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Progesterone Therapy to Decrease First-Trimester Spontaneous Abortions in Previous Aborters

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ABSTRACT: A study was designed to see if the use of prophylactic progesterone vaginal suppositories (PVS) reduced the risk of spontaneous abortions in women with a history of at least one spontaneous abortion. PVS was employed during the luteal phase to the end of the first trimester. The dosage was initially 50 mg/day, but was increased according to the endometrial biopsy and doubled as soon as pregnancy was established. Only 10 women (10%) aborted, and 8 of these 10 were successful in their next PVS-treated pregnancies. Overall there were 12 losses in 132 pregnancies (9%) in these PVS-treated patients. Forty-two percent of untreated controls aborted (10/24). The results suggest that PVS is effective in reducing the risk of spontaneous abortions in high-risk patients.

INTRODUCTION

PROGESTERONE IS A VITAL HORMONE for the maintenance of a pregnancy. The luteal phase defect (LPD) has been estimated to be the apparent etiologic factor in 35% of first-trimester abortions.[1] The standard way to establish the diagnosis of LPD is finding an endometrial biopsy to be two or more days out of phase in two cycles.[2] Thus, if in one of the two cycles the endometrium dates normally, then the diagnosis of LPD is not established, and the woman is not typically offered progesterone therapy.

However, having a previous abortion(s) does not ensure the inevitability of having another one—just, perhaps, an increased risk of loss. We therefore think it is reasonable to hypothesize that luteal phase defects may be intermittent, and that demonstrating LPD in any given cycle should be enough information to warrant treating all cycles in case the cycle of conception occurs at the time of inadequate luteal phase.

The possibility also exists that some spontaneous abortions occur not secondary to an inadequately progesterone-prepared endometrium within 2 weeks after fertilization, but secondary to failure of the corpus luteum of pregnancy to produce adequate progesterone several weeks into the pregnancy, before the placenta produces sufficient progesterone. Therefore, we decided to determine the efficacy of treating with progesterone vaginal suppositories (PVS) 100 consecutive women with a history of at least one previous spontaneous abortion. They were treated both during the luteal phase and through the

first trimester. Their treatment was prophylactic, i.e., was not given in accordance with an abnormal endometrial biopsy, but instead to all women with a previous history of spontaneous abortion(s).

PATIENTS AND METHODS

One hundred consecutive patients who were willing to use prophylactic progesterone therapy and had a history of at least one spontaneous abortion were enlisted in the study. All of these patients were willing to use PVS despite their having been made aware of the FDA's warning about teratogenicity;[3] we also informed them, though, of other data suggesting no risk of fetal anomalies with natural progesterone therapy.[4] A prerequisite for inclusion in the study was that they had never been treated previously in any pregnancy with progesterone. Some patients were also treated with ovulation-inducing drugs, e.g., clomiphene, human menopausal gonadotropins (hMG), or bromocriptine, if there was evidence of an immature follicle.[5] A mature graafian follicle was defined as one of 18 mm diameter associated with a serum estradiol level of over 200 pg/mL per mature follicle.[6,7] If it was determined that the woman did not make a mature follicle prior to the release of the ovum, she was treated with bromocriptine, 2.5 mg daily, if the prolactin level was elevated; and the dose was increased to 2.5 mg twice daily if the smaller dose did not correct the follicular maturation.[8,9] Otherwise the patient was given clomiphene citrate and switched to hMG if the clomiphene was associated with uncorrectable hostile cervical mucus even with the addition of supplemental estrogen.

After maturation of the follicle, release of the ovum was next established by sonography.[10] PVS was now initiated, after ovum release and four days from the demonstration of a mature follicle, at a dosage of 25 mg twice daily. The day of ovulation was assumed to be one day after the LH surge was noted and the serum progesterone level approached 1 ng/mL.

An endometrial biopsy was performed 12–14 days from the assumed day of ovulation, and the dating established from the time of ovulation rather than the time of the next ensuing menses because the PVS might delay menstruation. If the biopsy dated out of phase more than one day early, the dose of PVS was titrated upwards until a correctly dated biopsy was achieved. Thus, the biopsy would be repeated on consecutive cycles until the dating was correct. At this point, the patients were advised to cease mechanical contraception and try to achieve a pregnancy.

