European Journal of Obstetrics & Gynecology and Reproductive Biology 230 (2018) 6–9

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Vaginal progesterone for the prevention of preterm birth and the risk of gestational diabetes

Yaniv Zipori[a,*], Roy Lauterbach[a], Emad Matanes[a], Ron Beloosesky[a,b], Zeev Weiner[a,b], Amir Weissman[c]

[a] Department of Obstetrics and Gynecology, Rambam Health Care Campus, Haifa, Israel
[b] Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
[c] High Risk Pregnancy Unit, Lin Medical Center, Clalit Health Services, Haifa, Israel

ARTICLE INFO

Article history:
Received 31 May 2018
Received in revised form 20 August 2018
Accepted 10 September 2018
Available online xxx

Keywords:
Preterm birth
Gestational diabetes
Vaginal progesterone
Glucose challenge test

ABSTRACT

Introduction: We aimed to determine whether daily vaginal progesterone use for the prevention of preterm birth has an effect on the incidence of abnormal glucose challenge test or gestational diabetes.
Study design: A retrospective study in a large referral center. Women with cervical length ≤ 25 mm were given 200 mg vaginal micronized progesterone capsules daily at bed time until 36 weeks` gestation or delivery. Each progesterone-treated woman was matched randomly with three untreated controls. The main outcome measures were; mean plasma glucose level following the glucose challenge test and the rate of abnormal 1-hour glucose challenge test. Secondary outcome was the rate of gestational diabetes.
Results: We identified 108 progesterone-treated women that were matched by age and BMI to 324 controls during the same time period. The mean plasma glucose level following the glucose challenge test was similar in both groups (115.3 ± 33.8 mg/dL versus 109.2 ± 26.6 mg/dL). Despite a higher rate of an abnormal glucose challenge test in the progesterone-treated group compared to the control group (21.1% vs. 13.9%), it did not reach statistical significance. Similarly, we could not detect any difference in the rate of gestational diabetes in either the study or the control group (2.8% versus 2.5%).
Conclusion: Daily vaginal progesterone was not associated with higher rates of abnormal glucose challenge test or gestational diabetes. We are in a view that no earlier screening or diagnostic testing for gestational diabetes is required except the standard recommended schedule unless additional risk factors are present.

Introduction

Preterm birth (PTB) remains the leading cause of infants' morbidity and mortality, with a worldwide estimated incidence between 6–12% [1]. Several interventions with varying efficacy, including progesterone supplementation, are available for PTB overall risk reduction. Administration of a weekly dose of 250 mg of intramuscular 17-alpha hydroxyprogesterone caproate is recommended for all women with a prior history of singleton spontaneous PTB under 37 weeks' gestation, preferably given between 16 and 36 weeks` gestation or until delivery in a subsequent pregnancy [2]. Similarly, vaginal progesterone preparations of 100–200 mg daily are indicated for women presenting with a short cervix of ≤25 mm as measured sonographically in a current pregnancy [3].

Pregnancy is known to be accompanied by an increased rate of insulin resistance which is mediated primarily by placental secretion of diabetogenic hormones, including GH, CRH, placental lactogen, and progesterone [4]. Consequently, women may be more prone to have glucose intolerance and gestational diabetes (GDM) for the first time during their pregnancy [5,6]. In turn, GDM is associated with an increased risk of adverse pregnancy outcomes, including fetal macrosomia, shoulder dystocia, operative vaginal and cesarean deliveries, metabolic complications of the newborn and long-term risk of developing type II diabetes mellitus [7].

The use of intramuscular 17-alpha hydroxyprogesterone caproate for the prevention of recurrent PTB has been previously reported to be associated with an increased risk of GDM [8,9]. On the contrary, Gyamfi et al. concluded that weekly administration of 17-alpha hydroxyprogesterone caproate for prevention of PTB was not associated with higher rates of GDM in either singleton or twin

* Corresponding author at: Department of Obstetrics and Gynecology, Rambam Health Care Campus, Haifa 3109601, Israel.
E-mail address: y_zipori@rambam.health.gov.il (Y. Zipori).

https://doi.org/10.1016/j.ejogrb.2018.09.011
0301-2115/

pregnancies [10]. Similarly, Wolfe et al. confirmed that 17-alpha hydroxyprogesterone caproate administration did not significantly affect glucose tolerance [11].

Thus far no study has specifically addressed the effect of vaginal progesterone administration on glucose tolerance during pregnancy. As 17-alpha hydroxyprogesterone caproate and vaginal progesterone may vary in their effect due to inherent differences (17-alpha hydroxyprogesterone caproate is a synthetic progesterone, vaginal progesterone is a natural progesterone that bypasses hepatic first-pass metabolism), their effect on glucose intolerance may also vary [12].

In the current study, we sought to determine whether the incidence of abnormal glucose challenge test (GCT) or GDM is altered in women receiving long-term daily vaginal progesterone preparations indicated for women with cervical shortening and no prior spontaneous preterm birth.

