INCREASED INCIDENCE OF GESTATIONAL DIABETES IN WOMEN RECEIVING PROPHYLACTIC 17 ALPHA-HYDROXYPROGESTERONE CAPROATE FOR PREVENTION OF RECURRENT PRETERM DELIVERY

Received for publication 21 March 2007 and accepted in revised form 28 May 2007.

Andrei Rebarber, MD\textsuperscript{1}; Niki B. Istwan, RN\textsuperscript{2}; Karen Russo-Stieglitz, MD\textsuperscript{3}; Jane Cleary-Goldman, MD\textsuperscript{1}; Debbie J. Rhea, MPH\textsuperscript{2}; Gary J. Stanziano, MD\textsuperscript{2}; Daniel H. Saltzman, MD\textsuperscript{1}

\textsuperscript{1}Mount Sinai School of Medicine, Division of Maternal Fetal Medicine, New York, New York, \textsuperscript{2}Matria Healthcare, Department of Clinical Research, Marietta, Georgia, \textsuperscript{3}Valley Health System, Division of Maternal Fetal Medicine, Ridgewood, New Jersey

Corresponding Author:
Andrei Rebarber MD
70 East 90\textsuperscript{th} Street
New York, N.Y 10029
Email: arebarber@mfmnyc.com

Running Title: Progesterone and gestational diabetes.

Condensation: Injections of 17P for the prevention of recurrent preterm delivery increases the incidence of gestational diabetes.
Abstract

OBJECTIVE: Progesterone has a known diabetogenic effect. We sought to determine if the incidence of gestational diabetes (GDM) is altered in women receiving weekly 17 alpha-hydroxyprogesterone caproate (17P) prophylaxis for the prevention of recurrent preterm birth.

RESEARCH DESIGN AND METHODS: Singleton gestations having a history of preterm delivery were identified from a database containing prospectively collected information from women receiving outpatient nursing services related to a high-risk pregnancy. Included were patients enrolled for outpatient management at <27 weeks' gestation with documented pregnancy outcome and delivery at >28 weeks. Patients with pre-existing diabetes were excluded. The incidence of GDM was compared between patients receiving prophylactic intramuscular 17P (250mg weekly injection initiated between 16.0 and 20.9 weeks gestation) and those that did not.

RESULTS: Maternal body-mass-index and age were similar. The incidence of GDM was 12.9% in the 17P group (n=557) compared with 4.9% in controls (n=1524), \( p<0.001 \); Odds Ratio (95% CI) 2.9 (2.1, 4.1).

CONCLUSION: The use of 17P for the prevention of recurrent preterm delivery is associated with an increased risk of developing GDM. Early GDM screening is appropriate for women receiving 17P prophylaxis.
Preterm birth is the leading cause of perinatal mortality and morbidity for non-anomalous infants in the United States where over 12% of infants, approximately 480,000, are born prematurely each year. (1) Though past studies of progestational agents for the prevention of preterm delivery reported varied results, there has been renewed interest in the use of 17 alpha-hydroxyprogesterone caproate (17P) as a secondary preterm birth prevention strategy following a recent study from the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. (2, 3) The NICHD-MFMU Network study examined the effectiveness of 17P in reducing the rate of preterm delivery in women with a singleton gestation and a history of prior preterm delivery. The 17P was administered via weekly injections initiated between 16 and 20 weeks’ gestation and was shown to decrease the incidence of recurrent preterm birth in the study population by 33%. (3) Meta-analysis including both older and current studies has provided further support for the use of 17P for preterm birth prevention, (4) though the mechanism of action by which 17P prevents preterm birth remains poorly understood.

