

Effect of Normoglycemia Before Conception on Early Pregnancy Hormone Profiles

V. DANIEL CASTRACANE, Ph.D., LOIS JOVANOVIĆ, M.D., AND JAMES L. MILLS, M.D., M.S.

Insulin-dependent diabetic women have been shown to have subnormal hormone levels in the first trimester of pregnancy. To determine whether these abnormalities were the result of poor diabetes control, testosterone, androstenedione, human chorionic gonadotropin (HCG), and prolactin were studied longitudinally in diabetic women made normoglycemic before conception (N = 11) and normal (N = 6) control subjects beginning at the fifth week of gestation. HCG levels rose normally in all 11 diabetic and six control subjects and then declined as expected, with peak levels between 8 and 12 wk of gestation. Prolactin levels similarly rose significantly ($P < 0.00001$) during the period studied. Plasma androstenedione did not increase during the course of this study, but testosterone levels increased significantly ($P = 0.0001$). Androgen levels were consistently higher in diabetic subjects despite the normoglycemic state, although the differences reached statistical significance at only one point. This study demonstrates that when normoglycemia is achieved before conception, HCG and prolactin are normal at 5 wk after the last menstrual period. The possibility that androgen levels may be higher in insulin-requiring diabetic women, perhaps due to peripheral hyperinsulinemia, should be explored. DIABETES CARE 1985; 8:473-76.

Diabetic women who have glucose levels twice the normal range at the time of conception have been shown to have subnormal human chorionic gonadotropin (HCG), estradiol, and prolactin (PRL) levels.¹ The three hormone levels were shown to return to normal range within 2-6 wk after normoglycemia was achieved. However, the question of whether the abnormal hormonal profile could be prevented if normoglycemia were achieved before conception remained unanswered. If it could, it would lend support to the claim that normoglycemia results in a normal pregnancy.²⁻⁷

There is evidence that serum hormones in the first trimester reflect the integrity of the trophoblastic implantation and the subsequent vascular status of the placental-maternal interchange.^{8,9} The reason for subnormal hormonal levels in women whose diabetes is out of control is not known; however, the possibilities include poor implantation, poor vascular status, small placenta, or glycosylation of these hormones resulting in inaccurate assay by antibody or receptor techniques. Whatever the reason for a subnormal profile, there is reason to suspect that the consequence would be a poor prognosis for the fetus. Recent studies indicate that hyperglycemia during

the first trimester is associated with a higher risk of congenital malformations.^{4,7} Whether these malformations are the result of hyperglycemia, hormonal imbalance, or other unknown aspects of poor control remains to be elucidated. This study was designed (1) to determine whether diabetic women who normalized their glucose levels before conception would produce appropriate amounts of HCG and prolactin early in pregnancy and (2) to examine serum androgen levels since this aspect of early pregnancy in the diabetic woman has not been investigated.

MATERIALS AND METHODS

Subjects. The women selected for study were from two groups. One group of subjects consisted of type I, insulin-dependent diabetic (C-peptide 0.03 pmol/L) pregnant women (N = 11). The control group consisted of nondiabetic pregnant women (N = 6). The age range was 21-32 yr in both groups. Duration of diabetes was 2-21 yr (mean 11 ± 8 yr). All women in the diabetic group were brought into the normoglycemic range before pregnancy by multiple daily injections of insulin. Dosage was adjusted based on 7-10 daily home blood glucose

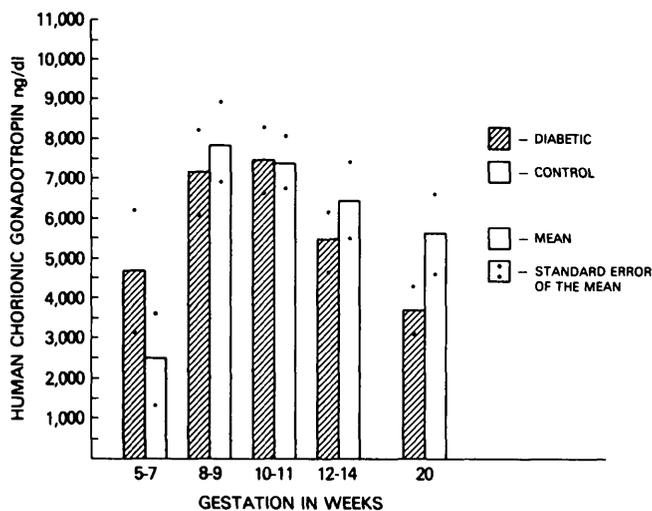


FIG. 1. Plasma HCG levels in normoglycemic diabetic and control subjects by week of gestation. HCG levels rose early in pregnancy, then fell by the end of the period studied; there was no significant difference between the two groups.

measurements.¹⁰ Glycosylated hemoglobin (HbA_{1c}) was normal in all diabetic subjects before conception (HbA_{1c} 8.5%). The control group was documented not to have diabetes based on a negative 50-g oral glucose challenge test.

