DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF DIRECTOR

ACTION REFERRAL

TO	DATE
Myers	8-25-08

DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOG NUMBER 000105	[ ] Prepare reply for the Director's signature DATE DUE _____
2. DATE SIGNED BY DIRECTOR Cleared 9/8/08, letter attached.	[X] Prepare reply for appropriate signature DATE DUE 9-4-08 [ ] FOIA DATE DUE _____ [ ] Necessary Action

APPROVALS (Only when prepared for director's signature)	APPROVE	* DISAPPROVE (Note reason for disapproval and return to preparer.)	COMMENT
1.			
2.			
3.			
4.			

SUMTER OB-GYN, P.A.
POST OFFICE BOX 1469
SUMTER, SOUTH CAROLINA 29151

BARNEY L. WILLIAMS, JR., M.D.
JOHN J. BRITTON, M.D.
G. MURRELL SMITH, M.D.
THOMAS W. HEPFER, M.D.
SAMUEL M. RIDDLE, III, M.D.
HELEN D. LATHAM, M.D.
TRIZ V. SMITH, M.D.
TONIA STEVENSON, CNM

115 NORTH SUMTER STREET
SUITE 200
(803) 775-8351
FAX (803) 773-2635

8/25/8
P/s log to Rec
B2

August 21, 2008

Unison Pharmacy Department
1001 Brinton Road
Pittsburgh, PA 15221

Attn: Dr. Ward

Dear Dr. Ward:

I would like to formally petition you to consider Prometrium for treatment of preterm labor. I received a note that states, "the current literature does not support the use of Prometrium in this manner or for this indication."

I respectfully disagree with your above statement and am providing you with the current literature that most certainly does support treatment of vaginal progesterone for threatened preterm labor in appropriate patients.

Specifically, the patient was Sharon Hunter, who has a history of preterm delivery. I have many other patients in which this treatment has been refused. I am concerned about the medical legal risks that your company is taking by not providing the standard of care; effectively restricting low income patients from appropriate care. Because of my above concerns, I am also sending a letter to the Litigation Department of the SCMA, the Insurance Commission, Melanie Giese, SC DHHS as well as the OB Task Force Committee.

I would appreciate an immediate response to my letter and most of all, I would like my patients to receive medication that is prescribed by their physicians, whose area of expertise is high risk obstetrics.

Thank you very much for your consideration with this grievance.

Sincerely,

Helen D. Latham, MD

HDL/md
Enclosure:
(1) Literature

cc: Litigation Dept. Of SCMA
SC OB Task Force
Melanie Giese, RN, Bureau Director, SC DHHS
Scott Richardson, CPCU Director - SC Department Of Insurance

Unison Pharmacy Department
1001 BRINTON ROAD
PITTSBURGH, PA 15221
PHONE: (412)380-6015; 877-651-2217
FAX: (412)457-1328

#15580 OB + FU 7/31/08

Unison

Fax

To: Dr. Riddle	**From:** Kathy T.
Fax: 803-773-2462	**Pages:** 1
Phone: 803-775-8351	**Date:** 07/31/2008 3:21 PM
Re: Sharon Hunter	**ID#:** 000909346

☑ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments**

Prometrium 200mg 1 cap in vagina at bedtime has been reviewed and denied by Dr. Ward.

The request is not authorized as it is not medically necessary. The information reviewed does not support the medical necessity of using the requested drug, after review by Unison Health Plan. "Current literature does not support the use of Prometrium in the manner or for this indication."

A denial letter will be sent to you and to your patient.

Thank you

A written denial notice will be mailed to both the provider and Unison member pursuant to this initial notification. The letter will explain the grievance/appeal process. Providers may file a written or fax request for a grievance/appeal, with documented member consent.

If the requesting physician wishes to discuss the denial decision with the medical director who made the decision he/she may call within 7 working days of this denial notification, (please call the Pharmacy Department Medical Director Line at 1-800-701-7189). Any request for discussion of a denial decision received after 7 working days must follow the grievance/appeal process.

ACOG Committee Opinion

Committee on Obstetric Practice

Number 291, November 2003

Use of Progesterone to Reduce Preterm Birth

ABSTRACT: Preterm birth affects 12% of all births in the United States. Recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women (ie, those with a prior spontaneous birth at <37 weeks of gestation). Despite the apparent benefits of progesterone in this high-risk population, the ideal progesterone formulation is unknown. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice believes that further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug.

Preterm birth affects 12% of all births in the United States. This statistic has led multiple investigators to identify those women at greatest risk (eg, those with prior preterm delivery, maternal weight <50 kg, African-American race, bleeding, and concurrent sexually transmitted diseases). Despite identification of these risk factors, no interventions to date have been associated with a decrease in preterm delivery rates.

