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Original Article

The effect of 17-alpha-hydroxyprogesterone caproate on 75 g oral glucose tolerance test results and the prevalence of gestational diabetes mellitus

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Abstract

Aim: The goal of the present study was to investigate the effects of 17-alpha-hydroxyprogesterone caproate (17-OHPC) on oral glucose tolerance test (75 g OGTT) results and the prevalence of gestational diabetes mellitus (GDM).

Material and Methods: : In the present case-control study, 1,472 pregnant women were enrolled. Of these pregnant women, 146 had used 17-OHPC for at least one month between 16–24 weeks of gestation and the remaining 1,326 were the healthy control group. Diagnostic criteria presented by International Association of Diabetes and Pregnancy Study Group were applied for diagnosis GDM.

Results: Maternal demographic characteristics were similar between groups. The mean starvation serum glucose level was importantly greater in the study group at 81.7 ± 9.3mg/dL versus 79.6 ± 13.3mg/dL in the control group. Mean first hour serum glucose was 144.4 ± 30.4mg/dl in the study group and 130.8 ± 36.9mg/dl in the control group, importantly greater in the study group. Mean second hour serum glucose was importantly greater in the study group at 111.5 ± 26.1mg/dl versus 104.8 ± 31.4mg/dl in the control group. Additionally, there was no statistically significant difference between the groups for GDM prevalence.

Conclusion: The present study showed that 17-OHPC was importantly related to greater starvation, first hour, and second hour serum glucose levels compared with the healthy group.

Keywords: 17-alpha-hydroxyprogesterone caproate; 17-OHPC, 75 g OGTT; gestational diabetes mellitus; GDM prevalence

INTRODUCTION

Preterm birth is defined as delivery before 37 gestational weeks which is a significant problem in pregnancy and is a major large public health issue. A large proportion (9.6%) of pregnancies in the United States (1) as well as approximately 15 million pregnancies worldwide annually result in preterm birth (2). Preterm birth is related with increased risk for neonatal morbidity and mortality (3). Preterm birth has been shown to be related with adverse health outcomes, including neurodevelopmental, visual, and hearing impairment, low birth weight, lung disease, neonatal and infant death (4,5). Thus, although the exact pathogenesis is not currently well understood, preventing or reducing preterm births is an important global issue.The incidence of preterm delivery has started to decrease owing to various medical treatments and the preventive effects of progesterone use in high-risk patients have been shown in a wide range of studies (6-8). It is known that progesterone decreases spontaneous myometrial contractility activity by a dose-dependent relaxation effect. This inhibition of contractile activity by progesterone is explained by modulation of potassium channel activity (9,10).

17-alpha-hydroxyprogesterone caproate (17-OHPC) is a progesterone derivative commonly used in preventing preterm birth. Hormones produced during pregnancy, including placental lactogen, estrogen and progesterone, have been linked with the development of hyperglycemia and insulin resistance. Progesterone in particular is known to reduce insulin sensitivity (11). Considering the effects of progesterone, we aimed to investigate the effects of 17-OHPC on 75 g oral glucose tolerance test (OGTT) results and the prevalence of gestational diabetes mellitus (GDM) in the current study.

MATERIAL and METHODS

The present study was done in a tertiary center hospital as a retrospective case-control study. Ethics committee approval was received (2019/390). A total of 1590 women, who were followed at the Kayseri City Hospital between May 2018 and May 2019, were evaluated. Of these, 118 were excluded, because they did not meet the inclusion criteria, 146 of them had used 17-OHPC for at least one

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month between 16 and 24 weeks of gestation, because they were at risk for preterm delivery or with a history of preterm delivery. Therefore they were included in the study group. The remaining 1,326 healthy pregnant women were included in the control group. All pregnant women in the groups were singleton pregnancy and were aged 18-35 years old. Women were excluded from the study in case of multiple pregnancies, chromosomal or congenital fetal anomalies, chronic hypertension, pre-gestational diabetes, smoking, alcohol or drug use, hepatic or renal disease, or an endocrine disease known to affect blood glucose levels (e.g., Cushing's disease, Addison's disease, pituitary failure, acromegaly) (12).

