A Randomized Trial of Micronized Progesterone for the Prevention of Recurrent Preterm Birth

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ABSTRACT

We sought to evaluate the effectiveness of daily oral micronized progesterone (MP) in preventing recurrent spontaneous preterm birth (RSPB) and whether MP increases maternal serum progesterone. We performed a pilot, single-center, randomized, double-blind, placebo-controlled trial in women with a prior preterm birth and current singleton gestation at 16 to 20 weeks (n = 33). The primary outcome was the rate of RSPB. Subjects were given either daily MP (400 mg) or placebo from 16 to 34 weeks. Serum progesterone was obtained at enrollment and in the late second/early third trimester. Pregnancy outcome data were collected. RSPB occurred in 5/19 (26.3%) in the MP group versus 8/14 (57.1%) in placebo group (p = 0.15). The mean age at delivery was 37.0 ± 2.7 weeks for the MP group versus 35.9 ± 2.6 weeks for the placebo (p = 0.3). Mean serum progesterone at 28 weeks was 122.6 ± 61.8 pg/mL for MP group versus 90.1 ± 38.7 pg/mL for placebo (p = 0.19). MP was associated with a trend toward a reduction in RSPB and an increase in the maternal serum progesterone. Although the primary outcome in this pilot study did not reach statistical significance, the results suggest a favorable trend meriting further investigation.

KEYWORDS: Preterm delivery, micronized, progesterone, recurrent, prevention

Preterm birth, defined as delivery at less than 37 weeks gestation, complicates approximately 12% of pregnancies in the United States.1 Preterm births, particularly deliveries prior to 32 weeks gestation, account for a disproportionate amount of infant mortality and morbidity.1 Although numerous trials have evaluated interventions such as tocolysis, bed rest, uterine activity monitoring, and antibiotics for preterm birth prevention, an effective and reproducible intervention had not been found until recently.2-5

In a randomized trial of 17 α-hydroxyprogesterone caproate (17P) administered intramuscularly on a weekly basis, Meis et al demonstrated a significant decrease in the rate of recurrent spontaneous preterm birth (RSPB).3 Unfortunately, 17P users report significant discomfort associated with the injections. It is recognized that progesterone is locally irritating when injected into a muscle.6 This is compounded by the fact that the medium used to dilute the progesterone is quite viscous. The fact that the protocol proposed by Meis et al...
required weekly injections from 16 to 36 weeks gestation may present a logistical problem for the patient. Therefore, development of a therapy that obviates the need for injections has several benefits.

Bioavailability of natural progesterone administered orally is limited by first-pass effect through the liver. However, micronization of this substance increases the bioavailability of oral progesterone to the point where pharmacological serum levels may be attained. Furthermore, natural progesterone is readily synthesized from a plant source and is chemically identical to progesterone of human origin. This study was designed to test the feasibility of utilizing oral micronized progesterone (MP) to prevent RSPB in women with a prior preterm birth.

MATERIALS AND METHODS

This is a single-center, double-blind, placebo-controlled trial conducted at Miami Valley Hospital, Dayton, Ohio, from November 2006 to January 2009. Human subjects’ committee approval was obtained prior to initiation of the study (Institutional Review Board #06–0066). The study is registered with the U.S. FDA ClinicalTrials.gov, Study ID: MVH-MP-PilotRCT. Medical records of women presenting to our resident staff obstetric clinic for prenatal care prior to 20 weeks gestation were screened for eligibility. The initial gestational dating was based on the best obstetric estimate. Patients were considered eligible for the study if they were less than 20 weeks gestation and had at least one prior spontaneous preterm birth of a live-born singleton infant between 20/7 weeks and 36/7 weeks gestation. Exclusion criteria included multiple gestations, the presence of major fetal anomalies, progesterone use in the current pregnancy (ongoing or past), the presence of a cervical cerclage, and the presence of a placenta previa. Patients were also excluded from the study if they terminated their care at our clinic or if they delivered at another institution, if they did not complete the initial prerandomization evaluations, or if they had a spontaneous abortion prior to initiating the study medication. Eligible women were approached by a research nurse, the study protocol was explained, and a written informational brochure was provided. Each patient was offered weekly 17P injections as an alternative to participating in the study. Written informed consent was obtained prior to enrollment. Randomization was done by the hospital’s research pharmacy using a standard randomization table methodology for two groups.

