Original Article

Evaluation the effect of 17-alpha hydroxyprogesterone caproate on gestational diabetes mellitus in pregnant women at risk for preterm birth

Safoura Rouholamin, Elahe Zarean, Laleh Sadeghi

Department of Obstetrics and Gynecology, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: The mellitus exact role of 17-alpha hydroxyprogesterone caproate in increasing the rate of gestational diabetes mellitus (GDM) is still unclear. This study was aimed to investigate the association of treatment with 17-alpha hydroxyprogesterone caproate with GDM in pregnant women who are at risk for preterm birth (PTB).

Materials and Methods: In this clinical trial, 200 singleton pregnant women included 100 pregnant women at risk for PTB or with history of PTB as case group (received weekly injections of 17-alpha hydroxyprogesterone caproate) and 100 healthy pregnant women without history of PTB as control group (did not receive any drug) were evaluated. All women followed until detect or reject of GDM, and abnormal glucose challenge test (GCT) and GDM were calculated in all of them.

Results: During study follow-up, 36 women in both groups were excluded and 81 cases 83 controls completed the study and analyzed. Mean of GCT in all studied pregnant women was 128.2 ± 18.1, whereas, in cases was higher than controls but no significant difference was noted between groups ($P = 0.56$). Abnormality in GCT was observed in 32 (19.5%) of 164 studied women, (18 of cases and 14 of controls), which was not statistically significant ($P = 0.34$). The frequency of GDM among all studied women was 7.9% (13 of 164), 7 of cases and 6 of controls, which was not significant ($P = 0.74$).

Conclusion: In summary, results demonstrated that weekly administration of 17-alpha hydroxyprogesterone caproate is not associated with higher rates of GDM in pregnant women at risk for PTB.

Key Words: 17-alpha hydroxyprogesterone caproate, gestational diabetes, glucose tolerance, preterm birth

Address for correspondence:
Dr. Laleh Sadeghi, Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: Laleh_sade@yahoo.com
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INTRODUCTION

Pre-term birth (PTB) defined as birth at <259 days of gestation or 37 completed weeks since the 1st day of the women's last menstrual period and remains a major cause of neonatal morbidity and mortality worldwide.

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The rate of PTB is from 5% to 13% in high-income countries and has progressively increased from 9% to 12% over the past two decades in the United States, and the incidence is increasing.[1-3] Across the world, for the families and health-care systems, PTB has

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high economic and social cost in terms of neonatal intensive care and is an important perinatal health problem.[4-5]

Medical interventions and public health campaigns have yet to produce an effective and reliable model for PTB prevention, including trials of reduced maternal activity, home uterine activity monitoring, tocolytic therapy, and antibiotic therapy targeted against various organisms.[6-7]

The use of progestins showed a reduction in PTB among women at high risk for PTB. The use of progesterone is suggested to women with a singleton gestation and a prior PTB and state that other indications for the use of this drug needs further investigation.[8-10]

The potential impact of the use of progestagens throughout pregnancy on both mother and fetus should be ongoing evaluation. Pregnancy hormones such as progesterone, estrogen, cortisol, and human placental lactogen may affect insulin metabolism and alter the plenty of gestational diabetes mellitus (GDM).[11] The role of progesterone in pancreatic function and in signaling insulin release is reported in animal studies and raise the question of whether increases the risk of GDM is occurred after progesterone administration during pregnancy.[12]

Gestational diabetes mellitus, which, is rarely mentioned among the causes of maternal mortality and morbidity, affecting roughly 5% of women, is one of the most common diseases during pregnancy and is related with adverse perinatal outcomes,[13] and directly or indirectly increases the risk of some conditions, such as hypertensive disorders, obstructed labor, hemorrhage, and infection that are among the leading global reasons of maternal mortality.[14]

The first time that Food and Drug Administration approved a medication (17-alpha hydroxyprogesterone caproate injections) for the prevention of PTB was February 2011. Recently, some study examining the association of treatment with 17-alpha hydroxyprogesterone caproate with GDM in pregnant women and found a significantly higher rate of GDM in case women compared with controls,[15] in the other hand, it is shown that weekly administration of 17-alpha hydroxyprogesterone caproate is not associated with higher rates of GDM in either singleton or twin pregnancies.[11] The data about the association of 17-alpha hydroxyprogesterone caproate with GDM is controversial; therefore, the present study was designed to hypothesize the association of treatment with 17-alpha hydroxyprogesterone caproate with GDM in pregnant women who are at risk for PTB in a randomized controlled trial.