The last menstrual period of the patients was used to determine their gestational age. However, if the last menstrual period was not known, the gestational age of those was calculated according to ultrasonographic measurements performed in the first trimester. History of preterm delivery was defined as delivery before 37 completed weeks of gestation and high risk for preterm delivery was indicated by at least one of the following criteria: 1) history of previous preterm delivery; 2) history of previous PPROM (≤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. Pregnant women at risk of preterm delivery or with a history of preterm birth received weekly injections of 250 mg 17-OHPC (Proluton® Depot 500 mg/2 mL, BAYER, Turkey) beginning at 16–20 weeks of gestation.

All of the pregnant women were examined during the first trimester using a starvation serum glucose test; subjects having above 92 mg/dL were excluded from the study. The remaining subjects having below 92 mg/dL, then, were screened using the 75-g OGTT at 24–28 gestational weeks. Diagnostic criteria presented by International Association of Diabetes and Pregnancy Study Group were applied for diagnosis GDM. These criteria were starvation serum glucose levels ≥ 92 mg/dL, and 1st hour ≥ 180 mg/dL, 2st hour ≥ 153 mg/dL (13-15).

Statistics

Statistical analysis was performed using PASW Statistics 18 (SPSS, Inc., 2009, Chicago, IL, USA). To compare two groups, the Shapiro–Wilk test was used to determine the normality of the data, and the Levene's test was used to test the assumption of homogeneity of variance. The values are expressed as the mean ± standard deviation or n (%) or media (25th-75th percentiles). Parametric comparisons were made using the Student's t-test, and nonparametric comparisons were made using the Mann–Whitney U test. The difference among the groups was considered statistically significant when $p < 0.05$.

RESULTS

Overall, 1,472 subjects were evaluated in the study, 146 of which had used 17-OHPC for at least one month between 16 and 24 weeks of gestation. The remaining 1,326 formed the healthy control group. Maternal demographic characteristics were compared (Table 1) and were found to be similar between groups.

Table 1. Demographic features of the study participants

Characteristic	Study group (n = 146)	Control group (n = 1326)	p-value
Maternal age	26.60±5.10	26.42±6.02	0.723
BMI at initial examination (kg/m^2)	26.10 (25.80–27.10)	26.50 (26.10–27.60)	0.744
BMI at OGTT (kg/m^2)	27.35 (26.40–28.60)	27.80 (27–28.60)	0.570
Gestational age at OGTT screening (weeks)	26(25.25–27)	26(25–27)	0.125

BMI: body mass index; OGTT: oral glucose tolerance test. Values are expressed as mean ± standard deviation or median (25-75th percentiles)

Table 2. A comparison of 75 g OGTT screening levels and prevalence of gestational diabetes between the groups

	Study group (n = 146)	Control group (n = 1326)	p-value
Fasting plasma glucose (mg/dL)	81.7±9.3	79.6±13.3	0.046
1-hour plasma glucose (mg/dL)	144.4±30.4	130.8±36.9	<0.01
2-hour plasma glucose (mg/dL)	111.5±26.1	104.8±31.4	0.004
GDM prevalence (n%)	16 (11%)	212 (16%)	0.066*

* Pearson's chi-squared test used for this analysis. Values are expressed as mean ± standard deviation or n(%)

A comparison of 75-g OGTT results and the prevalence of GDM are presented in (Table 2). The mean levels of starvation serum glucose was importantly greater (p=0.046) in the study group than in the control group (81.7 ± 9.3 and 79.6 ± 13.3, respectively). The mean 1-hour plasma glucose level was 144.4±30.4mg/dl in the study group and 130.8±36.9mg/dl in the control group, with the level in the study group being significantly higher (p<0.001). The mean 2-hour plasma glucose was significantly higher (p=0.004) in the study group compared to the control group at 111.5±26.1mg/dl and 104.8±31.4mg/dl, respectively. Although the starvation, 1st hour, and 2st hour serum glucose levels were all importantly greater in the study group, there was no statistically important difference between the groups in terms of the prevalence of GDM.

DISCUSSION

The aim of this study was to clarify the effects of 17-OHPC on75 g OGTT screening and GDM prevalence. The present study showed that 17-OHPC was importantly related to greater starvation, 1st hour, and 2st hour serum glucose levels compared with the healthy group. However, no statistically significant difference was found between the groups in terms of GDM prevalence.