Seventeen days from the attainment of a mature follicle, an hCG beta subunit assay was obtained, as well as a rapid serum progesterone level. If negative, the woman stopped the suppositories. A positive hCG level would prompt the suggestion to double the dose of the PVS, and the patient would be seen again five days later, when another rapid serum progesterone level would be obtained. A level of 35 ng/mL or higher at this time, without bleeding or significant cramping, would indicate that no increase in PVS was needed. A level over 30, but under 35, would prompt a mild increase, of 50 mg PVS daily; a level under 30, but over 25, would prompt a 100-mg increase, and a level under 25 ng/mL would prompt a 200–300-mg increment. A patient with a low level of serum progesterone would be evaluated again five days later to see if the new increment adequately corrected the serum progesterone level, and if not, the PVS dosage would be adjusted upwards. Some women failed to absorb the vaginal suppositories properly, so that an adequate serum progesterone level was not achieved despite 400 mg PVS. The patient would then be started on progesterone in oil injections, 100 mg every other day.

Once the appropriate level of serum progesterone was obtained, the patient was evaluated at 2-week intervals and the dosage maintained until 12 weeks from conception, when the dosage was tapered, usually by 50 mg/week. The patient was evaluated every 1 to 2 weeks, and progesterone was measured. All PVS was stopped if the patient demonstrated a level over 40 ng/mL 1 week after stopping all PVS therapy. However, if the level dropped under 40 ng/ml during the time of decreasing PVS dosage or stopping, or if there was a significant increase of clinical symptoms of vaginal bleeding or cramping, the full maximum dosage that the patient had taken was resumed for one more month, when another attempt would be made to get the patient off the PVS. Failure to wean the patient successfully after another month of therapy would then generally lead to the suggestion to remain on PVS until 1 month prior to the due date. Levels of serum progesterone over 70 ng/mL during the first trimester were countered by a reduction in the dosage of the PVS.

All patients who refused to use PVS because of the fear of the FDA's warning on anomalies or who stopped them because of side effects (e.g., vaginitis) were included in the study as untreated controls.

There were 24 such patients. All of these patients had two endometrial biopsies without treatment. Those patients treated with PVS had at least one timed endometrial biopsy without therapy, and sometimes two biopsies.

A pregnancy was not included unless the hCG beta subunit level was 1000 mIU/mL or greater 3 weeks from conception. A fetal ultrasound examination was performed in all women at 5 to 9 weeks from conception and again at 12 weeks from conception.

RESULTS

Ten women (10%) had a first-trimester spontaneous abortion during this next pregnancy despite PVS therapy (see Table I). Nine of 10 aborters conceived again, and one aborted the second time also. Actually, a total of 33 patients achieved a second PVS-treated pregnancy and two aborted. Thus, there was a total of 12 losses in 133 pregnancies (9%). One of the women who successfully completed her first trimester was a previous primary aborter with a prior history of seven previous spontaneous abortions. Another primary aborter with five previous losses also successfully completed her first trimester. The highest percentage of abortions (33%) occurred in the group of women with three or more previous abortions (6 losses out of 18). Yet, all six successfully completed their first trimester during their next pregnancy using exactly the same therapy as during their last previous loss.

Thirty-three of these women achieved a second pregnancy and also employed PVS therapy. This group included eight women with three or more abortions (including six who lost their first PVS-treated pregnancy), 22 from the group with two previous abortions (in which three had first-trimester abortions during the initial study with PVS therapy), and three from the group with only one previous abortion (including one who had a previous abortion despite PVS therapy). Twenty-six women were successful in both pregnancies, six were successful in only one of two pregnancies, and one woman was unsuccessful in both PVS-treated pregnancies. Only one of the nine women (11%) aborting in this second pregnancy also had a first-trimester abortion with PVS therapy during the first attempt. Thus, only two of the original 100 women failed to complete successfully their first trimester, with one woman aborting in both and one woman failing to conceive again at the time of this study (she was from the group with only one previous abortion). The numbers of primary aborters never passing the first trimester were as follows: 8 of 20 with one previous abortion; 37 of 62 with two previous abortions, and 13 of 18 with three previous abortions (see Table II). There were 24 women who

TABLE I
Incidence of spontaneous abortions in previous aborters now treated with prophylactic progesterone therapy.

	No. Previous Abortions		
	1	*2*	*3+*
# in group	20	62	18
# aborting	1	3	6
Successful pregnancies	19	59	12
# attempting second pregnancy	3	22*	8†
# aborting a second pregnancy	0	2‡	0

*Three of these women had a first-trimester abortion in the previous PVS-treated pregnancy.
†Six of these women had a first-trimester abortion in the previous PVS-treated pregnancy.
‡One of these patients also aborted her first PVS-treated pregnancy.

