Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study

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OBJECTIVE: The purpose of this study was to evaluate the effect of prophylactic vaginal progesterone in decreasing preterm birth rate in a high-risk population.

STUDY DESIGN: A randomized, double-blind, placebo-controlled study included 142 high-risk singleton pregnancies. Progesterone (100 mg) or placebo was administered daily by vaginal suppository and all patients underwent uterine contraction monitoring with an external tocodynamometer once a week for 60 minutes, between 24 and 34 weeks of gestation. Progesterone (n = 72) and placebo (n = 70) groups were compared for epidemiologic characteristics, uterine contraction frequency, and incidence of preterm birth. Data were compared by χ^2 analysis and Fisher exact test.

RESULTS: The preterm birth rate was 21.1% (30/142). Differences in uterine activity were found between the progesterone and placebo groups (23.6% vs 54.3%, respectively; *P* < .05) and in preterm birth between progesterone and placebo (13.8% vs 28.5%, respectively; *P* < .05). More women were delivered before 34 weeks in the placebo group (18.5%) than in the progesterone group (2.7%) (*P* < .05).

CONCLUSION: Prophylactic vaginal progesterone reduced the frequency of uterine contractions and the rate of preterm delivery in women at high risk for prematurity. (Am J Obstet Gynecol 2003;188:419-24.)

Key words: Preterm delivery, preterm birth, prevention, progesterone

Preterm delivery is a leading cause of neonatal morbidity and mortality. It is directly responsible for 75% to 95% of all neonatal deaths not resulting from lethal congenital malformations.[1,2] Of the survivors, 10% to 15% have significant handicaps.[2,3] According to the World Health Organization, a preterm birth is defined as birth before 37 completed weeks of gestation.[4]

In developed countries, the incidence of preterm birth is about 7% to 12% of all deliveries,[5,6] and among these one third occur before 34th week.[1] The incidence of preterm birth in developing countries is higher than in developed countries.[1,7,8] In Brazil, preterm birth is a public health problem because of the striking social differences in the population. Because of the high prevalence of high-risk pregnancies, the incidence of preterm birth at Hospital das Clinicas, University of Sao Paulo Medical School, is 22.5%, and half of these resulted from spontaneous preterm labor. Thus, the prevention of preterm delivery has become one of the major objectives of perinatal medicine.

Primary prevention is desirable but not always possible.[5,9] The difficulties are due to unawareness of the cause and pathophysiologic mechanisms of preterm birth, and furthermore, it is not only a medical problem, but also a social and educational problem.

The early detection of pregnant women at high risk for preterm delivery[10-14] could be the best way to prevent preterm birth. Thereby, bed rest, cervical cerclage,[15] bacterial vaginosis treatment, and prophylactic use of progesterone could be one of the managements in this high-risk population.

Recent studies have shown that an increase in the number of uterine contractions precedes the onset of preterm labor,[13,16,17] and the frequency of uterine contractions in pregnancies with preterm delivery is higher than in women with term and postterm delivery.[18]

Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myo-

Table I. Exclusion cause in two study groups

Exclusion cause	Placebo (n = 76)	Progesterone (n = 81)	P value
PROM	4 (5.2%)	6 (7.4%)	NS
Lost follow-up	1 (1.3%)	0	NS
Therapeutic preterm delivery	1 (1.3%)	2 (2.4%)	NS
Allergic process	0	1 (1.2%)	

PROM, Preterm rupture of membranes; *NS,* not significant.

Table II. Characteristics of women at randomization

	Placebo (n = 70)	Progesterone (n = 72)
Age (y)*	26.8	27.6
Ethnicity*		
White	71.4%	68.0%
Nonwhite	28.6%	32.0%
Parity (>1 delivery)*	97.1%	90.2%
Risk factor*		
Previous preterm delivery	97.2%	90.3%
Uterine malformation	1.4%	5.6%
Incompetent cervix	1.4%	4.1%
Gestational age at intake (wk)*	25.2	26.5

*Not significant.

metrium, it blocks the oxytocin effect of prostaglandin F$_2\alpha$ and α-adrenergic stimulation and therefore increases the α-adrenergic tocolytic response.[6,19] Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain artificial progestagens and β-mimetics.[1,20]

Although some studies demonstrate that natural progesterone is effective in the prevention of preterm delivery and can be administered intramuscularly,[21,22] there are many controversies about their methods. There are few double-blind studies[23,24] that have only used synthetic progestational agents[21,23] with a sufficient number of women. To the best of our knowledge, this is the first study that uses natural progestational agents. Therefore, a placebo-controlled clinical trial in asymptomatic high-risk women would be of value.

