

The Efficacy of Progesterone in Achieving Successful Pregnancy: I. Prophylactic Use During Luteal Phase in Anovulatory Women

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ABSTRACT: We have previously shown that prophylactic supplementation of progesterone beginning in the luteal phase of patients treated with human menopausal gonadotropins (hMG) could reduce the risk of spontaneous abortions. The present study was initiated with 100 patients to evaluate the efficacy of a new progesterone therapeutic regime in patients requiring either hMG or clomiphene citrate. A significantly decreased risk of spontaneous abortion (6% vs. 28%) was seen in 50 patients prophylactically treated with progesterone as compared with 50 control patients. The progesterone regimen was then tried on 566 consecutive patients who were treated and conceived with hMG or clomiphene citrate, and approximately the same risk (6.2% by 20 weeks) was found. This incidence of spontaneous abortion is even less than the accepted risk for the general population.

INTRODUCTION

THE RISK FOR SPONTANEOUS ABORTION up to 20 weeks of gestation is about 15%, although the figures vary slightly from different centers. Harlap et al¹ studied over 30,000 cases and came up with a 14.4% risk of spontaneous abortion up to 28 weeks. Their population included women registering for antenatal care who had already missed two menses.

There are various causes of spontaneous first-trimester abortion, including chromosomal abnormalities and luteal phase defects. Luteal phase defects

were found by Jones and Delfs² to represent 35% of recurrent abortions, whereas Tho et al³ found the incidence to be 23%.

Luteal phase defects have been found to occur in increased frequency in anovulatory women treated with ovulation-inducing drugs. Garcia et al⁴ found a 50% incidence of luteal phase defects in women treated with clomiphene citrate, whereas Check et al⁵ found the incidence of luteal phase defects to be 30% in women treated with hMG.

There are no good data to indicate the actual risk of spontaneous abortion in women with luteal

phase defects. Certainly, we have all seen conception occur during a cycle in which the endometrial biopsy demonstrated a luteal phase defect—and yet the woman did not abort. Nevertheless, logic dictates that the risk should be higher than the 15% incidence in the general population. Thus, women with infertility related to ovulation problems should have an increased risk of spontaneous abortion. Andrews⁶ states that the accepted risk for infertility patients in general is 21%.

We have found that women on "ovulation-inducing" drugs may have intermittent luteal phase abnormalities. The suggested optimal time to perform the endometrial biopsy is one or two days prior to the succeeding menses,⁷ and dated according to the criteria of Noyes et al.⁸ However, since the best results occur when progesterone is employed three to four days after ovulation,⁹ obviously one cannot wait for the endometrial biopsy results taken in the late luteal phase and hope to significantly alter the risk of abortion.

Thus, we decided to initiate a research study to find whether the prophylactic use of progesterone vaginal suppositories, beginning three or four days after ovulation, in a group of infertility patients with ovulation problems could decrease the risk of spontaneous abortion.

MATERIALS AND METHODS

One hundred patients with ovulation defects (as defined by a serum progesterone level under 8 ng/mL taken 1 week premenstrally) were used in the first study. They were divided into two groups of 50, each one composed of 30 patients treated with clomiphene citrate and 20 patients treated with hMG. The two groups were also matched as to age (25.7 vs. 25.2 years) and duration of infertility (3.2 vs 3.4 years). One group was treated prophylactically with progesterone suppositories beginning three days after ovulation. The progesterone was extracted from natural sources, either yams or soybeans, and was suspended in polyethylene glycol (Baedernood Pharmacy, Jenkintown, PA). Ovulation was assumed to occur one day after the forming of a follicle of 18 to 24 mm in diameter, with an estradiol level of at least 200 pg/mL per mature follicle. Release of the ovum was confirmed prior to starting progesterone treatment by demonstrating a shrinkage of the follicle by at least 5 mm two or three days after follicular maturation was achieved.¹⁰

Each patient was started on progesterone suppositories, 25 mg twice daily, beginning three or four days after ovulation. An endometrial biopsy was performed with a pipelle de cornier 12 or 13 days after ovulation. The patients were warned that the endometrial biopsy could disrupt a pregnancy, but were advised that the risk would be under 5%. If the biopsy dated more than two days early, the progesterone was increased by 25 mg. If the biopsy had dated more than four days early, a repeat biopsy was performed to see if the endometrium was correctly dated to within two days. A serum hCG beta subunit measurement was obtained 18 days from ovulation and, if positive, the progesterone dose was increased to 100 mg/day unless the patient was already taking that amount.