A recent large randomized placebo-controlled trial comparing 17α hydroxyprogesterone caproate "17P" therapy to prevent preterm birth in a select, high-risk group of women (documented history of a previous spontaneous preterm birth <37 weeks of gestation) was conducted for the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (1). A total of 459 women with a history of previous spontaneous births at less than 37 weeks of gestation were enrolled between 16 weeks and 20 weeks of gestation. Of note, the mean gestational age of their previous preterm deliveries was 30.7 weeks. They were randomly assigned to receive weekly intramuscular injections of 17P (n = 306) or placebo (n = 153). The study was stopped early when results showed a significant protection against recurrent preterm birth for all races of women who received 17P (Table 1).

A recent small randomized placebo-controlled trial of supplemental vaginal progesterone (100 mg daily) in 142 women at high risk for preterm birth

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

ISSN 1074-861X

The American College of Obstetricians and Gynecologists
409 12th Street, SW
PO Box 96920
Washington, DC 20090-6920

12345/76543

Use of progesterone to reduce preterm birth. ACOG Committee Opinion No. 291. American College of Obstetricians and Gynecologists. Obstet Gynecol 2003;102:1115–6.

Table 1. Rates of Preterm Labor with Progesterone Therapy or Placebo

Gestation	Placebo Group (n = 153)	Progesterone Group (n = 306)	Relative Risk	Confidence Interval	P
<37 wk	54.9%	36.3%	0.66	0.54–0.81	.0001
<35 wk	30.7%	20.6%	0.67	0.48–0.93	.0165
<32 wk	19.6%	11.4%	0.58	0.37–0.91	.0180

Data from Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379–85.

(women with at least 1 previous spontaneous preterm birth, prophylactic cervical cerclage, and uterine malformation) revealed that for delivery at less than 34 weeks of gestation, the preterm birth rate was significantly lower among women receiving progesterone than among those receiving placebo (2.7% versus 18.6%) (2). The results of this study and the NICHD trial support the hypothesis that progesterone supplementation reduces preterm birth in a select very high-risk group of women.

Despite the apparent benefits of progesterone in a high-risk population, the ideal progesterone formulation is unknown. The 17P used in the NICHD trial was specially formulated for research and is not currently commercially available on a wide scale. Progesterone has been studied only as a prophylactic measure in asymptomatic women, not as a tocolytic agent. Whether vaginal progesterone is equally efficacious remains to be proved in a larger population. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice believes that further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug.

References

1. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379–85.
2. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. 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. Am J Obstet Gynecol 2003;188:419–24.

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

Eduardo B. da Fonseca, MD, Roberto E. Bittar, PhD, MD, Mario H. B. Carvalho, MD, and Marcelo Zugaib, PhD, MD

Sao Paulo, Brazil

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-

From the Obstetrics Clinic, University of São Paulo Medical School.
Supported by FAPESP.
Received for publication January 9, 2002; revised June 12, 2002; accepted September 11, 2002.
Reprint requests: Eduardo B. da Fonseca, MD, University of Sao Paulo Medical School, Obstetric Clinic, Av 11 de junho, 1006 apto 133, Vila Clementino, Sao Paulo–SP, 04041-003, Brazil. E-mail: riedu@uol.com.br

000-9278/2003 $30.00 + 0
doi:10.1067/mob.2003.41

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-

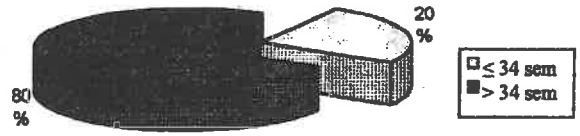

Fig 1. Incidence of preterm delivery before 34th week in natural progesterone group.

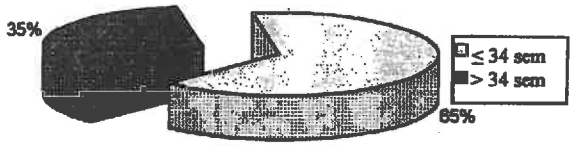

Fig 2. Percentage of preterm delivery before 34th week in placebo group.

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-

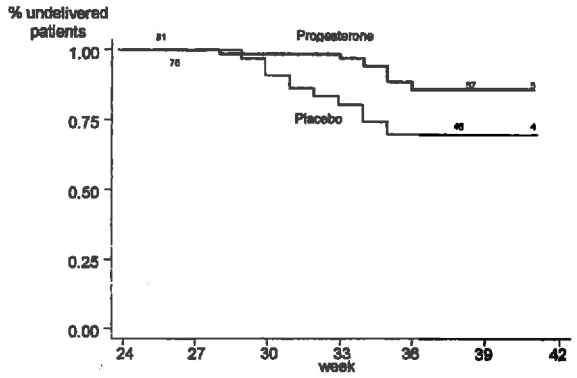

Fig 3. Cumulative percentage of undelivered patients per week, by placebo and progesterone group. Log-rank $\chi^2 = 5.33$, $P = .029$.