Material and methods

This was a retrospective cohort study from the hospital's database containing information regarding pregnant women who were diagnosed with a short cervix ≤ 25 mm on transvaginal ultrasound at 16–20 weeks` gestation and treated with vaginal progesterone preparations. The study data was based on case files from the time period between July 2014 to July 2017, and approved by the Research Ethics Board which waived signing an informed consent due to the retrospective and anonymous data collection. Gestational age was determined from the menstrual history and confirmed from the measurement of fetal crown–rump length at a first trimester scan. We offer and perform an early fetal morphology ultrasound almost routinely around 16 weeks` gestation with a transvaginal approach, thus allowing earlier evaluation of cervical length and timely intervention, should a short cervix be detected.

Eligible for analysis were women who had complete documentation of their pre-pregnancy body mass index, antenatal GCT and oral glucose tolerance test (OGTT) results. We intentionally included only women who recieved vaginal progesterone treatment for at least 4 weeks before GCT performence. Women with cervical length ≤ 25 mm were given 200 mg vaginal micronized progesterone capsules daily at bed time until 36 weeks` gestation or delivery. They were instructed to introduce one vaginal capsule every night before bed time from <20 weeks to 36 weeks` gestation and to avoid sexual intercourse. All women were informed that symptoms related to the administration of progesterone might include drowsiness, fatigue, headaches and mild vaginal irritation. Exclusion criteria included women with pre-existing diabetes or multifetal pregnancies, cases in which treatment with intramuscular 17-alpha hydroxyprogesterone caproate had been commensed due to obstetric history, major fetal abnormalities, presence of cervical cerclage, use of beta blockers, and cases in which intramuscular corticosteroids for fetal lung maturity had been administered prior to the GCT/OGTT.

Each progesterone-treated woman was matched randomly with three untreated controls by maternal age. This was achieved using electronic random assignment for all women delivering at our institution during the same time period. We then divided the data into treatment and control groups. The primary outcomes were the mean plasma glucose level following the GCT and the rate of abnormal 1-hour GCT. In the absence of early testing, we performed the universal GCT screening at 24–28 weeks of gestation. An abnormal GCT screening test was defined as a venous plasma glucose level of 140 mg/dL (≥ 7.8 mmol/L) 1-hour after a 50-g oral glucose load. Secondary outcome was the rate of GDM, which was diagnosed with either a 1-hour GCT screen of ≥ 200 mg/dL (11.1 mmol/L) or two or more abnormal results identified on a diagnostic 3-hour 100-g OGTT according to the Carpenter-Coustan criteria [13]. Candidates for one-step diagnostic OGTT were women with underlying risk factors for GDM such as; personal history of macrosomia or GDM in a previous pregnancy, family history of diabetes, especially in first-degree relatives, pre-pregnancy BMI > 30 kg/m^2 and previous unexplained intrauterine fetal death or major fetal malformation.

Table 1
Demographic characteristics and outcome variables in the study and control groups.

	Progesterone group (n=108)	Control group (n=324)
Maternal age, years	31.2 ± 5.5	30.5 ± 4.7
Parity (number of prior births)	1.8 ± 1.0*	2.1 ± 1.0
Body Mass Index, kg/m^2	28.9 ± 5.7	28.0 ± 4.7
Gestational age at delivery, weeks	38.1 ± 3.0†	39.3 ± 1.3
Mean blood glucose after GCT, mg/dL	115.3 ± 33.8	109.2 ± 26.6
Abnormal 1-h GCT ≥ 140 mg/dL, n (%)	23 (21.3)	45 (13.9%)
GDM, n (%)	3 (2.8%)	8 (2.5%)

GCT = glucose challenge test; GDM = gestational diabetes.
Results expressed as mean ± standard deviation.
* P < 0.02.
† P,0.01.

Statistical analyses

Assuming that 20% of pregnant women would have a positive 50-g GCT screening result with a screen positive cut-off of 140 mg/dL, we determined that our sample size was sufficient to evaluate a 30% increase in the incidence of an abnormal glucose screen in the progesterone treated group with 80% power and alpha = 0.05. Descriptive statistics were reported as mean (±SD) for continuous variables and as numbers (percentages) for categorical variables. Data were evaluated by $\chi 2$, analysis of variance, and *t*-test where appropriate. A multivariable regression model was then performed on glucose level following the GCT, controlling for significant univariate factors (maternal age, parity and BMI). A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Statgraphics statistical package (StatPoint technologies, Warrenton, VA).

Results

Demographic and outcome data are presented in Table 1. We identified 108 progesterone-treated women that were matched by age and BMI to 324 untreated women during the same time period. There was a statistical, though not clinical, significant difference in parity between the two groups. Although both groups delivered at term, the duration of pregnancy was significantly longer (a one week difference), in the untreated group compared with the treated group (39.3 ± 1.3 weeks versus 38.1 ± 0.3 weeks, p < 0.01). The mean plasma glucose level following the GCT was similar in both groups (115.3 ± 33.8 mg/dL versus 109.2 ± 26.6 mg/dL). Despite a higher rate of an abnormal GCT in the progesterone-treated group compared to the control group (21.1% vs. 13.9%), it did not reach statistical significance. Sub-analysis of women who had subsequent OGTT following their abnormal GCT showed no difference between the groups in the mean plasma glucose level, whether during fasting or after the first, second or third hour of the test (Table 2). Additionally, we could not detect any difference in the rate of GDM in either the study or the control group (2.8% versus 2.5%). By using multivariable regression analyses to control for confounding variables, no significant confounders were found to influence glucose levels following the GCT or the GDM rate in the study group.