Increased Incidence of Gestational Diabetes in Women Receiving Prophylactic 17α-Hydroxyprogesterone Caproate for Prevention of Recurrent Preterm Delivery

ANDREI REBARBER, MD[1]
NIKI B. ISTWAN, RN[2]
KAREN RUSSO-STIEGLITZ, MD[3]
JANE CLEARY-GOLDMAN, MD[1]
DEBBIE J. RHEA, MPH[2]
GARY J. STANZIANO, MD[2]
DANIEL H. SALTZMAN, MD[1]

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

RESEARCH DESIGN AND METHODS — Singleton gestations in women 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 preexisting diabetes were excluded. The incidence of GDM was compared between patients who received prophylactic intramuscular 17P (250-mg weekly injection initiated between 16.0 and 20.9 weeks' gestation) and those who did not.

RESULTS — Maternal BMI and age were similar. The incidence of GDM was 12.9% in the 17P group ($n = 557$) compared with 4.9% in control subjects ($n = 1,524$, $P < 0.001$; odds ratio 2.9 [95% CI 2.1–4.1]).

CONCLUSIONS — 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.

Diabetes Care 30:2277–2280, 2007

Preterm birth is the leading cause of perinatal mortality and morbidity for nonanomalous infants in the U.S. where >12% of infants, ~480,000, are born prematurely each year (1). Although past studies of progestational agents for the prevention of preterm delivery reported varied results, there has been renewed interest in the use of 17α-hydroxyprogesterone caproate (17P) as a secondary preterm birth prevention strategy after a recent study from the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (2,3). This 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. 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), although the mechanism of action by which 17P prevents preterm birth remains poorly understood.

The metabolic changes of normal pregnancy are essential to provide adequate nutrients to the growing fetus. As pregnancy progresses, increased levels of human chorionic sommatomammotropin, 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, which peak at 32 weeks' gestation, have been described in humans (6). The American Diabetes Association (ADA) recommends screening all women at risk for gestational diabetes mellitus (GDM). The ADA considers women to be at risk for GDM unless they are aged <25 years, have normal body weight, have no first-degree relatives with diabetes, 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 recommended a similar risk-based approach, but noted that because only a small percentage of patients meet the criteria for low risk, universal 50-g 1-h glucose challenge test screening may be a more practical approach (8). Conversely, the U.S. Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against routine screening for GDM (9). Because glucose intolerance increases during pregnancy, screening for GDM is most commonly conducted during the 24th–28th week of gestation (9,10). The purpose of the present study was to determine whether there is an increased incidence of GDM in women receiving supplemental proges-

From the [1]Mount Sinai School of Medicine, Division of Maternal Fetal Medicine, New York, New York; [2]Matria Healthcare, Department of Clinical Research, Marietta, Georgia; and [3]Valley Health System, Division of Maternal Fetal Medicine, Ridgewood, New Jersey.

Address correspondence and reprint requests to Andrei Rebarber, MD, 70 E. 90th St., New York, NY 10029. E-mail: arebarber@mfmnyc.com.

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

Published ahead of print at http://care.diabetesjournals.org on 11 June 2007. DOI: 10.2337/dc07-0564.

Abbreviations: 17P, 17α-hydroxyprogesterone caproate; ADA, American Diabetes Association; GDM, gestational diabetes mellitus.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Maternal characteristics*

	17P treatment	Control	*P* value
n	557	1,524	
Maternal age (years)	29 (16–44)	30 (16–45)	0.855
>37 years	53 (9.5)	125 (8.2)	0.376
Tobacco use	54 (9.7)	87 (5.7)	0.002
Married	421 (75.6)	1,190 (78.1)	0.214
History of preterm delivery	557 (100)	1,524 (100)	—
Prepregnancy BMI	26.2 ± 6.6	26.2 ± 6.7	0.791
Obese BMI	140 (25.1)	340 (22.3)	0.178
Betamimetic tocolysis	101 (18.1)	375 (24.6)	0.002
Gestational age at start of outpatient management (weeks)	19.0 (16.0–26.9)	21.6 (4.7–25.9)	<0.001

Data are median (range), means ± SD, or *n* (%).

terone 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 health care 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 allowing the use of her anonymous, de-identified data for research and reporting purposes is obtained from each patient upon enrollment for services. Each patient's physician was responsible for all antepartum testing and treatment decisions.