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

	Placebo	*Progesterone*	
Gestational age (wk)	*Mean ± SD*	*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

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 pregnancy 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).

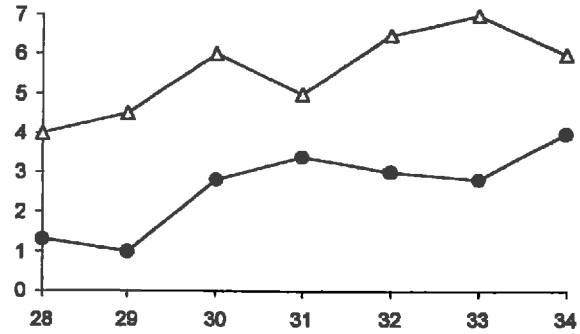

Fig 4. Mean contraction frequency based on 1 hour of monitoring per week, by placebo and progesterone group and by gestational age (28, 29, 30, 31, 32, 33, and 34 weeks' gestation). *Open squares,* Placebo group; *solid circle,* progesterone group. $F = 9.5$, $P = .004$.

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

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.

REFERENCES

1. Amon E. Preterm labor. In: Reece EA, Hobbins JC, editors. Medicine of the fetus and mothers. Philadelphia: Lippincott-Raven; 1999. p. 1529-79.
2. Rush RW, Davey DA, Segall ML. The effect of preterm delivery on perinatal mortality. Br J Obstet Gynaecol 1978;85:806-11.
3. Ehrenhaft PM, Wagner JL, Herdman RC. Changing prognosis for very low birth weight infants. Obstet Gynecol 1989;74:528.

4. Challis JRG. Characteristics of parturition. In: Creasy RK, Resnik R, editors. Maternal fetal medicine. 4th ed. Philadelphia: WB Saunders; 1999. p. 484-97.
5. Cunningham FG, Macdonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, et al. Preterm and postterm pregnancy and fetal growth retardation. In: Williams' obstetrics. 20th ed. New Jersey: Prentice-Hall International; 1997. p. 797-826.
6. Lockwood CJ, Senyei, AE, Dischie MR, et al. Fetal fibronectina in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med 1991;325:669-74.
7. Bittar ER, Yamasaki AA, Sasaki S, Zugaib M. Cervical fetal fibronectina in patients at increased risk for preterm delivery. Am J Obstet Gynecol 1996;175:178-81.
8. Katz M, Gill P, Newman RB. Detection of preterm labor by ambulatory monitoring of uterine activity: a preliminary report. Obstet Gynecol 1986;68:773-8.
9. Iams JD. Uterine contraction monitoring and preterm birth. In: Elder MG, Lamont RF, Romero R, editors. Preterm labor. Philadelphia: Churchill Livingstone; 1997. p. 185-93.
10. Newman RB, Campbell BA, Stramm SL. Objective tocodynamometry identifies labor onset earlier than subjective maternal perception. Obstet Gynecol 1990;76:1089-92.
11. Nageotte MP, Dorcheter W, Porto M, Keegan KA, Freeman RK. Quantitation of uterine activity preceding preterm, term and postterm labor. Am J Obstet Gynecol 1994;170:20-5.
12. Cunningham FG, Macdonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, et al. Parturition: biomolecular and physiology processes. In: Williams' obstetrics. 20th ed. NJ: Prentice-Hall International; 1997. p. 797-826.
13. Erny R, Pigne A, Prouvost C, Gamerre M, Malet C, Serment H, et al. The effects of oral administration of progesterone for premature labor. Am J Obstet Gynecol 1986;154:525.
14. Yemini M, Borestein R, Dreazen E, Apelman Z, Molginer BM, Kessler I, et al. Prevention of premature labor by 17 α-hydroxyprogesterone caproate. Am J Obstet Gynecol 1985;151:574-7.
15. Nobloz G, Andra P, Dargent D, Fagner B, Melner G. The use of micronized progesterone in the treatment of menance of preterm delivery. Eur J Obstet Gynecol Reprod Biol 1991;40:203.
16. Johnson JWC, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17-α hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med 1975;293:675-80.
17. Goldestein P, Berrier P, Rosen J, Sachs HS, Chalmers TC. A meta-analysis of randomized control trials of progesterone agents in pregnancy. Br J Obstet Gynaecol 1989;96:265-74.
18. Fuchs F, Stakeman G. Treatment of threatened premature labor with large doses of progesterone. Am J Obstet Gynecol 1960;79:172.
19. Fuchs AR, Fuchs F. Endocrinology of human parturition: a review. Br J Obstet Gynaecol 1984;91:948-67.
20. Keelan JA, Myatt L, Mitchell MD. Endocrinology and paracrinology of parturition. In: Elder MG, Lamont RF, Romero R, editors. Preterm labor. Philadelphia: Churchill Livingstone; 1997. p. 457-91.
21. Mazor M, Hershkomitz R, Cham W, Levy S, Sharony Y, Leiberman JR, et al. Human preterm birth is associated with systemic and local changes in progesterone 17 β-estradiol ratios. Am J Obstet Gynecol 1994;171:231-6.
22. Daya S. Efficacy of progesterone support for pregnancy in women with recurrent miscarriage: a meta-analysis of controlled trials. Br J Obstet Gynaecol 1999;96:275-80.
23. Check JH, Lee G, Epstein R, Vetter B. Increased rate of preterm deliveries in untreated women with luteal phase deficiencies. Gynecol Obstet Invest 1992;33:183-4.
24. Papiernik-Berkhauer E. Etude en double aveugle d'un médicament prevenant la survenue prématurée de l'accouchement chez les femmes 'à risque éleve' d'accouchement prématuré. In: Edition Schering, Serie IV, fiche. p. 65-8.
25. Keirse MJN. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol 1990;97:149-54.

