

*Jerome H. Check
Grace Lee
Richard Epstein
Beth Vetter*

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 and Infertility,
Camden, N.J., USA

Increased Rate of Preterm Deliveries in Untreated Women with Luteal Phase Deficiencies

Preliminary Report

Introduction

Some randomized studies have suggested a significant beneficial effect of 17-hydroxyprogesterone caproate in the prevention of preterm labor [1, 2]. The therapy in both studies was initiated at approximately 12-16 weeks and continued until labor.

We considered the possibility that a deficient progesterone effect during the first trimester may lead to a higher rate of preterm deliveries. A retrospective study was thus performed comparing the incidence of preterm versus full-term pregnancies in women with luteal phase defects who were either treated or not treated with progesterone supplementation during the first trimester.

Materials and Methods

A postdelivery questionnaire was answered by 540 primary infertility patients with known luteal phase defects (LPD) who conceived with singleton pregnancies and who completed 20 weeks of pregnancy. The questionnaires were sent within 6 months of delivery. The LPD had been diagnosed by late luteal phase endometrial biopsy and were required to be out of phase by more than 2 days in 2 consecutive cycles.

The patients were divided into three groups: (1) no progesterone supplementation; (2) progesterone supplementation for at least 12 weeks; or (3) progesterone supplementation for > 6 but < 10 weeks. All therapy was started after ovulation, and biopsies were in phase before attempts for conception were recommended. Those patients treated with progesterone used vaginal suppositories, beginning with a minimum of 25 mg twice daily in the luteal phase (dosage was increased if biopsy was still out of phase) and continuing with a mini-

mum of 50 mg twice daily once the pregnancy was confirmed by β human chorionic gonadotropin levels. The dosage during the first trimester was adjusted to keep the serum progesterone level over 30 ng/ml once the patient was 3 weeks from conception.

The progesterone therapy was recommended to all patients for at least 12 weeks. Group 1 was formed from patients who refused progesterone therapy for fear of teratogenicity; group 3 patients included those who discontinued progesterone therapy, usually because of side effects, especially vaginitis.

An analysis of variance was used to compare the three groups on both infant birth weights and number of days delivered early. The differences in preterm delivery rates were evaluated using χ^2 analysis.

Results

Comparisons of the three groups on the basis of days before delivery and birth weight are seen in table 1. A statistical difference ($p < 0.01$) was found only when comparing the percentage of deliveries before 37 weeks in group 1 (10 of 32) versus group 2 (64 of 469); group 1 versus group 3 was $p = 0.06$. No statistical differences in birth weights were noted. Evaluation of babies born < 2,500 g showed the following: group 1, 4 of 32 (12.5%); group 2, 43 of 469 (9.2%); and group 3, 6 of 39 (15.4%). No statistical differences were found, but comparison of births prior to 32 weeks showed a statistical difference ($p < 0.01$; Fisher's exact test) between groups 1 and 2.

Fetal anomalies seen in progesterone-treated women were no greater than those expected within the normal population (2.6%). The minimum use of progesterone in group 2 patients was 7 weeks.

Table 1. Effect of first trimester use of progesterone for LPD and subsequent preterm delivery

Group	Number of patients	Birth weight, g	Days delivered before EDC	Deliveries < 32 weeks, %	Deliveries < 37 weeks, %
1	32	3,113 ± 874	-16.0 ± 26.8	12.5 (4)	31.2 (10)
2	469	3,240 ± 679	-7.3 ± 13.0	1.3 (6)*	13.7 (64)*
3	39	3,440 ± 646	-5.5 ± 16.1	2.6 (1)	10.3 (4)

Values are given in means ± SD. Figures in parentheses indicate numbers of deliveries. Group 1: no progesterone; group 2: progesterone supplementation for at least 12 weeks; group 3: progesterone supplementation > 6 but < 10 weeks; * p < 0.01 versus group 1 (by Fisher's exact test).

Discussion

This study has several flaws, including the inequality of groups, retrospective nonrandomized nature, and reliance on the patient's statements as to facts of birth (we did not deliver these patients).

Since this group was composed of infertile patients with LPD, and a statistically significant increase in preterm births was seen in patients not treated with progesterone, these preliminary data might provide sufficient interest to initiate a prospective randomized trial of progesterone versus nonprogesterone therapy in patients with a history of preterm deliveries, or other high-risk

groups. This proposed study could then determine whether a correlation between preterm deliveries and out-of-phase preconception endometrial biopsies can be made, whether first-trimester progesterone therapy can prevent this problem, and whether the benefit is seen only in patients with diagnosed LPD.

Acknowledgements

The authors wish to acknowledge Laurie Aurand for the preparation of the manuscript and Lori Snyder for her computer assistance in compiling the data.

References

- 1 Johnson J, Austin KL, Jones GS, Davis GH, King TM: Efficacy of 17-hydroxyprogesterone caproate in the prevention of premature labor. *N Engl J Med* 1975;293:675-680.
- 2 Yemini M, Borenstein R, Drenzen E, Apelman Z, Mogilner M, Kessler I, Lancet M: prevention of premature labor by 17-hydroxyprogesterone caproate. *Am J Obstet Gynecol* 1985;151:574-577.