A targeted ultrasound to evaluate the fetal anatomy and gestational age was performed, and a baseline cervical length was obtained using transvaginal ultrasound prior to randomization. If the baseline cervical length was greater than 25 mm, repeat measurement was performed at 24 weeks gestation. If the initial cervical length was 10 to 25 mm, cervical lengths were evaluated at 2-week intervals up to 24 weeks gestation. Cervical length was measured on weekly basis in patients whose baseline cervical length was less than 10 mm. If a woman was found to have a cervical length of 5 mm or less prior to 24 weeks, then she was offered a cervical cerclage. A baseline serum progesterone level was obtained shortly after randomization. Repeat serum progesterone testing was performed during routine prenatal blood testing in the late second/early third trimester.

Study medications were formulated by Bellevue Pharmacy (St. Louis, MO). The placebo tablets were identical in appearance and packaging to those that contained the MP. The placebo capsule was formulated using the E4M filler and a blue gelatin No. 1 capsule with a weight of 311 mg. The oral MP capsule consisted of 200 mg MP, 111 mg of the E4M filler, and a blue gelatin No. 1 capsule, with a target weight of 311 mg. The tablets were shipped to Miami Valley Hospital and stored in the research pharmacy. After subjects were randomized to their respective group, the research pharmacy dispensed a 1-month supply (n = 60) of either progesterone or placebo tablets in identical prescription bottles, which were labeled identically as “progesterone study medication.”

The patient instructions were to take two tablets daily at bedtime. The bedtime dosing schedule was chosen to minimize reported side effects such as dizziness, hypnosis, nausea, and fatigue. The study group took 400 mg (two 200-mg capsules) of oral MP and the control group took two identical placebo capsules. The 400-mg dose of MP was empirically chosen as this was the largest dose for which there is reported human data. Administration of the tablets (MP or placebo) was initiated between 16/7 and 19/7 weeks and was continued until the completion of the 33rd week of gestation. The duration of treatment was chosen to include the weeks of gestation where the most serious complications from prematurity occur. Compliance was assessed by pill counts and verbally at each prenatal visit. At each prenatal visit, the subjects were queried about side effects and adverse effects.

The study subjects’ physicians were aware of the study participation but were blinded to the group assignment. Study subjects with symptoms of preterm labor between 24/7 and 33/7 weeks or symptoms suggestive of rupture of membranes were evaluated and treated according to established protocols. If a study subject was admitted to the hospital for an obstetric or medical complication of pregnancy, the study medication was continued. Records relating to prenatal care, delivery, and status of the newborn were reviewed. Maternal demographics, maternal risk factors, gestational age at delivery, birth weight, gender, and neonatal outcome were recorded.
The primary outcome was the rate of RSPB at less than 37.0 weeks gestation in each group and serum progesterone levels. We conducted a power analysis based on an estimated 23.4% rate of RSPB. To achieve 80% power, 400 women would be required in each group in order for a one-third reduction in RSPB to have statistical significance. Because this study was being conducted at a single center with ~5000 deliveries per year, it was not practical to enroll enough patients to achieve a statistical significance. Therefore the study was conducted as a pilot study with specific interest in the medication tolerance, outcome trends, and serum progesterone levels. Secondary outcomes evaluated neonatal morbidity and mortality. An interim analysis was conducted at the end of the 2-year period, and the practicality of continuing the study was assessed. Categorical variables were compared utilizing the two-tailed Fisher exact test. Continuous variables with a normal distribution were compared utilizing Student t test, and those without a normal distribution were compared using the Wilcoxon/Kruskal-Wallis rank sums. A p value of less than 0.05 was considered significant.