Log #105

State of South Carolina
Department of Health and Human Services

Mark Sanford
Governor

Emma Forkner
Director

September 8, 2008

Helen D. Latham, M.D.
Sumter OB-GYN, P.A.
Post Office Box 1469
Sumter, South Carolina 29151

Dear Dr. Latham:

We are in receipt of your letter of August 21, 2008 to Sheila Ward, MD, Medical Director, Unison Health Plan, regarding denial of the medication Prometrium for Sharon Hunter, a Unison Health Plan member. Prometrium is a medication which is used for prevention of preterm labor.

David Smith, the Program Manager assigned to Unison Health Plan, contacted Mr. Rob Brekosky, Manager, Pharmacy Operations, with Unison Health Plan on August 27, 2008 concerning the denial of this medication. On August 28, 2008, Mr. Brekosky provided Mr. Smith with a written summary prepared by Dr. Ward of the details of this case and the rationale for the decision to uphold the denial.

The literature provided by your practice from the product manufacturer (Solvay Pharmaceuticals), and the literature on the use of progesterone for the prevention of preterm delivery fails to support initiating treatment of patients in the 3rd trimester of pregnancy with progesterone, either by injection, orally or as a vaginal suppository.

After consulting with the OBGYN Department Chair at the University of South Carolina, Tan Platt, MD, Medical Director with the South Carolina Department of Health and Human Services (SCDHHS), concurs with Unison's decision to deny the request for the use of the drug Prometrium for pregnant women in their 3rd trimester.

SCDHHS certainly understands your position with this matter. If you have exhausted the appeals process with Unison Health Plan, and are still not satisfied with the results, you have the right to request a Fair Hearing through SCDHHS. This request must be received in writing, within thirty (30) days from the date of Unison Health Plan's notice of resolution, by SCDHHS at the following address:

Medical Services
P.O. Box 8206 • Columbia, South Carolina 29202-8206
(803) 898-2501 • Fax (803) 255-8235

Division of Appeals and Hearings
Department of Health and Human Services
Post Office Box 8206
Columbia, South Carolina 29202-8206

In order to preserve your appeal rights, you may also fax this request to the Division of Appeals and Hearings at (803) 255-8206. If you choose to fax your request, you will still need to mail the original request to the address above.

As is the goal of Sumter OB-GYN to provide the best healthcare possible to their patients, it is the mission of the SCDHHS to provide the best healthcare value for South Carolinians.

We appreciate your continued participation in the South Carolina Medicaid program. If you have any questions about this letter or need further assistance, please contact Mr. Smith at (803) 898-2639.

Sincerely,

Felicity Myers
Deputy Director

FM/hhc

cc: Litigation Department of SCMA
SC OB Task Force
Dan Gallagher, President, Unison Health Plan of South Carolina
Melanie Giese, RN, Bureau Director, SCDHHS
Scott Richardson, CPCU Director, SC Department of Insurance
Sheila M. Ward, M.D., Medical Director, Unison Health Plan
Tan Platt, M.D., Medical Director, SCDHHS