The objective of this study was to evaluate whether the prophylactic administration of progesterone by vaginal suppository can reduce the incidence of preterm birth in a high-risk population.

Material and methods

This study was performed in the Obstetrics Clinic, at Hospital das Clinicas, University of Sao Paulo Medical School, a tertiary medical center, in Brazil. A consent form was signed after detailed information was given to every pregnant women. The study was approved by the Ethical Commission of this hospital.

Data available at the start of the study showed that the preterm birth rate in the Obstetrics Clinic, Hospital das

Clinicas, University of Sao Paulo Medical School, was 25%.[12] Although some studies suggest that the prophylactic administration of progesterone in pregnant women at high risk for preterm birth is associated with a reduction of 60% to 78% in preterm delivery rate,[21,23,24] a more realistic assessment of the impact of progesterone may be a reduction of 50% in the preterm rate.

Therefore, to calculate the sample size, we have proposed a reduction of 50% in the preterm birth rate for the progesterone group (from 25% to 12.5%) and a reduction of 20% for the placebo group (from 25% to 20%).[24] A power calculation at the start of the study indicated that at least 48 pregnant women would have to be included in each group to obtain a study power of 90% at a significance level of .05 (two tailed) to prove the hypotheses were correct.

Among the women who sought high-risk prenatal care, 157 asymptomatic high-risk singleton pregnant women for preterm delivery were followed up from February 2, 1996, to March 30, 2001. Patients were allocated to progesterone or placebo according to a randomized number table. The numbers corresponded to sealed envelopes that indicated if drug A or drug B should be used. Numbers were given consecutively. Treatment assignment was blinded until the delivery of the last pregnant woman. Both the patients and the staff who were recording the study findings were blinded to the study medication allocation.

Fifteen (9.5%) patients were lost to follow-up or withdrew from the study. Nine (11.1 %) of these were in the progesterone group and 5 (6.5 %) in the placebo group, resulting in 72 assigned to the progesterone group and 70 to the placebo group. None of the patients in either study group had a multiple pregnancy.

Women at high risk for preterm delivery were considered to be those in the presence of at least one previous spontaneous preterm birth, prophylactic cervical cerclage, and uterine malformation. Gestational age at a prior preterm birth for the progesterone and placebo groups was 33.3 (±2.7) and 33.4 (±2.6) weeks. We did not observe a significant difference in the gestational age of previous preterm birth, uterine malformation, and cervix cerclage in these two groups. Multiple gestation and fetal malformations were excluded.

Women allergic to progesterone (n = 1), who missed follow-up (n = 1), those with preterm rupture of mem-
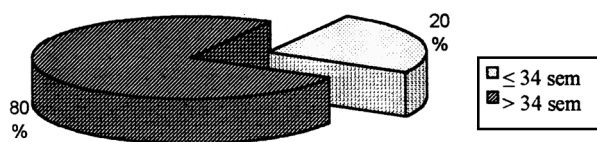
Fig 1. Incidence of preterm delivery before 34th week in natural progesterone group.
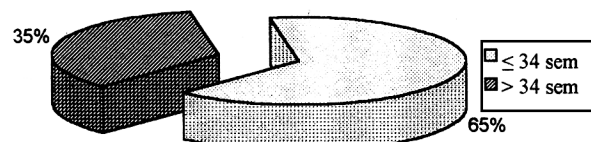

Fig 2. Percentage of preterm delivery before 34th week in placebo group.

Table III. Incidence of preterm delivery

	Placebo (n = 70)	Progesterone (n = 72)	P value
<37 wk	20 (28.5%)	10 (13.8%)	.03
34 wk	13 (18.6%)	2 (2.8%)	.002
Admission for threatened preterm labor	22 (31.4%)	14 (19.4%)	NS

NS, Not significant.

branes (PROM) (n = 10), and those having a therapeutic premature delivery (n = 3) were excluded from the study. One hundred forty-two women completed the study, and there was no statistically significant difference for the exclusion cause in both groups (Table I).