MATERIALS AND METHODS

This trial was performed between March, 2012 and February, 2013, on 200 pregnant women with singleton gestations who had been referred to "Shahid Beheshti" hospital in Isfahan, Iran. Studied subjects included 100 pregnant women at risk for PTB or with a history of PTB as case group and 100 healthy pregnant women without a history of PTB as a control group. The present study was reviewed by institutional ethics committee at the Isfahan University of Medical Sciences written informed consent was obtained from all women after the participating and explained about and informed of the purposes of the study. Pregnant women were eligible if they had ≥16 years old, gestational age between 16 and 20 weeks, no history of GDM and preeclampsia, no family history of diabetes mellitus, do not using aspirin and had no diagnosis of chronic hypertension or liver disease, gestational diabetes, and renal disease. Women with prepregnancy body mass index (BMI) more than 30 kg/m^2 and abnormal 50 g glucose challenge test (GCT) at first prenatal care visit were not eligible, and also, during follow-up period women who had severe preeclampsia, severe intrauterine growth restriction, PTB and intrauterine fetal demise before 28 weeks which lead to PTB and women who immigrated and unwilling to continue the study protocol were excluded from the study. Gestational age was always confirmed by standard sonographic biometric measurements at <20 weeks' gestation.

Preterm birth was defined as delivery before 37 completed weeks of gestation, and high risk for PTB as indicated by at least one of the follow criteria; (1) history of previous PTB/second trimester loss (≥16 weeks or ≤37 weeks gestation), (2) history of previous preterm premature rupture of the fetal membranes (≤37 weeks gestation), (3) history of acute preterm labor at this pregnancy that not delivered, (4) history of previous cervical procedure such as loop excision, cold knife conization or radical diathermy for treatment of abnormal smears. Cases, pregnant women at risk of preterm or with history of PTB, received the injections of 17-alpha hydroxyprogesterone caproate (femolife 250 mg/ml, aboreihan factory) beginning at 16–20 weeks gestation and continuing until 36 weeks gestation. Healthy pregnant women without a history of PTB in the control group did not receive any drug and just followed until detect or reject of GDM.

Data collection included maternal age, gestational age at delivery, BMI (normal <25, overweight 25–29.9, obese >30 kg/m^2), number of children history of

pregnancy, miscarriage, fetal death, and ectopic pregnancy, also 1 h GCT at 24–28 weeks gestation was performed in all studied women and then 3 h GCT was done in women with abnormal 1 h GCT, and the frequencies of GDM was calculated in all of them. 1 h GCT ≥ 140 was defined as abnormal. GDM as indicated by at least one of the follow criteria; fasting blood sugar ≥95, 1 h after 100 g glucose ≥180, 2 h after 100 g glucose ≥155, or 3 h after 100 g glucose ≥140.

Descriptive statistics are presented as mean ± standard deviation or number (%) as appropriate. SPSS version 16 (Bayer Schering Pharma Co., Iran) was used to all statistical analyzes. Continuous variables were compared by Student's *t*-test and Chi-square test (or fisher exact test when appropriate) was used to compare categorical variables. The level of significance is considered to be <0.05.

RESULTS

As shown in the algorithm of study [Figure 1], of 227 reviewed pregnant women, 200 women (100 in case group who were at risk for PTB and 100 healthy pregnant women in control group) were eligible, during follow-up period 19 and 17 women in case and control groups, respectively, were lost to follow-up (15 women) or excluded based on study protocol (21 women). Finally, 164 pregnant women (81 cases and 83 controls) completed the study and analyzed.

The mean of maternal age at delivery in all studied pregnant women was 27.1 ± 4.5 years old. Table 1 shows the comparison of maternal age, BMI, history of pregnancy, miscarriage, fetal death, and ectopic pregnancy and number of children. Most of the women had normal BMI and as shown, all these characteristics of studied pregnant women were similar in both groups and differences between groups were not statistically significant ($P > 0.05$).