For the present study, we used de-identified data from women with singleton gestations who had a history of prior preterm delivery and who enrolled for outpatient services at <27 weeks' gestation. Eligible for analysis were women who had a documented height and prepregnancy 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 preexisting diagnosis of diabetes at admission for outpatient services, those who had a medical history of diabetes before the current pregnancy, and those who had "Unknown" designated for GDM in the antepartum outcome record. Also excluded were women experiencing recurrent preterm delivery before 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 was 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 comprised 557 patients for whom weekly intramuscular injections of 250 mg of 17P were prescribed beginning at 16–20.9 weeks' gestation and administered by Matria Healthcare between April 2004 and January 2006, whereas the control group comprised 1,524 patients at similar risk for recurrent preterm delivery (history of prior preterm delivery) who did not receive 17P through Matria Healthcare or any other source. 17P was compounded by a qualified compounding pharmacy using an Insurance Service Organization 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 on 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 the 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 h/day. Prescription of betamimetic medications for tocolysis (in both groups) was at the discretion of each patient's individual health care provider.

Data were analyzed using Student's *t*, Mann-Whitney *U*, Pearson's χ^2, and Fisher's exact test statistics as appropriate on the basis of data distributions to compare differences between control and treatment groups. Because maternal weight and betamimetic medications are commonly thought to influence development of GDM, data regarding prepregnancy 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 1. As expected, because the recommended gestational age for initiation of 17P is 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), whereas 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. Betamimetic tocolytic medications were prescribed for almost 25% of control patients compared with 18.1% in the 17P treatment group ($P = 0.002$). Women in the treatment group received 14.9 ± 4.5 (mean ± SD) injections of 250 mg of 17P.

Women receiving 17P had a significantly higher incidence of GDM than control subjects (12.9% in the 17P group compared with 4.9% in control subjects, $P < 0.001$; odds ratio [OR] 2.9 [95% CI 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 control subjects, $P = 0.080$). There were similar rates of spontaneous recurrent preterm delivery at <35 weeks' gestation between women

Table 2—*Logistic model results*

	P value	OR (95% CI)
Obese BMI (≥30 kg/m^2)	<0.001	6.91 (2.93–16.28)
Overweight BMI (25.0–29.9 kg/m^2)	0.004	3.70 (1.53–8.92)
17P prophylaxis	<0.001	3.09 (2.17–4.40)
Normal BMI (20.0–24.9 kg/m^2)	0.192	1.80 (0.74–4.38)
Betamimetic tocolysis	0.852	1.04 (0.67–1.64)
Gestational age at start of outpatient care	0.050	0.97 (0.933–1.000)
Tobacco use	0.193	0.57 (0.24–1.33)

treated with 17P and control subjects (12.4 vs. 9.6%, respectively, $P = 0.062$).

Because of significant univariate differences found in rates of maternal smoking, betamimetic drug use, and gestational age at the start of outpatient management between the study groups (Table 1), 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 2). Although patients in the obese and overweight categories had the highest risk of developing GDM, the use of 17P continued to impart a positive, independent association with GDM incidence (overall adjusted OR 3.09).

CONCLUSIONS — It is estimated that one in eight infants in the U.S. is 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 consequences and financial costs to the health care system. There are >3 decades of data describing the use of various progesterone compounds administered for the prolongation of pregnancy (11). The use of progesterone supplementation as a preventative therapy for women with recurrent preterm birth was recently evaluated in two randomized, controlled trials (3,12). Both showed 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 <37 weeks of gestation, pending the outcome of further investigations (13). The effects of 17P on 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 on 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 who received 17P and those who did not, thus allowing a similar window of opportunity for development of GDM. Although all of the patients studied had a history of prior preterm delivery, >35% of patients in the control group received outpatient services unrelated to preterm birth prevention (e.g., hyperemesis related services) and thus may have had an overall lesser risk for preterm delivery than those in the study group.

GDM, 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 concerns with this therapy involved the timing of the recommended onset of initiation (e.g.,16–20 weeks' gestation) in comparison with standard timing for screening for GDM (e.g., 24–28 weeks' gestation). The ADA recommends that risk assessment for GDM should be performed at the first prenatal visit. Women with clinical characteristics consistent with a high risk for GDM (marked obesity, a 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' gestation. Women with an average risk should have testing performed at 24–28 weeks' gestation (7). If, in fact, exposure to supplemental 17P results in an increased risk for the development of GDM, 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 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 GLUT4 expressions or impairment of the normal β-cell adaptive response of enhanced insulin secretion (20). Given the biological plausibility of progesterone-mediated gestational hyperglycemia, we sought to define the actual clinical risk of GDM in pregnant women 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 as 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 250 mg 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 an adverse pregnancy outcome (19). Clinical implications of this finding may include screening women receiving 17P for GDM who otherwise would be considered to have a low risk for the condition and earlier or more frequent GDM screening for those with a moderate risk.