Gestational age was calculated on the basis of the last menstrual period and ultrasonography up to 12 weeks or by two concordant scans between 12 and 20 weeks.

At the first prenatal visit, a microscopic examination and culture of cervicovaginal secretions for *Trichomonas vaginalis, Candida* sp, *Neisseria gonorrhoeae, Chlamydia trachomatis, Gardnerella vaginalis,* and group B *Streptococcus* were carried out for all patients. Women with positive cultures were treated with specific antibiotics, and repeat cultures were performed to confirm the efficacy of treatment.

All pregnant women were submitted to uterine contraction monitoring by an external tocodynamometer once a week for 60 minutes from 24 to 34 weeks of gestation. We performed uterine monitoring between 8 and 10 AM using a Hewlett Packard tocodynamometer 50A series (Hewlett Packard, Houston, Tex) while women were in semi-Fowler position. We determined the frequency of contractions and compared mean values of both study groups. A positive test was considered when there were four or more contractions per hour before the 30th week of gestation and from 30 weeks onward, 6 or more contractions per hour.[12,21,23]

Preterm labor was defined as two or more regular uterine contractions every 10 minutes, recorded by external tocodynamometer, associated with cervical changes, represented by a dilatation of more than 2 cm, or the presence of progressive dilatation or effacement of the cervix. Women in preterm labor were treated in the hospital with intravenous tocolytic therapy. A preterm delivery was defined as birth before 37 weeks of pregnancy.

Both groups of pregnant women were randomly selected to receive the vaginal progesterone suppository (100 mg) or an identical-looking placebo. The suppositories were identical in appearance and thick. They were applied every night from 24 to 34 weeks of gestation. Patients had a thorough explanation of how to use the suppositories, including an orientation picture. The medication and the placebo were supplied by manipulation pharmacy at Hospital das Clínicas, University of Sao Paulo. Patient treatment was only unblinded after the delivery of the last pregnant women.

The clinical relevance of the prophylactic use of progesterone was determined as it correlated with the evolution of pregnancy to preterm delivery. Statistical analysis was performed with EPI-INFO 2000 1.0 (Centers for Disease Control and Prevention, Atlanta, Ga) and STATA 7.0 (USA) (Stata, College Station, Tex). The χ^2 tests or Fisher exact test were used for categoric variables. The two-tailed Student t test was used for continuous variables and the Wilcoxon rank sum test was used for interval variables. Kaplan-Meier survival analysis was used to determine the relationship between the administration of prophylactic vaginal progesterone and preterm birth. The log-rank χ^2 test was used to compare the differences in the generated survival curves. A P value of .05 was considered significant.

Results

Of 142 cases, there were 30 preterm births (21.1%). The incidence of preterm delivery in the progesterone group was 13.8% (10/72) and 28.5% (20/70) in the placebo group. When comparing these two groups, we observed a statistically significant difference in the preterm delivery rate (P = .03).

As shown in Table II, the two groups were found similar in regard to age, risk factors for preterm delivery, and ob-
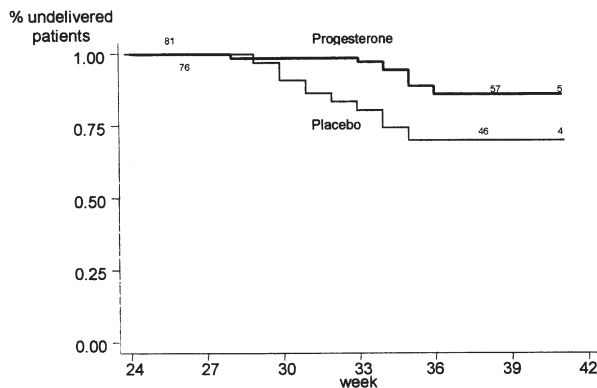
Fig 3. Cumulative percentage of undelivered patients per week, by placebo and progesterone group. Log-rank $\chi^2 = 5.33$, $P = .029$.