In the literature, several studies and one systematic review and meta-analysis (11,16-20) aimed to clarify this situation. While some of these studies showed that the use of 17-OHPC increased the rate of GDM and abnormal glucose challenge test rates (16-18), other studies have shown that GDM rates are not affected (11, 19, 20). Rebarber et al. carried out an observational study comparing 557 women who received a weekly injection of 250 mg of 17-OHPC with 1,524 women who did not receive this intervention; they found a significantly higher rate of GDM in the treatment group compared with the control group (16). A study by Thaddeus et al. reported that, versus unexposed controls, women receiving weekly intramuscular 17-OHPC had more frequent abnormal glucose test results and GDM (17). Similarly, Robert E., et al. reported that in obese women aged over 35 years initiation of 17-OHPC treatment at an earlier stage of pregnancy may increase the risk for GDM (18). Conversely, in a study by Gyamfı et al., women with singleton pregnancies with at least one previous spontaneous preterm delivery were randomized to receive weekly injections of 17-OHPC or placebo. In women receiving 17-OHPC, the GDM rate was not statistically significantly different (11). Similar to Gyamfı et al.'s study, Rouholaminet al. did not find a important relation between the use of 17-OHPC and GDM rates (19). Furthermore, Wolfe et al. reported that glucose values, rate of abnormal glucose challenge test, and rate of GDM were similar between case and control groups and the authors concluded that 17-OHPC administration to pregnant women at risk preterm delivery didn't affect glucose tolerance (20). More recently, a systematic review and meta-analysis by Eke et al. showed that the incidence of abnormal glucose test results and GDM were significantly higher in women with singleton gestations receiving 17-OHPC weekly for recurrent preterm birth prevention than the unexposed controls (21). There is conflicting data about the risk for the development of GDM in pregnant women. The study populations, study methods, and sample sizes may be the causes of the differences between these findings.

Mean starvation, 1. hour, and 2. hour serum glucose levels were found to be importantly greater in the study group compared to the control group in this work. However, no statistically significant difference was found between the groups regarding the prevalence of GDM. Our results may be explained by the diabetogenic effect of progesterone. Several placental hormones especially progesterone have been associated with the development of hyperglycemia and insulin resistance. Progesterone in particular has been demonstrated to decrease insulin sensitivity in several different ways. Treating pregnant rats with an infusion of exogenous progesterone resulted in decreased in insulin sensitivity and hyperglycemia (22,23). Furthermore, there have been several reports highlighting an association between progestin-only contraception and augmented resistance of insulin (24,25), which could be attributed to a reduction in GLUT-4 expression in adipose tissue and skeletal muscle mediated by progesterone along with impaired insulin release (26-29). The expression of GLUT-4 was shown by Cambellet al. to be reduced by progesterone with following reduces in glucose uptake (26,27). Moreover, Picard et al. reported that mice treated with exogenous progesterone showed hyperglycemia and a higher susceptibility to frank diabetes. In that study, progesterone receptor knockout mice were also reported to have improved glucose homeostasis, and improved pancreatic insulin release (23).

The results of the current study can be interpreted in several ways: 1) it is possible to say that performing 75 g OGTT screening before progesterone treatment may show more clearly the results of screening for pregnant group with a high risk for diabetes. 2) It may be appropriate to recommend the 75 g OGTT for pregnant women at low risk for diabetes due to the diabetic effect of progesterone when using 17-OHPC over one month period.

There are some limitations to our study, particularly its retrospective nature. Although the starvation, 1st hour, and 2st hour serum glucose levels were evaluated, the lack of fasting insulin and HOMA-IR levels, which can provide a better assessment of glucose metabolism, is another possible limitation. Thus, future studies should evaluate fasting insulin, HOMA-IR, and other glucose metabolism markers to clarify this situation.

CONCLUSION

The present study showed that 17-alpha hydroxyprogesterone caproate was importantly associated to greater starvation, 1st hour, and 2st hour serum glucose levels compared with the healthy control group. However, no statistically important difference was found among the groups for the prevalence of GDM.

Competing interests: The authors declare that they have no competing interest.
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