References

1. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S: Births: final data for 2004, in *National Vital Statistics Reports*. vol. 55 no. 1. Hyattsville, MD, National Center for Health Statistics, 2006
2. Goldstein P, Berrier J, Rosen S, Sacks HS,

Chalmers TC: A meta-analysis of randomized control trials of progestational agents in pregnancy. *Br J Obstet Gynaecol* 96: 265–274, 1989
3. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, Sprong CY, Hauth JC, Miodovnik M, Varner MW, Leveno KJ, Caritis SN, Iams JD, Wapner RJ, Conway D, O'Sullivan MJ, Carpenter M, Mercer B, Ramin SM, Thorp JM, Peaceman AM, Gabbe S, National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network: Prevention of recurrent preterm delivery by 17-α-hydroxyprogesterone caproate. *N Engl J Med* 348:2379–2385, 2003
4. Sanchez-Ramos L, Kaunitz AM, Delke I: Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol* 105:273–279, 2005
5. Picard F, Wanatabe M, Schoonjans K, Lydon J, O'Malley BW, Auwerz J: Progesterone receptor knockout mice have an improved glucose homeostasis secondary to β-cell proliferation. *Proc Natl Acad Sci U S A* 99:15644–15648, 2002
6. Carr DB, Gabbe S: Gestational diabetes: detection, management, and implications. *Clin Diabetes* 16:1–17, 1998
7. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 30:S42–S47, 2007
8. American College of Obstetricians and Gynecologists Committee on Practice Bulletins–Obstetrics: ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists. Number 30, September 2001. *Obstet Gynecol* 98:525–538, 2001
9. U.S. Preventive Services Task Force: *Screening for Gestational Diabetes Mellitus: Recommendations and Rationale*. Rockville, MD, Agency for Healthcare Research and Quality, 2003. Available from http://www.ahrq.gov/clinic/3rduspstf/gdm/gdmrr.htm. Accessed 14 March 2007.
10. Metzger BE, Coustan DR, Organizing Committee: Summary and recommendations of the 4th International Workshop Conference on gestational diabetes. *Diabetes Care* 21:B161–B167, 1998
11. Meis PJ: 17 Hydroxyprogesterone for the prevention of preterm delivery. *Obstet Gynecol* 105:1128–1135, 2005
12. da Fonseca EB, Bittar RE, Carvalho MHB, 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* 188: 419–424, 2003
13. American College of Obstetricians and Gynecologists: ACOG Committee Opinion, Number 291: use of progesterone to reduce preterm birth. *Obstet Gynecol* 102: 1115–1116, 2003
14. Johnstone EE, Franklin RR: Assay of progestins for fetal virilizing properties using the mouse. *Obstet Gynecol* 23:359–362, 1964
15. Courtney KD, Valerio DA: Teratology in the *Macaca mulatta*. *Teratology* 1:163–172, 1968
16. Carbone JP, Brent RL: Genital and nongenital teratogenesis of prenatal progesterone therapy: the effects of 17α-hydroxyprogesterone caproate on embryonic and fetal development and endochondral ossification in the C57B1/6L mouse. *Am J Obstet Gynecol* 169:1292–1298, 1993
17. Miller RE, Nelson GW, Johnson CK: Evaluation of teratogenic potential of Delalutin (17α-hydroxyprogesterone caproate) in mice. *Teratology* 28:201–208, 1983
18. Gonzalez-Quintero VH, Istwan NB, Rhea DJ, Rodriguez LI, Cotter A, Carter J, Mueller A, Stanziano GJ: The impact of glycemic control on neonatal outcome in singleton pregnancies complicated by gestational diabetes. *Diabetes Care* 30: 467–470, 2007
19. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS: Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 352:2477–2486, 2005
20. Branisteanu D, Mathieu C: Progesterone in gestational diabetes mellitus: guilty or not guilty? *Trends Endocrinol Metab* 14: 54–56, 2003