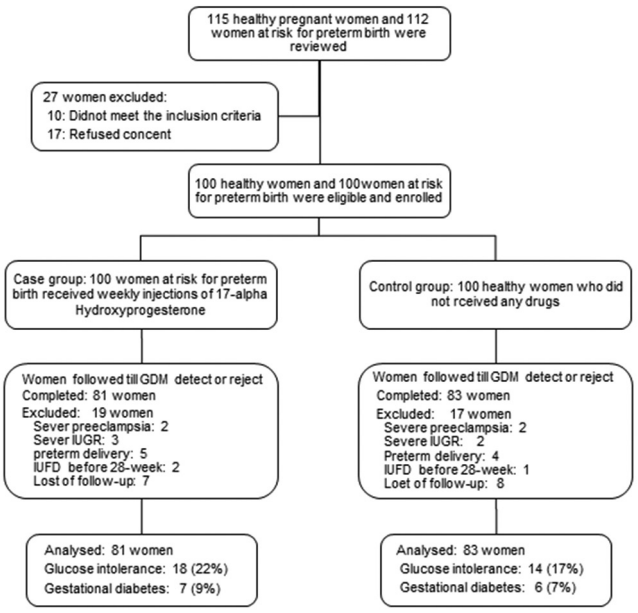

Figure 1: Subjects who entered to the study, followed and analyzed

Mean of GCT in all studied pregnant women was 128.2 ± 18.1, whereas, in cases was higher than controls, but no significant differences in mean of GCT were noted among the case and control groups ($P = 0.56$). Furthermore, abnormality in GCT was observed in 32 (19.5%) of 164 studied women, which 18 (56%) 0f 32 studied women with abnormal GCT were in case group and 14 (44%) 0f them were in control group, but this difference between groups was not statistically significant ($P = 0.34$). The frequency of GDM among all studied women was 7.9% (13 of 164). The frequencies of GDM were observed in 9% of the case group and 7% in the control group, and no significant difference was noted among the groups [Table 2].

Mean of BMI in all studied women with GDM was significantly more than women without GDM (29.9 ± 5.9 vs. 25.1 ± 5.9 respectively, $P < 0.0001$). Associations between maternal age and BMI with

Table 1: Comparison of characteristics of studied pregnant women

Baseline characteristics	Case group (*n*=81)	Control group (*n*=83)	*P*
Maternal age (year)	27.2±4.1	26.4±4.5	0.25*
BMI (kg/m^2)			
Mean	25.1±3.3	25.8±4.4	0.25*
Normal	48 (59.3)	47 (56.7)	0.82†
Overweight	24 (29.6)	24 (28.9)	
Obese	9 (11.1)	12 (14.4)	
History of pregnancy			
1	34 (42)	33 (39.8)	0.22†
2	30 (37)	22 (26.5)	
≥3	17 (21)	28 (33.7)	
Number of children			0.12†
0	56 (69.1)	43 (51.8)	
1	17 (21)	23 (27.7)	
≥2	8 (9.9)	17 (20.5)	
History of miscarriage			0.99†
No	64 (79)	64 (77.1)	
Yes	17 (21)	19 (22.9)	
History of fetal death			0.99†
No	68 (83.9)	75 (90.4)	
Yes	13 (16.1)	8 (9.6)	
History of ectopic pregnancy			0.99†
No	78 (96.3)	80 (96.4)	
Yes	3 (3.7)	3 (3.6)	

Data are mean±SD and number (%). Cases included pregnant women at risk for preterm birth who received weekly injection of 17-alpha hydroxyprogesterone caproate. Controls included pregnant women who did not receive any drug. *P* values calculated by *independent sample *t*-test and †Chi-square test. SD: Standard deviation, BMI: Body mass index

the frequency GDM in studied women were reported in Table 3. Maternal age in cases, controls and all women with GDM were significantly higher than those women without GDM ($P = 0.05$). In case group, there was no significant difference between BMI and GDM, but in all studied women and also, control group most of women with GDM were obese in compare to those women who did not have GDM ($P < 0.05$).

DISCUSSION

Preterm birth has the short-term and long-term medical consequences and financial costs to the health-care system, and primary prevention of PTB is a public health priority. The use of various progesterone compounds administered for the prolongation of pregnancy described during the past three decades.[16] And the reduction in the rate of PTB after the use of progesterone was reported in some randomized, controlled trials[8,9] as a preventative therapy for women with recurrent PTB. Insulin resistance is occurred after increased levels of human progesterone, prolactin, cortisol progesterone, and estrogen in pregnancy progresses.[12] The role of progesterone in signaling insulin release and pancreatic function is reported in animal models studies,[17] and the results on the effect of progesterone on GDM was different in human studies.[17] Results of the present study, shows that administration of 17-alpha hydroxyprogesterone caproate to singleton pregnancies did not increase the rate of GDM, and GDM was observed in 7.9% of studied women and was not significant between groups. Other risk factors such as maternal age and BMI, rather, continued to be significantly associated with an increased risk for GDM in all studied women, but in case group there was no association between BMI and GDM.