The patients were monitored at 3-week intervals until 20 weeks. Pelvic ultrasound examinations were performed at 7 to 10 weeks, and at 20 weeks. Serum progesterone levels were measured at each visit, and if the level dropped under 20 ng/mL, the progesterone dose was increased by 50 mg or 17-hydroxyprogesterone was added (500 mg IM weekly). Bleeding or cramping would, similarly, lead to an increment in progesterone. Progesterone treatment was stopped at 14 weeks' gestation. The 50 control patients were similarly monitored, but were not given any supplemental progesterone.

The same progesterone regimen was then applied to 566 infertility patients with a history of ovulation defects who conceived. Three hundred eighty-four were treated with clomiphene citrate and 182 were treated with hMG. The average age was 28.5 years, and their average duration of infertility was 3.7 years; there were no controls for this group. The intention was strictly to determine, in a larger series, the true benefit of prophylactic progesterone.

RESULTS

Fourteen of 50 patients (28%) who did not receive progesterone had spontaneous abortions by 20 weeks of gestation; however, only three of 50 matched patients (6%) receiving prophylactic progesterone aborted by 20 weeks. Analysis by the χ^2 test showed the results to be significant ($P < .05$). Ten of the control patients who aborted had been treated with clomiphene citrate, while four were treated with hMG. The three abortions in the progesterone-treated group included two patients on clomiphene citrate and one treated with hMG.

The data concerning the incidence of abortions in

a much larger series of patients treated prophylactically with progesterone were as follows: 30 of 566 (5.3%) aborted by 12 weeks, 35 of 566 (6.2%) by 20 weeks, and there were 37 losses (6.5%) up to 28 weeks.

Over 90% of the losses presented as "silent" abortions; i.e., the patients showed poor fetal development on pelvic ultrasound, without heavy bleeding. Only seven patients who had seemingly normal fetal ultrasound results at 7 to 10 weeks subsequently aborted by 28 weeks, and five had losses by 20 weeks. There was no evidence of a higher proportion of abortions in patients treated with either clomiphene or hMG.

The dosage of progesterone, which was initiated at 50 mg/day, was increased by 25 mg daily if the endometrial biopsy taken in the late luteal phase dated more than two days early. The precise dosage was titrated by biopsy. Twelve of the first group of 50 women (24%) required an increase in progesterone to correct the endometrial biopsy. One hundred twenty-four patients (22%) of the second group of 566 patients required an increase in progesterone. Ninety-eight patients required 75 mg daily, 20 patients required 100 mg, and six, 150–200 mg to correct the biopsy. The progesterone dosages of 35% of the patients were increased during the first trimester because of bleeding, cramping, or low serum progesterone levels.

DISCUSSION

We have previously shown that the use of prophylactic progesterone therapy in the luteal phase reduces the risk of spontaneous abortion in patients whose ovulations were induced with hMG.⁵ One hundred thirty patients were treated with a fixed dosage of 50 mg/day of progesterone in the luteal phase in this previous study, and 21 (16%) had spontaneous abortions.

The present study was aimed at determining whether a modified approach in progesterone therapy could effect even a further decrease in spontaneous abortion rates. Twenty-two percent of the patients required more than 50 mg/day of progesterone during the luteal phase, and as soon as the pregnancy was diagnosed, the progesterone was increased to 100 mg/day. Furthermore, in 35% of the patients, the progesterone dosage was increased during the first trimester. Another difference between this study and the previous one with hMG is that whereas the first one involved patients who

ovulated exclusively with hMG, the present study also included patients treated with clomiphene citrate.