TABLE II
Abortion history prior to progesterone therapy (progesterone vaginal suppositories).

	No. Previous Abortions		
Category	*1*	*2*	*3+*
A	8	37	13
B	7	11	3
C	5		
D		8	2
E		6	

A: 0 successful pregnancies before seeing us (primary aborters);
B: first or second pregnancy completed first trimester; aborted thereafter;
C: aborted first pregnancy; completed first trimester of second;
D: aborted first pregnancy; completed first trimester of second and third and then aborted last pregnancy prior to PVS therapy;
E: aborted first two pregnancies; successfully completed first trimester of third.

also needed ovulation-inducing drugs plus PVS in order to form a mature follicle. Three of these women (12.5%) had first-trimester spontaneous abortions. At the time of writing, 42 had delivered, with no incidence of birth defects.

None of the 10 first-trimester abortions treated with PVS presented with spontaneous passage of products of conception. Instead, 9 of the 10 women during the first PVS-treated attempt showed no evidence of a fetal pole on sonography at 5 to 7 weeks from conception, and one woman showed tenting of the sac and a crown-rump length that appeared 2 weeks earlier than it should have despite some evidence of a fetal heart beat. However, 1 week later there was no further growth or evidence of a fetal heart beat by sonography.

Ten of the 24 untreated controls (47%) aborted. Endometrial biopsy data on these 24 women showed 19 to have an out-of-phase biopsy in at least one of two cycles (79%), and 9 of 24 had an out-of-phase biopsy in both cycles (37%). Fifteen women (63%) had an abnormal endometrial biopsy on their first evaluation cycle. Seven of the 10 abortions occurred in the group of nine women who had two consecutive cycles with an abnormal endometrial biopsy, and two of the abortions occurred in the 10 women with an out-of-phase biopsy in only one of two cycles. One abortion occurred in a woman with normal biopsies on both occasions. χ^2 analysis comparing the 42% abortions in the controls with the 10% incidence in the PVS-treated patients showed $P < .01$.

Fifty-eight of the 100 women treated with PVS had an abnormal first biopsy. Only 18 patients treated with PVS had two biopsies without progesterone therapy: 5 of 18 (27%) were abnormal on both. Only four of the 10 losses in this group occurred in women with an out-of-phase endometrial biopsy, and none of the five women with two abnormal biopsies aborted.

Thirty-one of the women had been previously cultured for *Mycoplasma* and *Ureaplasma*; 10 had positive cultures, and 8 had been treated with doxycycline and yet still aborted. Twelve couples underwent chromosomal analysis, and all were normal. No immunological studies were performed.

DISCUSSION

The incidence of spontaneous abortions in the normal population is estimated at approximately 14%.[11] The risk of spontaneous abortion in women with previous abortions has been estimated at 33%.[12] Our series revealed an incidence of spontaneous abortions in these previous aborters who were treated with PVS to be lower than expected for the general population. The elimination of the group with only one previous abortion would still yield 9 abortions out of 80, or an incidence of 11% (still lower than normal). However, the percentage incidence of abortion despite PVS therapy in patients with three or more previous abortions was higher than normal; but all six women who lost their first PVS-treated pregnancy successfully completed their first trimester in the second PVS-treated pregnancy.

Unfortunately, the nature of our clinical practice prevented us from using a control group with placebo suppositories not containing progesterone. To get some idea of what this group might have expected without therapy, we evaluated the abortion incidence in all of the women who had had one abortion before the pregnancy treated by PVS. The patients thus included in this study (refer to Table II) are those in category A with two or more abortions, category C, category D, and category E. Thus, there was a total of 77 patients in this category, and 50 aborted (70%). Eight of the 10 aborters with PVS occurred in this group, so that 8 of 70 aborted with PVS (11.4%). Although the cases are somewhat biased in that these patients sought our help because of habitual abortion, we think the risk of another loss should be at least as high as the time before. Furthermore, though we only had 24 untreated controls, there was a significant statistical difference between the 42% abortion rate in this group in comparison with 10% for PVS-treated patients. Nevertheless, there exists the possibility of a placebo effect of therapy in decreasing abortion risks.

Finally, the benefits of PVS therapy might not be simply related to correcting luteal phase deficiency or serving as a bridge between corpus luteum production of progesterone during pregnancy until there is adequate progesterone production by the placenta: Perhaps—in some way—progesterone decreases the risk of abortion secondary to infectious or immunological causes.

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