Blood samples were collected between 9 a.m. and noon as both serum and plasma. Serum samples were used for HCG and prolactin determination and plasma for steroid assays. Since insulin administration was almost continuous over the course of the day, diabetic subjects had peripheral hyperinsulinemia throughout the portion of the day when blood was drawn.

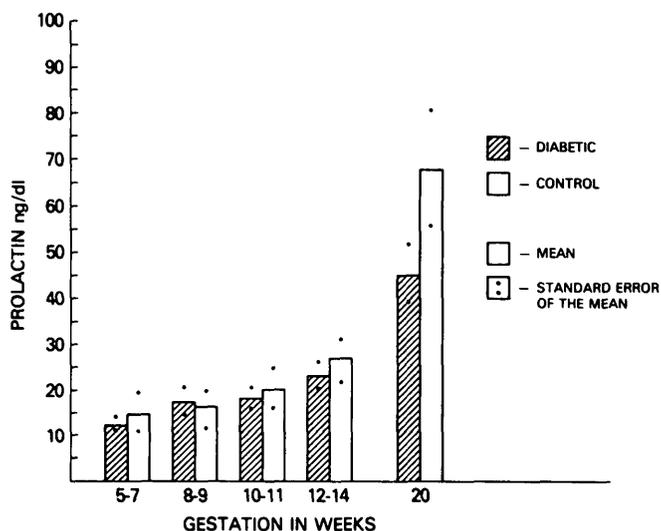


FIG. 2. Plasma prolactin levels in normoglycemic diabetic and control subjects by week of gestation. Prolactin levels rose continuously throughout the study and were not significantly different between the two groups.

The timing of conception and the gestational week during which each blood sample was drawn was based on the following observations: (1) The temperature rise on a basal temperature graph for 15–20 days or missed menstrual period for 1–5 days in women with regular menstrual cycles. (2) A positive pregnancy test within 6 days after missed period to confirm that conception had occurred. (3) Serial pelvic examinations to document uterine size and confirmed subsequently by quickening at 18 wk and by neonatal examination.

HCG was determined by radioreceptor assay;¹ prolactin, testosterone, and androstenedione were determined by RIA as previously reported.^{1,11}

Statistical methods. To determine whether hormone levels changed significantly over time, Student's *t*-test was used to determine whether the slope was significantly different from zero. Differences in hormone levels between diabetic and control subjects were examined by the Wilcoxon rank sum test.

RESULTS

Figure 1 shows HCG levels in the diabetic and control groups. As expected, HCG rose early in pregnancy and fell subsequently. Because of the serum pattern of HCG, it was inappropriate in this case to plot the slope of the curves. There were no significant differences in HCG between diabetic and control subjects.

Prolactin levels rose very early in gestation and continued to rise over the study period ($P < 0.00001$) (Figure 2). Diabetic and control subjects did not have significantly different prolactin levels at any time during the study.

Testosterone levels rose significantly over the period studied ($P = 0.0001$). Diabetic subjects had significantly higher levels ($P = 0.024$) at the beginning of pregnancy (week 6)

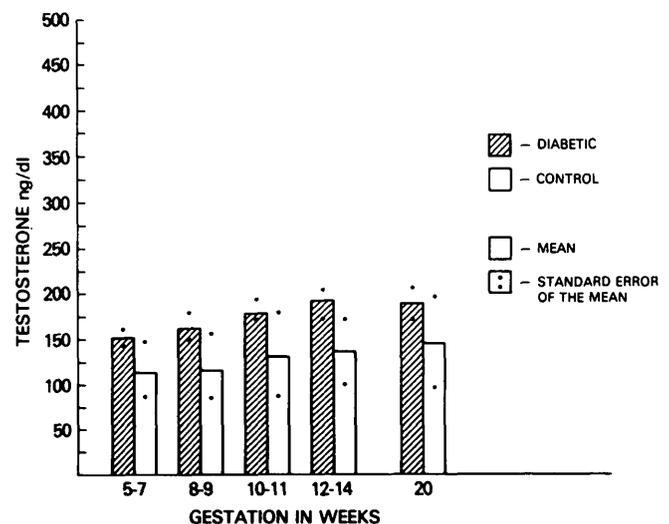


FIG. 3. Plasma testosterone levels in normoglycemic diabetic and control subjects by week of gestation. Testosterone levels increased significantly over the period studied in both groups.