RESULTS
From November 2006 to January 2009, 45 eligible women were evaluated for randomization. During this period, there were ~140 women with a history of spontaneous preterm birth who were receiving obstetric care in our clinic. During the study period, 35 women with a history of a prior spontaneous preterm birth were ineligible for the study due to treatment with 17P injections. Nine women did not complete the initial evaluation (ultrasound and blood collection) or failed to present to the pharmacy for randomization and were excluded. Three more subjects were excluded. One subject from the MP group initially gave a history of spontaneous preterm labor and delivery but it later became apparent that she had been induced at 36 weeks gestation for severe preeclampsia. One subject from the placebo group had a spontaneous abortion at 14 weeks gestation for severe preeclampsia. One subject from the placebo group did not complete her prenatal care at our facility and delivered elsewhere. There were 33 subjects who remained for the analysis. Fourteen received placebo and 19 received MP. Two subjects (one from each group) ended their participation in the study at 4 and 27 days, respectively, after filling their first prescriptions. Both stopped for reasons other than an adverse reaction to the medication. They both delivered at our institution and were included in their respective group for all of the analyses. There were no reported side effects or adverse effects from the study medications.

There were no statistically significant differences in the baseline demographic between the two groups (Table 1). Overall, the two groups had similar risk factors for RSPB. The only exception was that the patients who were assigned to the MP group had a somewhat greater number of previous preterm deliveries (mean = 2.2 ± 1.2 standard deviation) than the patients in the placebo group (mean = 1.5 ± 0.9; Table 1). However, this difference did not reach statistical significance (p = 0.07). No subjects required a cervical cerclage. Two of the patients in the MP group and one patient in the placebo group failed to get a baseline maternal serum progesterone level drawn. The gestational ages of the patients who did have the level done were not statistically different (mean = 17.7 ± 2.1 in the MP group [n = 17] and mean = 18.5 ± 2.5 in the placebo group [n = 13]; p = 0.3). Likewise, the baseline serum progesterone levels were not statistically different between the two groups (mean = 34.5 ± 15.3 pg/mL in the MP group and mean = 39.8 ± 14.5 pg/mL in the placebo group; p = 0.5).

A trend toward a later delivery was noted in the MP group (mean = 37.0 ± 2.7 weeks) as compared with the placebo group (mean = 35.9 ± 3.8 weeks; p = 0.3). Also, the RSPB rate in the MP group was less (26.36% [5/19]) than in the placebo group (57.1% [8/14]; relative risk of RPTB with MP 0.55, 95% confidence interval 0.26 to 1.16), but the difference did not reach statistical significance (p = 0.15).

A repeat maternal serum progesterone level was drawn at a mean gestational age of 25.9 ± 2.4 weeks in

<table>
<thead>
<tr>
<th>Maternal Demographics and Risk Factors</th>
<th>Placebo (n = 14)</th>
<th>Oral Micronized Progesterone (n = 19)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Maternal age at delivery (y)</td>
<td>27.2 ± 4.9</td>
<td>29.3 ± 4.7</td>
<td>0.3</td>
</tr>
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<td>Gravidity (mean)</td>
<td>4.1 ± 2.1</td>
<td>5.2 ± 2.1</td>
<td>0.11</td>
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<tr>
<td>Mean gestational age at randomization (wk)</td>
<td>18.2 ± 2.7</td>
<td>16.9 ± 2.6</td>
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<tr>
<td>Maternal risk factors</td>
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<tr>
<td>Non-Caucasian race (%)</td>
<td>50.0</td>
<td>42.1</td>
<td>0.73</td>
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<td>Prepregnancy body mass index (lb/in²)</td>
<td>27.3 ± 7.5 (12/14)</td>
<td>28.1 ± 8.1 (18/19)</td>
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<td>Tobacco use (%)</td>
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<td>55.0</td>
<td>1.0</td>
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<tr>
<td>No. of prior spontaneous preterm birth (mean)</td>
<td>1.5 ± 0.9</td>
<td>2.2 ± 1.2</td>
<td>0.07</td>
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<tr>
<td>Mean baseline cervical length (mm)</td>
<td>34.0 ± 4.5</td>
<td>34.9 ± 6.9</td>
<td>0.67</td>
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15 subjects in the MP group and at a mean gestational age of 28.4 ± 4.7 weeks in 8 subjects in the placebo group (p = 0.11). The mean serum progesterone in the placebo group was 90.1 ± 38.7 pg/mL and 122.6 ± 61.8 pg/mL for the MP group (p = 0.19).

