

Comparing the glucose kinetics of adolescent girls and adult women during pregnancy^{1–3}

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ABSTRACT

Background: Fetal energy demands are met mostly from oxidation of maternally supplied glucose. In pregnant adults this increased glucose requirement is met by an increase in gluconeogenesis. It is not known, however, whether, like their adult counterparts, pregnant adolescent girls can increase gluconeogenesis—hence, glucose production.

Objective: Our objective was to measure glucose kinetics in 8 pregnant adolescents and 8 adult women.

Design: We measured glucose kinetics after an overnight fast by using a primed-constant 6-h U-¹³C-glucose infusion at the end of trimester 1 and early trimester 3.

Results: From trimester 1 to trimester 3, whole-body glucose production increased significantly in both groups ($P < 0.01$). However, whereas the weight-specific rate in adults increased by 18.2%, it increased by only 14.3% in adolescents. In adults, the increase in whole-body glucose production was largely due to a significant increase ($P < 0.01$) in the rate of gluconeogenesis, but in adolescents there was no change in whole-body gluconeogenesis, and weight-specific gluconeogenesis actually decreased by 11.7%. In both groups, the rate of whole-body glycogenolysis increased significantly ($P < 0.05$) in trimester 3, and in adolescents, it increased by 95%.

Conclusions: These findings suggest that, in the fasted state in late pregnancy, pregnant adolescents cannot increase weight-specific glucose production by the same magnitude as their adult counterparts. Furthermore, whereas adult women increase glucose production primarily through gluconeogenesis, adolescents do so through glycogenolysis. *Am J Clin Nutr* 2010;91:604–9.

INTRODUCTION

Adolescent pregnancy in Jamaica, as elsewhere, is a major health concern. It is associated with a high prevalence of low-birth-weight (LBW) infants and premature births (1), which are major contributors to an increased perinatal mortality rate (2). In Jamaica, 40% of women aged <20 y have had at least one pregnancy (3).

Whereas socioeconomic factors such as unmarried status, poor education, and poor antenatal care contribute to poor outcome, younger age alone increases the risk of LBW infants (4, 5). On the basis of the observation that adolescent girls who grow during pregnancy give birth to infants that weigh less than those of nongrowing adolescents and adults (6), it is possible that the growing adolescent cannot supply sufficient nutrients to support both her own growth and that of her fetus. Because fetal energy

demands are met exclusively from oxidation of glucose and amino acids (7, 8), it is possible that the growing adolescent gives birth to a smaller baby because she cannot provide the extra glucose and amino acids needed for optimal fetal growth.

In pregnant adult women the increased glucose requirement of pregnancy is met by an $\approx 20\%$ increase in glucose production (9, 10), primarily from gluconeogenesis (10). Whereas it is known that overnight-fasted, nonpregnant adolescent girls produce glucose at approximately the same rate as adults (11), it is not known whether adolescents can increase glucose production to the same extent as their adult counterparts during pregnancy. We (12) as well as others (13) have reported that pregnant adolescents gain more weight than do their adult counterparts during pregnancy. We also showed that most of this weight gain was in lean body mass (12), suggesting that pregnant adolescents may require more amino acids than adult women to support the increased protein synthesis associated with their own growth plus the growth of their reproductive tissues and fetus. Hence, as pregnancy progresses, unlike their adult counterparts, pregnant adolescents may not have sufficient gluconeogenic precursors to support increased gluconeogenesis. On the basis of these observations, we propose that pregnant adolescents will not be able to increase gluconeogenesis, hence glucose production, to the same extent as their adult counterparts as pregnancy progresses. To test this hypothesis, glucose kinetics were measured in pregnant adult women and in adolescent girls at the end of the first trimester and at the beginning of the third trimester of pregnancy.