The metabolic changes of normal pregnancy are essential in order to provide adequate nutrients to the growing fetus. As pregnancy progresses, increased levels of human chorionic somatomammotropin (hCS), cortisol, prolactin, progesterone, and estrogen lead to insulin resistance. Studies in animal models demonstrate that progesterone plays an important role in signaling insulin release and pancreatic function. (5) The relatively diabetogenic properties of progesterone peaking at 32 weeks of gestation have been described in humans. (6) The American Diabetes Association (ADA) recommends screening all women at risk for GDM. The ADA considers women to be at risk for GDM unless they are less than 25 years of age, have normal body weight, have no first-degree relatives with diabetes, and have no history of glucose intolerance or poor obstetrical outcome, and are not a member of a high-risk ethnic group. (7) A 2001 Practice Bulletin of the American College of Obstetricians and Gynecologists (ACOG) recommends a similar risk-based approach, but notes that since only a small percentage of patients meet criteria for low risk, universal 50-gram 1-hour glucose challenge test (GCT) screening may be a more practical approach. (8) Conversely, the U.S. Preventive Services Task Force (USPSTF) concluded that the evidence is insufficient to recommend for or against routine screening for gestational diabetes. (9) Because glucose intolerance increases during pregnancy, screening for GDM is most commonly conducted during the 24th to 28th week of gestation. (9, 10)

The purpose of the present study is to determine if there is an increased incidence of gestational diabetes (GDM) in women receiving supplemental progesterone by weekly 17P injection for the prevention of preterm birth.

**Research Design and Methods**

The study population was identified retrospectively from a large database containing information from women who received outpatient perinatal services for pregnancy-related conditions through Matria Healthcare. Information stored in
the database is collected prospectively from the patient and her healthcare provider at the start of outpatient services as well as during the course of care. The data include medical and pregnancy history, current pregnancy risk factors and diagnoses, biometric clinical data relative to services provided, medications received, and maternal and neonatal outcome data. All information is collected using standardized operating procedures, forms, and computer systems. Written consent is obtained from each patient upon enrollment for services allowing for the use of her anonymous, de-identified data for research and reporting purposes. Each patient’s physician was responsible for all antepartum testing and treatment decisions.

For the present study we utilized de-identified data from women with singleton gestations having a history of prior preterm delivery, enrolled for outpatient services at less than 27 weeks of gestation. Eligible for analysis were women who had a documented height and pre-pregnancy weight, and complete documentation of pregnancy outcome (including antepartum complications documented in discrete fields of Yes, No, or Unknown answers and GDM status) in the outpatient record. We excluded patients reporting a pre-existing diagnosis of diabetes at admission for outpatient services, a medical history of diabetes prior to the current pregnancy, or who had “Unknown” designated for GDM in the antepartum outcome record. Also excluded were women experiencing recurrent preterm delivery prior to 28 weeks in the current pregnancy, as these women may not have yet received testing for GDM. Timing of GDM testing was determined by each patient’s physician and not documented in the outpatient record. For most women, glucose screening is conducted between 24 and 28 weeks’ gestation unless they are known to have carbohydrate intolerance before the 24th week of gestation. (9, 10)

Data were divided into treatment (17P) and control (no 17P) groups. The treatment group was comprised of 557 patients prescribed weekly intramuscular injections of 250 mg of 17P initiating at 16-20.9 weeks’ gestation and administered by Matria Healthcare between April 2004 and January 2006, while the control group was comprised of 1524 patients at similar risk for recurrent preterm delivery (history of prior preterm delivery) that did not receive 17P through Matria Healthcare or any other source. The 17P was compounded by a qualified compounding pharmacy using an ISO Class 5 Clean Room with adequate quality control procedures and documentation to assure sterility and potency of each vial. Unit dose vials were delivered to the patient’s home for weekly administration by a perinatal nurse. During the weekly visits patients were counseled regarding the signs and symptoms of preterm labor. Between weekly visits nurses and pharmacists were available at any time for patient questions and concerns through a toll-free number. Patients in the control group received specialized education and counseling from a perinatal nurse based on their clinical condition and outpatient program in which they were enrolled. All patients received scheduled clinical assessment, which included evaluation of any patient reported signs or symptoms of preterm labor and had nursing support available via telephone 24 hours per day. Prescription of betamimetic medications for tocolysis (in both groups) was at the
discretion of each patient’s individual healthcare provider.