There were no significant differences in the secondary outcomes (Table 2). However, 21.4% (3/14) of newborns in the placebo group required mechanical ventilation versus none in MP group (p = 0.067).

**DISCUSSION**

This is a pilot study of MP for the prevention of RSPB with specific interest in the medication tolerance, outcome trends, and serum progesterone levels. As the study progressed, it became apparent that with the availability of an accepted mode of treatment (i.e., 17P injections), the rate of uptake for the study was such that it was impractical to show a statistically significant difference in the rate of uptake for the study was such that it was impractical to show a statistically significant difference in RSPB with just one center. Therefore the study was terminated after an interim analysis demonstrated a clear trend toward a decrease in RSPB and an increase in progesterone levels in the MP group.

In our study, the RSPB is similar to the multicenter trial of intramuscular 17P conducted by the Maternal–Fetal Medicine Units Network of the National Institute of Child Health and Human Development. In that study, delivery less than 37 weeks gestation was reduced from 54.9% in the placebo group to 36.3% in the treatment group, and we observed 57.1% in placebo versus 26.3% in the MP group. Rai et al investigated MP for the prevention of RSPB and also found a reduction in RSPB similar to ours (59.5% in the placebo group, 39.2% in the oral MP group). In that study, a twice daily 100-mg dosing was used as opposed to the higher once daily dose (400 mg) used in our study.

Our study also attempted to evaluate how administration of oral MP affects the maternal serum progesterone level. Though underpowered, our data suggests that the 400-mg daily dosing regimen of oral MP does raise the maternal serum progesterone level.

This study is unique in that 400 mg, which is a relatively high dose of MP, was used. We did not find any increase in maternal side effects or adverse effects that resulted to discontinuing the use of MP. The majority (31/34 or 91.2%) of the patients who proceeded to the stage where administration of medications was initiated completed the study. Neither of the two patients (one in the MP group and one in the placebo group) who self-discontinued participation in study did so due to medication-related symptoms.

One of the strengths of this study is the fact that it was done in a randomized, double-blind, placebo-controlled fashion. It was performed at a single center in which all prenatal and peripartum care was delivered. Therefore, the protocols used for evaluation, diagnosis, and treatment of preterm labor and other pregnancy complications were standardized. Similarly, all neonates requiring neonatal intensive care were admitted to one level III neonatal intensive care unit (NICU) located within our medical center, ensuring comparable NICU care for each neonate.

A major limitation of the study is the fact that the number of subjects did not reach the number estimated by our a priori power analysis. An additional limitation of the study is the fact that the number of subjects randomized into the two groups was not equal (19 in the MP group versus 14 the placebo group). We would expect this to self-correct as the number of subjects increases.

This study supports the contention that oral MP has the potential to be an effective agent in reducing RSPB. Its use as a single oral dose appears to be well tolerated by patients and may improve patient compliance. The oral route of administration obviates the discomfort that results from intramuscular injections and the need for a logistical support that is required for administration of injections. The cost of this type of treatment regimen has the potential to be significantly less expensive than a treatment protocol that includes administration of injectable medications. Further studies are required to further delineate the effectiveness of single-dose oral MP treatment in reducing the RSPB rates.

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<th>Table 2 Secondary Outcomes</th>
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<td><strong>Secondary Outcomes</strong></td>
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<td>Birth weight (g)</td>
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<tr>
<td>Male gender (%)</td>
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<tr>
<td>5-minute Apgar (mean)</td>
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<td>Ventilator use (%)</td>
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<td>Neonatal length of stay (mean), d</td>
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foundation. There are no financial or other conflicts of interest to disclose.

NOTE
Presented as a poster at the Society for Maternal-Fetal Medicine 30th Annual Scientific Meeting, February 5, 2010.

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