Table IV. Mean contraction frequency for each gestational week between placebo and progesterone groups

Gestational age (wk)	Placebo Mean ± SD	Progesterone Mean ± SD	P value
28	4.0 ± 3.0	1.0 ± 0.6	.00001
29	4.0 ± 2.1	1.0 ± 0.9	.00001
30	6.2 ± 3.0	2.8 ± 2.7	.00001
31	5.1 ± 2.5	3.2 ± 2.0	.0001
32	6.5 ± 3.1	2.5 ± 2.5	.01
33	7.0 ± 4.2	2.8 ± 2.4	.0001
34	6.5 ± 3.1	3.5 ± 2.0	.0001

Fig 4. Mean contraction frequency based on 1 hour of monitoring per week, by placebo and progesterone group and by gestational age (28, 29, 30, 31, 32, 33, and 34 weeks' gestation). *Open squares,* Placebo group; *solid circle,* progesterone group. $F = 9.5$, $P = .004$.

Table V. Frequency of uterine contraction

Contraction	Placebo (n = 70)	Progesterone (n = 72)	P value
<4	32 (45.7%)	55 (76.4%)	.0001
4–5	12 (17.1%)	3 (4.1%)	.0118
≥6	26 (37.2%)	14 (19.4%)	.0190

stetric history. There was no significant difference between gestational age at study admission and vaginal infection. Socioeconomic status, estimated by the educational level as well as ethnicity, was similar in both groups.

Twenty-two women in the placebo group (31.4%) and 14 in the progesterone group (19.4%) were admitted for preterm labor. However, this difference was not significant. The use of β-mimetic drugs in the management of preterm labor demonstrated a significant benefit in the progesterone group ($P = .031$). In the progesterone group, 85.7% of pregnant women had their delivery delayed for more than 72 hours, whereas in the placebo group this was observed in only 36.4% of the patients. Twelve of the 22 pregnant women in the placebo group (54.5%) and 10 of the 14 pregnant women (71.4%) in the progesterone group had a second episode of preterm labor, with an interval time of 3.9 ± 3.2 days and 5.7 ± 2.3 days in the placebo and progesterone groups, respectively ($P = .02$).

The average gestational age for those who had preterm birth was 33.5 ± 2.4 weeks in the progesterone group and 32.0 ± 0.7 weeks in the placebo group. Because preterm birth before 34 weeks is associated with the worst preg-
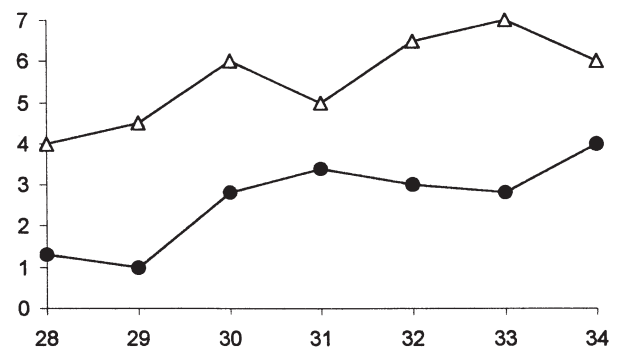
nancy outcome, we were especially interested in decreasing preterm birth incidence in this period. In Table III, it can be seen that more women were delivered before 34 weeks in the placebo group (18.6%) than in the progesterone group (2.8%). Figs 1 and 2 show the frequency of preterm delivery before 34 weeks. When the difference in the frequency of preterm birth in the progesterone (2.8%) and placebo (18.8 %) groups was compared, a statistically significant difference was observed ($P = .002$).

When survival analysis was used to establish the relationship between prophylactic vaginal progesterone administration and preterm birth, a lower gestational age at delivery correlated with the placebo group (mean 36 ± 3.3 weeks, range 29–41 vs mean 37 ± 2.8 weeks, range 28–41; $P = .029$). The probability of undelivered patients at 34 weeks of gestation was higher in the progesterone group than in the placebo group (97.2% vs 81.4%; $P = .029$) (Fig 3).

Mean contraction frequency for each gestational week studied was significantly greater for the placebo group than the progesterone group (Table IV). We calculated the maximum number of contractions per hour for each week between 28 and 34 weeks' gestation. The frequency of contractions was inferior in the group treated with progesterone than in the placebo group ($P < .004$) (Fig 4). As shown in Table V, the frequency of uterine contractions of more than four contractions per hour was more frequently found in the placebo group than in the progesterone group (54.3% vs 23.6%, respectively; $P = .0001$).

Comment

The results of this study confirm the findings of other studies reporting that progesterone is effective in preventing preterm delivery.[20-24] The real mechanism of action of this drug is not well known; however, its clinical usefulness was shown in our study by the decrease in the incidence of preterm birth from 28.1% in the placebo group to 13.8% in the progesterone group.