There is conflict on data about the risk for the development of GDM in pregnant women. Rebarber *et al.*,[15] in an observational study examining the association of treatment with 17-alpha hydroxyprogesterone caproate with gestational diabetes in singleton pregnancies history of preterm delivery. 557 women received weekly injection of 250 mg of 17-alpha hydroxyprogesterone caproate were compared to 1,524 women who did not receive this intervention and found a significantly higher rate of GMD treatment group compared with the control group. The incidence of GDM in case and control groups in our study were 9 and 7%, respectively, and was not significant between groups ($P = 0.74$), which these results were different than those of Rebarber *et al.*,[15] Studied population, different study method, and sample size nay be are the causes of differences between these findings, Rebarber *et al.* study was an observational study on pregnancies women with history of preterm delivery in treatment and control groups and lack of information regarding timing of GDM testing and maternal risk factors for GDM, therefore, by design the possibility for selection bias and ascertainment bias may be effect on the findings, but present study is a clinical trial and cases were at risk for PTB whereas, controls were not at risk of PTB also information about maternal risk factors for GDM were assessed between study groups. Furthermore, our results support findings of Wolfe *et al.* study which reported that glucose values, rate of abnormal GCT, and rate of GDM were similar between case and control groups and authors concluded that 17-alpha hydroxyprogesterone caproate administration to women at risk of recurrent preterm delivery did not significantly affect glucose tolerance.[18]

Table 2: Comparison of GCT and GDM between study groups

Lab data	Case group (*n*=81)	Control group (*n*=83)	*P*
GCT	130.2±18.6	128.5±19.6	0.56*
GCT			
Normal	63 (78)	69 (83)	0.34†
Abnormal	18 (22)	14 (17)	
GDM			
Yes	7 (9)	6 (7)	0.74†
No	74 (91)	77 (93)	

Data are mean±SD and number (%). Cases included pregnant women at risk for preterm birth who received weekly injection of 17-alpha hydroxyprogesterone caproate. Controls included pregnant women who did not receive any drug. *P* values calculated by *independent sample *t*-test and †Chi-square test. GCT: Glucose challenge test, GDM: Gestational diabetes mellitus, SD: Standard deviation

Table 3: Association between maternal age and BMI with the frequency GDM in studied women

GDM	Cases (*n*=81)		Controls (*n*=83)		Total (*n*=164)	
	Positive	Negative	Positive	Negative	Positive	Negative
Maternal age (year)	29.5±4.6	26.2±4.4	30.5±3.4	27.3±4.5	30.1±3.9	26.9±4.5
*P**	0.035		0.013		0.002	
BMI (kg/m^2)						
Normal	3 (43)	45 (60.8)	1 (16.7)	46 (59.7)	4 (30.8)	91 (60.3)
Overweight	2 (26.5)	22 (29.7)	1 (16.7)	23 (29.9)	3 (23.1)	45 (29.8)
Obese	2 (26.5)	7 (9.5)	4 (66.6)	8 (10.4)	6 (46.1)	15 (9.9)
P†	0.28		0.006		0.003	

Data are mean±SD and number (%). Cases included pregnant women at risk for preterm birth who received weekly injection of 17-alpha hydroxyprogesterone caproate. Controls included pregnant women who did not receive any drug. *P* values calculated by *independent sample *t*-test and †Chi square test. BMI: Body mass index, GDM: Gestational diabetes mellitus, SD: Standard deviation

Thaddeus *et al*. demonstrated that women receiving weekly intramuscular 17-alpha hydroxyprogesterone caproate have more frequent abnormal glucose testing and gestational diabetes compared with unexposed controls.[19] Furthermore, in Gyamfi *et al*. study,[11] data were gathered as part of one of two randomized, double-blind, placebo-controlled trials, 463 women with at least one previous spontaneous preterm delivery were randomized to receive weekly injections of 17-alpha hydroxyprogesterone caproate or placebo. The rate of GDM was 5.4% in singleton pregnancies in Gyamfi *et al*. study[11] whereas in women receiving 17-alpha hydroxyprogesterone caproate was 5.8% versus in placebo group was 4.7%, and this difference was not statistically significant. Similar to Gyamfi *et al*. study we do not find a significant association between the uses of 17-alpha hydroxyprogesterone caproate and GDM. Furthermore, in similar findings in both study reported a significant association between maternal age and BMI with GDM. Despite the similar findings between Gyamfi *et al*. study[11] and the present study, some differences are noticeable; studied population, randomization, and sample size.

Gathering data on the potential complications associated with the use of 17-alpha hydroxyprogesterone caproate on GDM should continue as the use of progesterone becomes common practice. Furthermore, it is noticeably, that pregnant women receiving 17-alpha hydroxyprogesterone caproate must be considered at high risk for GDM, if, an increased risk for the development of GDM In these women observed after exposure to 17-alpha hydroxyprogesterone caproate. And earlier screening in these women is warranted.

In conclusion, results of the present study demonstrated that weekly administration of 17-alpha hydroxyprogesterone caproate is not associated with higher rates of GDM in pregnant women at risk for PTB. However, additional well-designed, prospective, randomized trials of supplementation with good sample size will be necessary to determine a potential role of 17-alpha hydroxyprogesterone caproate in the rise of GDM in pregnant women who are at risk for PTB.

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Conflicts of interest

There are no conflicts of interest.

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