

Effect of short follicular phase with follicular maturity on conception outcome

J. H. Check, J. R. Liss, K. Shucoski, M. L. Check

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

Purpose: To determine if a short follicular phase despite attaining a mature follicle is associated with a lower pregnancy rate. Furthermore the study would determine if delaying the maturation of the follicle by the use of ethinyl estradiol could improve the pregnancy rate.

Methods: The clinical and viable pregnancy rates of 32 infertile patients were matched to 32 similar controls who ovulated at or past day 11. After 2-3 cycles of demonstrating ovulation before day 11 some patients were treated with ethinyl E₂, 20 mcg daily, from day 2 of the cycle until ovulation.

Results: Clinical and viable pregnancy rates for the normal ovulators (84.4%, 59.3%) were significantly higher than the rates for early ovulators (21.8%, 9.3%). However, the pregnancy rates were 83.3% and 66.7% for the subset of early ovulators who were made to ovulate later by ethinyl E₂.

Conclusions: The short follicular phase per se reduces fecundity.

Key words: Mature follicle; Conception outcome; Duration; Follicular phase.

Introduction

A previous study found that there was reduced fecundity in patients who attained the maximum mature follicle before day 11 (ultrasound demonstrating an 18-24 mm diameter follicle with a serum estradiol (E₂) > 200 pg/ml) vs those who attained the most mature follicle day 11 or after [1]. The problem of attaining mature follicles with a short follicular phase was estimated to be found in 3% of the infertility population [1].

The nature of our practice has changed and we are seeing an older group of patients with borderline high or increased early follicular phase serum follicle stimulating hormone (FSH) levels [2]. This group especially has a tendency for a short follicular phase [3].

The purpose of this study was to once again perform a matched controlled study using the same number of patients (n = 32) as a previous study to either corroborate or refute the previous conclusions [1]. Furthermore this study would determine if the lower pregnancy rates were related to a lower intrinsic pregnancy rate in view of a potential decrease in ovarian reserve with less quality oocytes or actually related to the shortness of the follicular phase per se.

Materials and Methods

In contrast to the previous study where the study group consisted of women whose maximum mature follicle occurred before day 11, in this case the study group needed to actually demonstrate oocyte release before day 11. The study group was matched to the same number of patients releasing the oocyte from the follicles day 11 or later.

Matching was based on age of female partner, duration of infertility, infertility vs history of recurrent miscarriages, primary vs secondary infertility, luteal phase defect or anovulation as the cause of infertility. Only mild male factor was allowed that would seem amenable to treatment with intrauterine insemination (IUI). If a male factor was present that was also matched. Both tubes were required to be patent. Mild endometriosis was allowed, and if present, was also matched.

If follicle maturing drugs, e.g., clomiphene citrate or gonadotropins were used in a woman with early ovulation the control had to be treated with a similar drug (i.e., clomiphene vs gonadotropins). In contrast to the previous study, the demonstration of early ovulation could be treated by using ethinyl E₂, 20 micrograms, in the early follicular phase for several days to try to delay follicular maturation in a succeeding cycle [4]. This would only be attempted after 2-3 cycles of early follicular maturation.

Only cycles where follicular maturation was achieved as evidenced by attaining a follicle with a mean diameter of 18-24 mm associated with a serum E₂ of \geq 200 pg/ml were counted. A maximum of six cycles per patient were evaluated.

Both groups were treated with progesterone (P) vaginal suppositories 100-200 mg twice daily from the early luteal phase. Endometrial biopsies were performed to establish the diagnosis of luteal phase defect initially. Repeat biopsies were performed on cycles where follicular maturation was demonstrated to determine if the dosage of vaginal P was sufficient. Comparisons of pregnancy rates were made using Fisher's exact test.

Results

Only 21.8% (7/32) of the early ovulation group demonstrated ultrasound evidence of pregnancy compared to 84.4% (27/32) of normal ovulators ($p < .05$). If an early ovulator ovulated later in a given cycle, that cycle was not

included in this analysis but analyzed separately. Four early ovulators miscarried (57.1%) vs eight of 27 (29.6%) normal ovulators.