A potential problem with prophylactic progesterone is the apparent failure of some women so treated to conceive; however, this represents only a minority of patients. Twenty-one patients who did not conceive after at least eight cycles of a fertility drug and progesterone did so when progesterone was withheld. Progesterone was reinitiated in 15 of these patients as soon as the diagnosis of pregnancy was established; three of the patients (20%) aborted by 20 weeks. Six patients did not receive any progesterone, and two (33%) aborted by 20 weeks. Although the samples are small, the data support the concept that to achieve the protective effect of progesterone therapy to reduce the chance of abortion, the hormone must be used after ovulation and before implantation.

Thus, the results show a significant decrease in spontaneous abortions in patients treated with hMG and clomiphene citrate by using progesterone prophylactically in the luteal phase as compared with unsupported controls. The new technique of determining the precise dosage of progesterone to correct the luteal phase, and automatically increasing the dosage to 100 mg once the diagnosis of pregnancy is established and individually adjusting the dosage in case of bleeding or cramping during the first trimester, seems to have a better protective effect against spontaneous abortions than does fixing the dosage at 50 mg/day. However, since the studies were performed at different times and the patients were not matched, the results can at best only suggest that the new progesterone regimen is superior to the previous, fixed-dosage one.

Nevertheless, this new prophylactic progesterone therapy did reduce the incidence of spontaneous abortions as compared with untreated matched controls, and this was confirmed by demonstrating the same degree of protection in 566 pregnancies. Naturally, the individual physician must take into account the data presented here and weigh them against the risk of inhibiting fertility in some cases and possibly increasing teratogenicity in deciding whether to recommend this therapy to all, or some, patients. The patients are all advised of the FDA's warning concerning increased risk of fetal anomalies in women who take progesterone during pregnancy,⁶ but they are also made aware of more recent data demonstrating *no* increased risk of birth defects in the babies born to women who take progesterone during pregnancy.^{11–13}

REFERENCES

1. Harlap S, Shiono PH, Ramcharan S: A life table of spontaneous abortions and the effects of age, parity, and other variables, in Porter IH, Hook EB (eds): *Human Embryonic and Fetal Death*. New York, Academic Press, p 145, 1980.
2. Jones GS, Delfs E: Endocrine patterns in term pregnancies following abortions. *JAMA* 146:1212, 1961.
3. Tho PT, Byrd JR, McDonough PG: Etiology and subsequent reproductive performance of 100 couples with recurrent abortion. *Fertil Steril* 32:389, 1979.
4. Garcia J, Jones GS, Wentz AC: The use of clomiphene citrate. *Fertil Steril* 28:707, 1977.
5. Check JH, Wu CH, Adelson HG: Decreased abortions in HMG-induced pregnancies with prophylactic progesterone therapy. *Int J Fertil* 30(3):45, 1985.
6. Andrews WC: Luteal phase defects. *Fertil Steril* 32:501, 1979.
7. Jones GES: Some newer aspects of management of infertility. *JAMA* 141:1123, 1949.
8. Noyes RW, Hertig A, Rock J: Dating the endometrial biopsy. *Fertil Steril* 1:3, 1950.
9. Soules MR, Wiebe RH, Aksel S, et al: The diagnosis and therapy of luteal phase deficiency. *Fertil Steril* 28:1033, 1977.
10. Check JH, Chase JS, Adelson HG, et al: New approaches to the diagnosis and therapy of the luteinized unruptured follicle syndrome. *Int J Fertil* 30(4):29, 1986.
11. Rock JA, Wentz AC, Cole KA, et al: Fetal malformations following progesterone therapy during pregnancy: a preliminary report. *Fertil Steril* 44:17, 1985.
12. Resseque L, Hick JF, Bruen JA, et al: Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota, 1936-1974. *Fertil Steril* 43(4):514, 1985.
13. Check JH, Rankin A, Teichman M: The risk of fetal anomalies as a result of progesterone therapy during pregnancy. *Fertil Steril* 45:575, 1986.

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