SUBJECTS AND METHODS

The study was conducted at the obstetrics ward of the University Hospital of the West Indies in Kingston, Jamaica. The

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Department of Obstetrics and Gynecology conducts antenatal clinics, which enroll pregnant women during the first trimester, at ≈ 8 wk gestation. The experimental protocols were reviewed and approved by the Ethics Committee of the University of the West Indies and by the Institutional Review Board for Human Subject Research of Baylor College of Medicine and Affiliated Hospitals. Enrollment of subjects started in February 2007. Written informed consent was obtained from each subject at recruitment.

Pregnant adolescents and adult women who were at < 13 wk of gestation and registered at the antenatal clinic at the University Hospital of the West Indies were invited to join this prospective study and were enrolled consecutively. Women were excluded for any of the following conditions: chronic illnesses, such as diabetes mellitus, hypertension, or heart disease; a genetic abnormality, such as sickle cell disease; or multiple gestations. Sixteen subjects (8 adolescents and 8 adult women) with normal body mass index [BMI (in kg/m^2): > 18.5 and ≤ 25] were enrolled in the study. Maternal weight was determined to the nearest 0.01 kg by using a Tanita digital scale (CMS Weighing Equipment Ltd, London, United Kingdom), and height was measured to the nearest 0.1 cm by using a stadiometer (CMS Weighing Equipment Ltd). Maternal weight was again assessed at ≈ 28 wk and at 36 wk gestation.

Sociodemographic, gestational age, and anthropometric data

Once written informed consent was obtained, a questionnaire, which provided information on demographics, socioeconomic status, substance use (eg, cigarette, alcohol, marijuana, and cocaine), and menstrual details, was administered to all subjects. A socioeconomic score was calculated by using education and occupation of the mother and father, household possessions, and a crowding index (calculated as the number of habitable rooms in the dwelling divided by the number of people living in that dwelling). A higher score denoted a better socioeconomic status. Gestational age was determined by the last menstrual period and confirmed by an ultrasound measurement performed at the time of the first experimental study (trimester 1 study). We calculated maternal weight gain from the trimester-1 study to the trimester 3 study and from 12 to 36 wk gestation. Birth weight was determined to the nearest 0.01 kg by using a Tanita model 1583 digital baby scale (CMS Weighing Equipment Ltd), crown-heel length was measured to the nearest 0.1 cm by using a Harpenden Infantometer (CMS Weighing Equipment Ltd), and head circumference was measured by using a fiberglass tape measure.

Tracer infusion protocol

All subjects were studied after an 8 h fast on 2 occasions, at the end of the first trimester (gestation: 12.8 ± 0.39 wk) and the beginning of the third trimester (gestation: 27.8 ± 0.4 wk). Subjects were admitted to the obstetrics ward in the evening and had their last meal at 2200. Eight hours later, an intravenous catheter (Sesecure, 18 G; Morningside Pharmaceuticals Ltd, Leicester, United Kingdom) was inserted into the antecubital vein of one arm for the infusion of isotopes, whereas another catheter was inserted in an anteflow direction into the dorsal vein of the contralateral hand for drawing blood samples. This can-

nula was kept patent with intermittent small infusions of heparinized saline.

A sterile solution of $\text{U-}^{13}\text{C}_6$ glucose (Cambridge Isotope Laboratories, Woburn, MA) was prepared in 9 g NaCl/L. After a baseline 5-mL blood sample was taken, a primed (prime = $48 \mu\text{mol}/\text{kg}$) continuous infusion of $\text{U-}^{13}\text{C}_6$ glucose was started immediately (rate = $0.8 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) for the next 6 h. Additional blood samples were collected at 3, 4, 5, and 6 h after the infusion. At the end of the infusion, the catheters were removed, and the subjects were given lunch and discharged.

