

The risk of fetal anomalies as a result of progesterone therapy during pregnancy

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The Food and Drug Administration issued a warning in 1977 advising of an increased risk of teratogenicity in infants born to women taking synthetic progestins or progesterone (P) during their first trimester of pregnancy.¹ However, this warning was questioned at a symposium sponsored by The American Fertility Society, especially concerning the use of natural P.¹ The authors of a recent article even questioned that there was any increased risk of teratogenicity from taking progestogens during the first trimester.²

We sent questionnaires to 475 women with previous ovulation problems who were given supplemental P and who conceived in 1983, then recorded the incidence of birth defects.

MATERIALS AND METHODS

Four hundred seventy-five questionnaires concerning the results of fetal outcome were sent to patients who were part of a study, to determine whether P given prophylactically to high-risk pa-

tients could reduce the rate of spontaneous abortions. We received 382 responses.

Two types of P had been given either P vaginal suppositories or 17-hydroxyprogesterone (17-OHP) intramuscularly. The 17-OHP was added to the vaginal P if there was clinical or laboratory evidence for a need for increased P therapy; sometimes the vaginal suppositories were replaced by 17-OHP if local side effects (e.g., pruritus) occurred. Each patient had been started on a minimum of 50 mg/day of P 3 or 4 days after forming a mature follicle, as evidenced by a follicle 18 to 24 mm in diameter by ultrasound and a minimum serum estradiol level of 200 pg/ml per mature follicle. Generally, release of the ovum was confirmed on sonographic examination before the P was given.

As soon as the diagnosis of pregnancy was confirmed by a beta-subunit human chorionic gonadotropin test 18 days after forming a mature follicle, the P was increased to 100 mg/day. Whenever 17-OHP was used, it was given as 500 mg/week. The majority of the patients were able to stop P therapy by 14 weeks, but some extended the therapy a few weeks beyond 14 and others remained on it until 34 weeks, depending on clinical circumstances. The questionnaires were sent a minimum of 1 year after the birth of the infant, in case some problem would develop during the first year.

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Table 1. Dosage and Duration of P-Treated Patients with Congenital Abnormalities

Patient	Dosage	Duration	Abnormalities	Follicular phase drugs
		<i>wks</i>		
1	19,600 mg P supplement	15	Club foot, cleft palate	Diethylstilbestrol
2	8400 mg P supplement	12	Hydrocephaly	hMG
3	10,500 mg P supplement	16	Transposition of great vessels	Diethylstilbestrol
4	8750 mg P supplement	13	Ventricular septal defect and pulmonic stenosis	None
5	6250 17-OHP 8750 mg P supplement	13	Sprengle's deformity and omphalocele	Clomiphene citrate

RESULTS

Responses were returned from 382 patients. Five women reported birth defects. The nature of these defects are listed in Table 1. Thus the incidence of anomalies in infants born to women treated with P during their pregnancy was 1.3% (13 of 1000).

The total number of patients treated exclusively with P vaginal suppositories was 198, and 189 had taken both P vaginal suppositories and 17-OHP. All but 14 patients had been treated with P for at least 12 weeks. The minimum amount used by one woman who was only treated for 7 weeks was 4200 mg throughout the first trimester. A minimum of 9000 mg was given during the first trimester in 373 patients. Thirty-four patients stayed on P longer than 30 weeks, and 96 took P and 17-OHP for longer than 30 weeks. These 130 patients took a minimum of 21,000 mg P during their pregnancy. The maximum taken by a patient combining both P and 17-OHP was 48,000 mg. One hundred thirty-three patients had been treated in the follicular phase with clomiphene citrate. Ninety-three patients had been treated with human menopausal gonadotropins (hMG).

Four of the five patients who had infants with anomalies had been treated with only P. All five patients had infants with different birth defects. The longest duration of treatment was 16 weeks.

DISCUSSION

The study by Katz et al.² presented data on the risk of taking progestins, especially oral medroxyprogesterone acetate, during the first trimester. They stated that medication was started before the tenth week in 56% of the cases. Two other studies, by Michaelis et al.³ and Resseguie et al.,⁴

also revealed no evidence for increased congenital malformations in women ingesting progestogens during the first trimester. This is similar to the results of Katz et al.² Most of the studied patients used the progestogens after they had missed their expected menses. However, the most efficacious way of using P to prevent spontaneous abortions is to employ it 3 or 4 days after ovulation and before implantation.

This study was aimed at determining the risk of teratogenicity in pregnant women who used P from the third or fourth day after ovulation and thus was used much earlier in the pregnancy than in the study by Katz et al.² The possibility existed that the lack of increased teratogenicity found in their study may have been from employing the P later in the first trimester. However, all patients in this study used the P early, even before implantation would have occurred. The total rate of incidence of malformations per 1000 in the P-treated group in our study was only 13.

Rock et al.⁵ could not find any increase in malformations in patients given physiologic P when the P was started on the third day of the temperature rise. The incidence of malformations in our study compares quite favorably to that of Rock's study.⁵ Our study included a much larger number of patients (387 versus 78) than that by Rock et al.⁵ Furthermore, our data substantiates the relative safety of P by demonstrating no increment in birth defects, despite a much higher dosage of P given to the pregnant mothers. The patients of Rock et al.⁵ had been given an average of 1000 mg P during the first trimester, whereas the patients in our study averaged > 9000 mg P. The smallest total first trimester dosage of P in their study was 75 mg, versus 4200 mg in our study. Although 4 of 198 patients treated exclusively by P developed congenital malformations and only 1 of 189 treated with both P and 17-OHP developed anom-

alies, the difference is not statistically significant. We think this supports the concept that 17-OHP and P are not teratogenic. Further support for the lack of risk of anomalies from 17-OHP was provided by Seegmiller et al.,⁶ who found no increase in malformations or androgenic effects in treated mice given 200 times the human dosage. Only 1 of 133 patients treated with clomiphene citrate developed a congenital malformation, and only 1 of 93 patients treated with hMG developed an anomaly. Three defects occurred in 156 women not treated with ovulation drugs. No other drugs had been administered to these pregnant women during the pregnancy, other than acetaminophen and occasional antiemetics and vitamins.

SUMMARY

The incidence of congenital anomalies in infants born to 382 women treated with P was noted. Only five anomalies occurred in the infants born to women who had taken P. This study supports the data of Rock et al.⁵ by demonstrating a similar low incidence of birth defects in a much larger series of patients who also took a much

higher dosage of P. Similarly, because only 1 of 189 patients treated with both P and 17-OHP developed anomalies, the data supports the study by Katz et al.,² suggesting no increase in anomalies related to 17-OHP therapy.

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