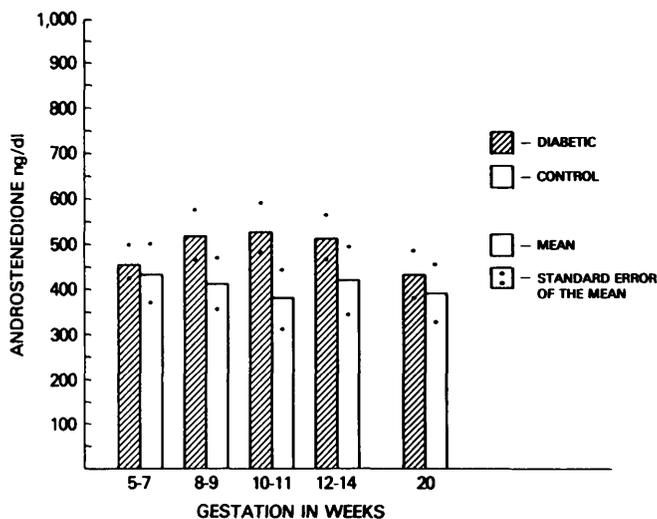


FIG. 4. Plasma androstenedione levels in normoglycemic diabetic and control subjects by week of gestation.

even when adjustment was made for multiple comparisons (Figure 3). Differences later in pregnancy did not reach statistical significance. Because of the limited number of observations each week, the power to detect true differences between the diabetic and control groups is low.

Androstenedione did not increase significantly over the period studied (Figure 4). Although diabetic subjects had higher androstenedione levels at each week studied, only at week 6 were the differences close to significant statistically ($P = 0.055$).

Linear regression was performed to determine whether HCG was an important determinant of testosterone or androstenedione production. The correlation between both HCG and testosterone ($r < 0.001$ not significant), and HCG and androstenedione ($r < 0.009$ not significant), was low. These results indicate that HCG is not an important factor in androgen production.

DISCUSSION

A previous study has reported subnormal levels of HCG and prolactin in the first trimester of poorly controlled diabetic pregnancies.¹ Once maternal glucose levels were normalized, however, both hormones rose into the normal range. The present study demonstrates that when diabetic women are made normoglycemic before conception, HCG and prolactin levels early in pregnancy are no different from those measured in normal control women. Thus, whatever the underlying etiology of the abnormal hormone profile, it must be mediated by poor diabetes control and prevented by normoglycemia.

The situation appears to be different for testosterone and androstenedione. Despite normoglycemia, diabetic women had significantly higher testosterone levels shortly after conception and generally higher androgen levels throughout the period studied. HCG does not appear to be responsible for the elevated androgen levels for several reasons: HCG levels

were not higher in diabetic than in control subjects and, unlike the situation in nonhuman primates,¹¹⁻¹³ rising HCG levels did not stimulate an increase in androgen production. Since sex hormone binding globulin is known to be elevated in diabetic pregnancies,¹⁴ the increased testosterone may be the result of sequestration by the binding protein with consequent decreased metabolic degradation.

Alternatively, the increased androgen levels may not be related to pregnancy. Increased androgen levels have been reported in nonpregnant diabetic women^{15,16} and in female streptozocin-diabetic rats.¹⁷ In vitro studies suggest that insulin may stimulate ovarian androgen production;¹⁸ it is possible that the peripheral hyperinsulinemia produced by exogenous insulin administration¹⁵ could lead to elevated androgen levels. This study's finding of higher androgen levels in diabetic pregnancies, despite normalization of blood glucose before conception, warrants further investigation.

Since HCG and prolactin levels may reflect the integrity of trophoblastic implantation^{8,19} our finding that these hormones can be normalized by better diabetes control before conception may be of considerable clinical importance. We hypothesize that diabetic women who achieve normoglycemia before conception may be able to reduce their risk for a fetal loss.

ACKNOWLEDGMENTS: The NICHD-Diabetes in Early Pregnancy project provided the subjects who participated in this study. Clinical Research NIH Grant No. RR-00047 supported some aspects of this study. Drs. George Reed and Barry Graubard provided valuable statistical advice. The assistance of Edna Wright and J. Luis de la Cruz in steroid RIAs and of Sandra Cole, Debbie Green, and Felicia Anzel in the preparation of the manuscript are greatly appreciated.

From the Southwest Foundation for Research and Education, Dept. of Clinical Sciences and Reproductive Biology, San Antonio, Texas (V.D.C.); The New York Hospital-Cornell University Medical College, New York, New York (L.J.); and the National Institute of Child Health and Human Development, NIH, Bethesda, Maryland (J.L.M.).

Address reprint requests to V. Daniel Castracane, Ph.D., Department of Obstetrics and Gynecology, Texas Tech University Health Science Center, Regional Academic Health Center at Amarillo, 1400 Wallace Boulevard, Amarillo, Texas 79106.

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