Laboratory analysis

Blood was drawn in prechilled tubes containing sodium fluoride and potassium oxalate, centrifuged at 4°C , and the plasma was removed and stored at -70°C . Plasma glucose concentrations were measured by the glucose oxidase reaction by using a glucose analyzer (YSI, Yellow Springs, OH), and plasma insulin concentrations were measured by using an enzyme-linked immunosorbent assay kit (Linco Research, St Charles, MO). The plasma glucose tracer-to-tracee ratio (Tr/tr) was measured by using positive chemical ionization gas chromatography-mass spectrometry on its pentaacetate derivative, monitoring ions from m/z 331–336. To facilitate mass-isotopomer distribution analysis of plasma glucose (14), the Tr/tr of the $\text{U-}^{13}\text{C}_6$ glucose tracer and natural glucose was also measured by monitoring ions from m/z 331–339.

Calculations

Glucose production ($R_a\text{Glu}$) was calculated by the following steady state equation:

$$\begin{aligned} R_a\text{Glu} (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ = \text{Tr/tr of infused glucose (mol \%)} / \text{Tr/tr } M \\ + 6 (\Delta \text{ over baseline}) \text{ plasma glucose} \times i \end{aligned} \quad (1)$$

where i was the tracer infusion rate and $M + 6$ refers to the uniformly labeled mass isotopomer of plasma glucose at steady state.

Endogenous $R_a\text{Glu}$ was obtained by subtracting the rate of infusion of labeled glucose. Under steady state conditions, $R_a\text{Glu}$ would be equal to $R_d\text{Glu}$ (rate of disappearance). Hence,

$$\begin{aligned} \text{Glucose clearance (mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ = R_a\text{Glu} / \text{plasma glucose concentration} \end{aligned} \quad (2)$$

The fractional rate of gluconeogenesis (GNG) was calculated according to the reciprocal pool model of Haymond and Sunehag (14) using the mass isotopomer distribution analysis of plasma glucose,

$$\begin{aligned} \text{Fractional GNG} = [\sum_{M1-M5} (^{13}\text{C}) / \sum_{M1-M6} (^{13}\text{C})] \\ \times [\sum_{M1-M5} (^{12}\text{C}) / \sum_{M1-M5} (^{13}\text{C})] \end{aligned} \quad (3)$$

where $\sum_{M1-M5} (^{13}\text{C})$ represents the sum of all glucose molecules labeled with ^{13}C on carbons 1–5 (ie, those labeled molecules arising from gluconeogenesis); $\sum_{M1-M6} (^{13}\text{C})$ represents those molecules with ^{13}C on carbons 1–6 (ie, those labeled molecules arising from gluconeogenesis and the infused tracer);

and $\sum_{M1-M5} (^{12}\text{C})$ and (^{13}C) represent the sum of ^{12}C and ^{13}C in all glucose molecules derived from gluconeogenesis.

Absolute GNG was calculated as follows:

$$\begin{aligned} \text{Absolute GNG} (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ = \text{fractional GNG} \times R_a\text{Glu} \end{aligned} \quad (4)$$

and

$$\begin{aligned} \text{Rate of glycogenolysis} (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ = \text{endogenous } R_a\text{Glu} - \text{absolute GNG} \end{aligned} \quad (5)$$

Because individual subjects' fluid retention may differ during pregnancy, as well as the fact that we have shown that adolescent girls lay down more lean body mass than adult women during pregnancy (12), each glucose kinetic parameter was also expressed per each subject's whole-body weight to determine the change within each group from trimester 1 to 3. This was achieved by multiplying each weight-specific kinetic parameter by the subject's body weight. For example:

$$\begin{aligned} \text{Whole-body glucose } R_a (\mu\text{mol}/\text{kg}) \\ = \text{endogenous } R_a\text{Glu} (\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) \\ \times \text{body wt (kg)} \end{aligned} \quad (6)$$

To assess pregnancy-induced insulin resistance, the homeostatic model assessment (HOMA) was calculated as the product of plasma insulin and glucose concentrations divided by 22.5.