The difference between the two groups could not be explained in terms of epidemiologic characteristics, obstetric history, or frequency of premature membrane rupture because these parameters were similar in both groups. Our high incidence of spontaneous preterm delivery is related to the presence of a history of at least one preterm birth in the inclusion criteria.

The role of progesterone in pregnancy is unclear; however, we know that the effect of progesterone on the myometrium is 2-fold: it suppresses the action of estrogen by inhibiting the replacement of cytosolic estrogen receptors and it exerts a direct effect on the biosynthetic processes of the uterus through its own cellular receptor.[1,18,19] Thus, the contractile capacity is maintained under the influence of progesterone, as indicated by the development of tension in the electrically stimulated uterus of progesterone-treated rabbits or rats.

In the pregnant ewe, very close to the delivery, there is progesterone withdrawal and a surge in estrogen secretion. Myometrial oxytocin receptors appear, gap junctions are developed, and cervical ripening commences.[19]

On the other hand, progesterone withdrawal in primates is not an accepted theory, especially when viewed from a classic endocrine aspect.[1,19] In humans, serum progesterone-estrogen ratio does not show significant changes. Progesterone level in the blood does not decrease, there is no unusual metabolism of progesterone in the tissues, and there is no major extraplacental site of progesterone production.[20,21] However, a myometrial decrease in progesterone receptors was observed in patients in labor compared with those not in labor in preterm and term pregnancies. This may play a role in the onset of labor in women with term or preterm pregnancies.[5,7,19,21]

Thus, the concept of progesterone withdrawal as a quiescent biologic phenomenon in humans cannot be easily abandoned. First of all, such mechanisms are dominant in the mammalian world. Second, during the normal menstrual cycle, physiologic progesterone withdrawal occurs after ovulation and before menses.[5,20,21] Third, corpus luteectomy before the 8th week of gestation is followed by spontaneous abortion,[22,23] and abortion also follows the use of pharmacologic antiprogesterone agents in early pregnancy.[22,23] Some investigators suggest that labor may be stimulated later in pregnancy by these agents.[22]

In humans, the effects of progesterone on the frequency of preterm birth were consistent among similar trials. Johnson et al[16] and Yemini et al[14] used 250 mg of 17α-hydroxyprogesterone caproate by intramuscular injections per week until the 37th week. Papiernik-Berkhauer[24] used the same agent, twice a week, started between 28 and 32 weeks and stopped after eight doses. These authors demonstrated a reduction in preterm delivery rate in the progesterone group and concluded that 17α-hydroxyprogesterone caproate could be effective in preterm birth prevention.

Daya[22] and Goldstein et al[17] reported separate meta-analyses assessing the effects of progestogen administration in pregnancy but reached contradictory conclusions. Daya[22] showed a beneficial effect, whereas Goldstein et al[17] concluded that the data did not support this finding. These authors failed to distinguish between the use of progestogens for early miscarriage because of inadequate luteal phase and the use of progestogens for prophylaxis of preterm labor. Furthermore, in these two meta-analyses, the authors did not compare the same progestational agent. Because there are many differences between these agents, Keirse[25] conducted a third, more restricted meta-analysis. He demonstrated that 17α-hydroxyprogesterone caproate is effective in the prevention of preterm labor and preterm birth with an odds ratio of 0.43 (0.2-0.89) and 0.5 (0.3-0.85), respectively.

The probability to term delivery was higher in the progesterone group; however, there was no significant difference on the incidence of preterm labor in both groups. β-Mimetic drugs showed a significant benefit in the management of preterm labor in the progesterone group compared with the placebo group. This important result strongly suggests steroids could be used to stimulate surfactant synthesis in type II alveolar cell in this period.

This study indicates that the prophylactic use of natural progesterone may be associated with the decrease of uterine contractions. However, the lower incidence of preterm delivery in the progesterone group cannot be explained by these findings because uterine activity was only assessed weekly for just 1 hour.

Although we observed better results in the progesterone group, the mechanisms involved are unclear and cannot be explained by this article. Our study strongly suggests that, by administering vaginal natural progesterone in pregnant women with high risk for preterm delivery, it is possible decrease the frequency of preterm birth. However, multicenter randomized clinical trials with others risk factors are required to confirm these results.

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