Data were analyzed using Student’s t, Mann-Whitney U, Pearson’s $\chi^2$ and Fisher’s Exact test statistics as appropriate based on data distributions to compare differences between control and treatment groups. Since maternal weight and betamimetic medications are commonly thought to influence development of GDM, data regarding pre-pregnancy body mass index (BMI) (<20, 20-24.9, 25-29.9, and ≥30 kg/m$^2$) and use of betamimetics for tocolysis were also examined. The primary study outcome was the incidence of GDM.

Results
Maternal characteristics are presented in Table I. As expected, since the recommended gestational age for initiation of 17P is at 16-20 weeks, women receiving 17P started outpatient services earlier than those in the control group. The majority of women in the control group (62.1%) received outpatient preterm labor surveillance services (daily outpatient uterine contraction monitoring and nurse assessment), while those remaining received outpatient services for conditions such as hyperemesis gravidarum or pregnancy-related hypertension. All patients in both groups had a history of at least one prior preterm delivery. Almost 25% of control patients were prescribed betamimetic tocolytic medications compared with 18.1% in the 17P treatment group, $p=0.002$. Women in the treatment group received a mean of 14.9 ± 4.5 injections of 250mg of 17P.

Women receiving 17P had a significantly higher incidence of GDM compared with controls [12.9% in the 17P group compared with 4.9% in controls, $p<0.001$; Odds Ratio (95% CI) 2.9 (2.1, 4.1)]. Gestational age at delivery was similar between the groups (36.9 ± 2.3 weeks in the 17P group compared with 37.1 ± 2.4 weeks in controls, $p=0.080$). There were similar rates of spontaneous recurrent preterm delivery at <35 weeks’ gestation between women treated with 17P and controls (12.4% vs. 9.6% respectively, $p=0.062$).

Due to significant univariate differences found in rates of maternal smoking, betamimetic use, and gestational age at start of outpatient management between the study groups (see Table I), plus the known association between maternal weight and GDM, a logistic regression model was tested to assess relative independent associations on the dependent outcome of GDM incidence (Table II). While patients in the obese and overweight categories had the highest risk of developing GDM, use of 17P continued to impart a positive, independent association with GDM incidence – overall adjusted odds ratio 3.09.

Conclusions
It is estimated that 1 in 8 infants in the United States are born preterm, accounting for nearly 500,000 preterm births each year. (1) Primary prevention of preterm birth is a public health priority because of the short term and long term medical/financial costs to the health care system. There are over three decades of data describing the use of various progesterone compounds administered for the prolongation of pregnancy. (11) Two recent randomized controlled trials (3,12) evaluated the use of progesterone supplementation as a preventative therapy for women with recurrent preterm birth. Both found that
progesterone use substantially reduced the rate of preterm delivery. The American College of Obstetricians and Gynecologists’ Committee on Obstetric Practice recommends that progesterone supplementation be considered only for women with a history of a previous spontaneous birth at less than 37 weeks of gestation, pending the outcome of further investigations.(13) The effects of 17P upon pregnancy in experimental animals has been studied in rats, rabbits, mice, and monkeys.(14-17) These earlier studies found no evidence of androgenic or glucocorticoid activity, no virilizing effects upon female fetuses, and no teratogenic effects.

The present study was not designed to assess the efficacy of 17P for the prevention of preterm delivery. Gestational age at delivery was similar between women receiving 17P and those that did not, thus allowing a similar window of opportunity for development of GDM. Though all patients studied had a history of prior preterm delivery, over 35% of patients in the control group received outpatient services unrelated to preterm birth prevention (e.g. hyperemesis related services), thus may have been at overall lesser risk for preterm delivery than those in the study group.

Gestational diabetes, particularly if uncontrolled is associated with an increased risk of perinatal morbidity.(18) The risks for shoulder dystocia, death, bone fracture, and nerve palsy can be increased without appropriate therapy.(19) It is therefore prudent to investigate the impact of weekly supplemental 17P on the incidence of GDM, particularly given its new found popularity. Initial concern with this therapy involved the timing of the recommended onset of initiation (eg.16-20 weeks’ gestation) in comparison to standard timing for screening for gestational diabetes (eg. 24-28 weeks’ gestation). The ADA recommends risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation.(7) If, in fact, exposure to supplemental 17P results in an increased risk for the development of gestational diabetes, we postulate that women receiving 17P prophylaxis be considered at high risk for GDM and that earlier screening in this population is warranted.