Statistics

Data are expressed as means \pm SEs. Differences in subject characteristics between the adolescent and adult groups were assessed by unpaired Student's *t* test. Fisher exact test was used to compare fetal loss, prematurity, and LBW between the 2 groups (*see* Table 2). Differences in metabolic variables between the groups were analyzed by mixed-model analysis of repeated measures with 2 fixed effects (age group and time of pregnancy) and 1 random effect (subject) by using the PROC MIXED procedure of SAS/STAT, version 9.2 (SAS Institute, Cary, NC). The model included age group (adults and adolescents), time of pregnancy (trimester 1 and 3), and interaction between age group and time of pregnancy. The residuals of metabolic variables were approximately normally distributed. Because each group had different body weights, whole-body glucose kinetics were not compared between groups. Only within-group comparisons were made between trimester 1 and trimester 3 values by using the paired Student's *t* test. Tests were considered statistically significant if $P < 0.05$. Correlations between measured kinetic variables and subject characteristics were performed by using Pearson's correlation. We performed Student's *t* tests, Fisher exact tests, and correlations by using GraphPad Prism software, version 4 (GraphPad Software, San Diego, CA).

RESULTS

There was no report of substance abuse such as cigarette, alcohol, marijuana, or cocaine use during pregnancy among the

16 subjects, and there was no significant difference in socio-economic scores between the adults and adolescents (44.4 ± 3.8 and 36.3 ± 3.0 , respectively). Maternal characteristics at the trimester 1 study and the trimester 3 study are presented in **Table 1**. Maternal weight and BMI at the trimester 1 study were significantly lower ($P < 0.05$) in adolescent girls than in their older counterparts. Weight gain from the first trimester to the end of the third trimester, weeks 12–36 of gestation, was significantly greater in adolescents than in adults ($P < 0.005$). Mean \pm SE hemoglobin concentrations were at the lower end of the normal range in both groups with 3 adolescents and 2 adults having values <12 g/dL.

Pregnancy outcomes and newborn characteristics are presented in **Table 2**. Among the 16 participants in the study, there was one fetal loss in the adolescent group. Although there was no significant difference in gestational age between the groups, the adolescents had 2 premature deliveries, whereas the adults had none. Mean \pm SE birthweights of the groups were not significantly different, and each group had one LBW infant. However, Fisher exact test analyses showed that there were no significant differences between the groups in fetal loss, premature delivery, and LBW. Similarly, there were no significant differences in placental weight, newborn head circumference, and crown-heel length, although the latter trended shorter in the adolescent group.

There were no significant interactions between age group and time of pregnancy in any of the glucose kinetic parameters measured (**Table 3**). For weight-specific glucose production in both groups, there was a significant main effect ($P < 0.01$) of pregnancy time, such that in trimester 3, glucose production was significantly faster compared with the rate at trimester 1. However, the magnitude of the change was greater in the adults. Whereas in the adult women there was an 18.2% increase in glucose production from trimester 1 to 3, in the adolescents there was only a 14.3% increase. Whole-body glucose production also increased significantly in both groups from trimester 1 to trimester 3 ($P < 0.01$).

For weight-specific gluconeogenesis, there was no significant effect of age or pregnancy time. Although gluconeogenesis increased by 20% from trimester 1 to 3 in the adult women, it decreased by 11.7% in the adolescents. At the whole-body

TABLE 1
Maternal characteristics¹

Variables	Adult women (n = 8)	Adolescent girls (n = 8)
Age (y)	26.1 \pm 0.4	16.1 \pm 0.4 ²
Height (cm)	165.0 \pm 2.2	162.0 \pm 1.9
BMI (kg/m ²)	22.6 \pm 0.4	20.8 \pm 0.3 ²
Trimester 1 study weight (kg)	61.9 \pm 2.2	54.9 \pm 1.3 ²
Trimester 3 study weight (kg)	64.9 \pm 1.7	61.1 \pm 2.1
Weight gain from 12 to 27 wk (kg)	4.66 \pm 1.44	7.13 \pm 1.18
Weight at 36 wk (kg)	71.2 \pm 2.7	69.1 \pm 1.8
Weight gain from 12 to 36 wk (kg)	9.0 \pm 1.9	15.8 \pm 1.1 ²
Hemoglobin at trimester 1 study (g/dL)	12.3 \pm 0.9	11.4 \pm 1.7

¹ All values are means \pm SEs. The trimester 1 study was performed at 12.8 \pm 0.39 wk of gestation, and the trimester 3 study was performed at 27.8 \pm 0.4 wk of gestation.

