.92 ± 33.25 ^a	48.63 ± 33.04 ^a
FSH, mIU/ml	15.86 ± 14.23 ^b	15.43 ± 7.08 ^b
FSH (initial), mIU/ml	10.30 ± 4.98 ^a	11.68 ± 6.09 ^a

All serum hormone levels except for initial FSH were measured on the day of peak E₂ level. Initial FSH was measured on days 2–3 of follicular phase. Means ± SD.

^a Based on n = 24. ^b Based on n = 14.

The results of the life table analysis is presented in table 4. The cumulative 12-month pregnancy rate of 66.3% for the controls was significantly higher than the cumulative rate of 31.4% for the early ovulators (p < 0.05 log rank test).

Discussion

Our data showed that early ovulation despite attainment of a mature follicle occurs in approximately 3% of infertile patients. Since the pregnancy rate in the early ovulators was much lower, the data suggest that a short follicular phase can contribute to infertility even if the follicle is mature by criteria of pelvic sonography and serum estradiol levels. Although the mechanism for this discrepancy is not known, there may have been insufficient time for early ovulators to have developed an appropriate endometrial environment despite the development of histologic changes in the late luteal phase consistent with an in phase endometrium. Another possibility is that there was insufficient time to develop adequate endometrial biochemical factors needed for implantation.

While other studies have focused on the adverse effects on pregnancy rates of a long luteal phase [4] and a long follicular phase [3], we believe our study evaluating the adverse effects of short follicular phase on pregnancy rates is unique. Our data demonstrate that the short follicular phase is associated with reduced fertility and suggest that the treating physician might consider other methods of lengthening the follicular phase of infertile females who have failed to conceive despite apparent normal follicular

Table 4. Clinical life table for early ovulators

Cycle	Women entering cycle	Withdrawn/lost to follow-up	Adjusted number at risk	Pregnancies during cycle	Probability of pregnancy during cycle	Probability of no pregnancy during cycle	Cumulative probability of no pregnancy by end of cycle	Cumulative probability of pregnancy by end of cycle
3	32	0	32	0	0.0000	1.0000	1.0000	0.0000
4	32	0	32	2	0.0625	0.9375	0.9375	0.0625
5	30	0	30	0	0.0000	1.0000	0.9375	0.0625
6	30	1	29.5	0	0.0000	1.0000	0.9375	0.0625
7	29	0	29	0	0.0000	1.0000	0.9375	0.0625
8	29	1	28.5	1	0.0351	0.9649	0.9046	0.0954
9	27	2	26	2	0.0769	0.9231	0.8350	0.1650
10	23	2	22	1	0.0454	0.9546	0.7971	0.2029
11	20	2	19	2	0.1053	0.8947	0.7132	0.2868
12	16	2	15	1	0.0667	0.9614	0.6856	0.3144

maturation. We also believe that controlled clinical studies are needed to see if lengthening the follicular phase in these patients really does make a difference. There is some evidence that endometrial thickness and/or echo pattern may correlate with pregnancy rates [5, 6]. Finally, it would be interesting to sonographically measure the endometrial thickness and evaluate the endometrial echo pattern to see if there is any correlation with rate of pregnancy and with length of follicular phase. An older patient or a female in incipient menopause might be expected to ovulate earlier because of elevated gonadotropins, yet have a reduced pregnancy rate related to poor quality oocytes. However, since the controls were age matched and no significant difference in early follicular serum FSH was found in early ovulators (10.3 mIU/ml) versus controls (11.7 mIU/ml), this does not appear to be the

explanation for our data. The difference in pregnancy rates cannot be explained by better follicular maturation since there was no statistical difference in the peak serum E₂ levels reached by early ovulators (261 pg/ml) versus controls (283 pg/ml).

Future studies will compare pregnancy rates in early ovulators treated with placebo versus low dose estrogen to lengthen follicular phase. Whether the estrogen interferes with follicular maturation will be determined by future studies.

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