The pregnant state is characterized by decreased insulin-stimulated tissue glucose uptake and increased liver glucose production. The adaptive response to this increased insulin resistance is an increased production of insulin by the pancreatic β cells. Progesterone is known to exhibit diabetogenic properties during pregnancy. Mechanisms proposed for this effect include: enhancement of insulin resistance through a reduction in glucose transporter 4 expressions or impairment of the normal β cell adaptive response of enhanced insulin secretion. (20) Given the biologic plausibility of progesterone-mediated gestational hyperglycemia, we sought to define the actual clinical risk of gestational diabetes in pregnancies treated with 17P.
To our knowledge, this is the first study to examine the impact of 17P prophylaxis on the incidence of GDM. Limitations of the present study include the inability to fully evaluate fetal outcomes and the measurable metabolic impact on the maternal milieu, inability to stratify data by maternal race and ethnicity since these data were not consistently available in the database, and lack of information regarding timing of GDM testing and maternal risk factors for GDM. Further studies are warranted to better elucidate the association between 17P and GDM in women with and without other risk factors for development of GDM and to clarify the quantifiable impact of 17P therapy on insulin resistance during pregnancy. In this early study, supplemental 17P injections of 250mg given weekly for the prevention of preterm delivery appear to increase the incidence of GDM, a condition that has now been clearly shown to be associated with adverse pregnancy outcome.(19) Clinical implications of this finding may include screening women receiving 17P for GDM who otherwise would be considered low risk for the condition and earlier or more frequent GDM screening for those at moderate risk.
References


16. Carbone JP, Brent RL. Genital and nongenital teratogenesis of prenatal progesterone therapy: the effects of 17alpha-hydroxyprogesterone caproate on


<table>
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<tr>
<th></th>
<th>17P Treatment</th>
<th>Control</th>
<th>p-value</th>
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<tr>
<td></td>
<td>n=557</td>
<td>n=1524</td>
<td></td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;37 years</td>
<td>53 (9.5%)</td>
<td>125 (8.2%)</td>
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<td>Tobacco use</td>
<td>54 (9.7%)</td>
<td>87 (5.7%)</td>
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<td>Married</td>
<td>421 (75.6%)</td>
<td>1190 (78.1%)</td>
<td>0.214</td>
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<td>History of preterm delivery</td>
<td>557 (100%)</td>
<td>1524 (100%)</td>
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<tr>
<td>Pre-pregnancy BMI</td>
<td>26.2 ± 6.6</td>
<td>26.2 ± 6.7</td>
<td>0.791</td>
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<tr>
<td>Obese BMI</td>
<td>140 (25.1%)</td>
<td>340 (22.3%)</td>
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<td>Betamimetic tocolysis</td>
<td>101 (18.1%)</td>
<td>375 (24.6%)</td>
<td>0.002</td>
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<td>GA at start of outpatient management (wks)</td>
<td>19.0 (16.0, 26.9)</td>
<td>21.6 (4.7, 25.9)</td>
<td>&lt;0.001</td>
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Data presented as mean ± SD, Median (range), or n (percentage) as indicated. BMI = body-mass-index. GA = gestational age.
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<tr>
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<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
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<td>Obese BMI (≥ 30 kg/m²)</td>
<td>&lt;0.001</td>
<td>6.91</td>
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<td>Overweight BMI (25.0 – 29.9 kg/m²)</td>
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<td>Normal BMI (20.0 – 24.9 kg/m²)</td>
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<td>(0.67, 1.64)</td>
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<td>0.97</td>
<td>(0.933, 1.000)</td>
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<tr>
<td>Tobacco use</td>
<td>0.193</td>
<td>0.57</td>
<td>(0.24, 1.33)</td>
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