There were 11 early ovulators who were treated with ethinyl E₂ after the first two cycles of early ovulation and their ovulation was successfully pushed past day 11. Six of 11 (54.5%) achieved a pregnancy within six cycles of normal ovulation time. Only one aborted (16.6%).

Thus the viable pregnancy rates were 9.3% for early ovulators, 58.7% for normal ovulators and 66.7% for early ovulators who were made to ovulate later than day 11 by ethinyl E₂ ($p < .05$ early vs normal ovulators).

The clinical pregnancy rate per cycle was 10.9% (7/64) for the early ovulators vs 25.0% (27/108) for normal ovulators and 15.7% (6/38) for early ovulators with subsequent delayed ovulation. The respective viable pregnancy rates per cycle were 6.2% (4/64), 17.5% (19/108) and 13.4% (5/38) ($p < .05$, early vs normal ovulators).

Day 3 serum E₂ levels on the first cycle of evaluation ranged from 25-231 pg/ml. Serum follicle stimulating hormone (FSH) ranged from 0.1 to 42 mIU/ml. Serum E₂ was significantly higher in the early ovulators (Table 1). Serum FSH level was significantly lower in the early ovulators (Table 1).

Table 1. — Median day 3 hormone levels according to early or normal time of ovulation.

	Early Ovulators	Normal Ovulators
Day 3 serum E ₂ (pg/ml) ^a		
Minimum	25	19
Maximum	231	144
Median	59.0	33.5
Mean	69.2	40.1
Standard Deviation	40.7	23.0
Baseline serum FSH (mIU/ml) ^b		
Minimum	.1	1.0
Maximum	15.90	42.0
Median	6.0	8.0
Mean	6.0	10.1
Standard Deviation	3.7	7.9

^a $p < .05$ comparing day 3 median and mean serum E₂ levels between early ovulators and normal ovulators.

^b $p < .05$ comparing day 3 median and mean serum FSH levels between early and normal ovulators.

Discussion

There have been no reports since our original publication in 1992 either corroborating or refuting the results which found a 28.1% six-month pregnancy rate in early ovulators vs 59.4% in matched controls with follicle maturation past day 11. Similar conclusions were found in this most recent study - 21.8% vs 84.4% pregnancy rate for ovulators before day 11 vs day 11 or later.

One may question whether the selection of women with early follicular maturation may merely represent women with decreased oocyte reserve and possibly poor oocyte quality [3, 4]. However, the late ovulators had a significantly higher serum FSH level, bordering, in fact, on the top-normal level. This suggests that the matching process was probably sufficient to equally match patients in both categories with poor oocyte reserve.

The fact that the early ovulators when made to ovulate later had an improved pregnancy rate during these later ovulation cycles is further evidence that the early ovulation per se contributes to the lower pregnancy rates with early ovulation.

Though a larger group than six patients is needed to make more definitive statements, these data do suggest that attempts to increase follicular length and delay the maturation of the dominant follicle may improve pregnancy rates for women with the short follicular phase.

References

- [1] Check J.H., Adelson H., Lurie D., Jamison T.: "Effect of the short follicular phase on subsequent conception". *Gynecol. Obstet. Invest.*, 1992, 34, 180.
- [2] Check J.H., Peymer M., Lurie D.: "Effect of age on pregnancy outcome without assisted reproductive technology in women with elevated early follicular phase serum follicle-stimulating hormone levels". *Gynecol. Obstet. Invest.*, 1998, 45, 217.
- [3] Scott R.T., Toner J.P., Muasher S.J., Oehninger S., Robinson S., Rosenwaks Z.: "Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome". *Fertil. Steril.*, 1989, 51, 651.
- [4] Check J.H., Check M.L., Katsoff D.: "Three pregnancies despite elevated serum FSH and advanced age". *Hum. Reprod.*, 2000, 15, 1709.

Address reprint requests to:
J. H. CHECK, M.D., PH.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)