² $P < 0.001$ (unpaired Student's *t* test).

TABLE 2
Pregnancy outcome and newborn characteristics¹

Variables	Adult women (n = 8)	Adolescent girls (n = 8) ²	P value
Fetal loss ³	0	1	0.1
Gestational age at birth (wk)	38.4 ± 0.4 ⁴	37.6 ± 0.8	0.38
No. of premature deliveries (<37 wk) ³	0	2	0.2
Birth weight (kg)	3.14 ± 0.2	2.87 ± 0.1	0.22
No. of LBW infants (<2.5 kg) ³	1	1	0.1
Placenta weight (g)	631.3 ± 48.2	645.7 ± 1.7	0.79
Head circumference (cm)	34.2 ± 0.7	33.8 ± 0.5	0.69
Crown-heel length (cm)	49.2 ± 1.2	46.2 ± 1.2	0.10

¹ LBW, low-birth-weight.

² For the adolescent group, all mean values were for n = 7.

³ Group comparisons were performed by Fisher exact test. All other comparisons were performed by unpaired Student's t test.

⁴ Mean ± SE (all such values).

measurement, gluconeogenesis increased significantly (P < 0.01) in the adult group from trimester 1 to trimester 3 but remained unchanged in the adolescent group.

For weight-specific glycogenolysis in both groups, there was a significant main effect (P < 0.05) of pregnancy time, such that in trimester 3, glycogenolysis was significantly faster compared with the rate at trimester 1. Whole-body glycogenolysis increased significantly (P < 0.01) in the adolescent group only, by 95% from trimester 1 to trimester 3.

In both groups at trimester 1, gluconeogenesis contributed 60% of glucose produced and glycogenolysis contributed 40%. In trimester 3, this relation remained the same in adults. However, in adolescents, the contribution of gluconeogenesis decreased to 47% of glucose produced and that of glycogenolysis increased to 53%.

With respect to plasma glucose concentration, there was a significant main effect of pregnancy time in both groups, such that in the third trimester, the concentration was modestly but significantly lower (P < 0.01) compared with that in the first

trimester (Table 4). Similarly, with respect to glucose clearance, there was a significant main effect of pregnancy time, such that in the third trimester, clearance was significantly faster (P < 0.001) compared with that in the first trimester. However, the magnitude of the change seems to be greater in the adults. Whereas in adult women there was a 28% increase in glucose clearance from trimester 1 to 3, in adolescents there was only a 17.8% increase.

With respect to plasma insulin concentration and HOMA, there were significant main effects of pregnancy time as both parameters increased significantly from trimester 1 to trimester 3 (P < 0.001 and P = 0.01, respectively). The effect of age on insulin was not significant (P = 0.087), but the point estimate was ≈>50% in the adolescent group compared with the adult group at both trimesters.

The pooled data of the 15 subjects who had successful pregnancies were used to look for correlations between maternal glucose and insulin parameters and other maternal and baby variables. In trimester 1, there was a significant negative correlation between plasma insulin and gluconeogenesis (r = -0.5, P = 0.046), and in trimester 3 plasma insulin correlated negatively with the fraction of glucose produced from gluconeogenesis (r = -0.5, P = 0.07) and positively with glycogenolysis (r = 0.5, P = 0.05). In trimester 3, there was a significant negative correlation between trimester 3 glucose clearance and baby's birth length (r = -0.52, P = 0.045) and a positive correlation between HOMA and placental weight (r = 0.50, P = 0.058).

DISCUSSION

To test the hypothesis that pregnant adolescents will not be able to increase gluconeogenesis, hence glucose production, to the same extent as their adult counterparts as pregnancy progresses, aspects of glucose metabolism were measured in pregnant adult women and adolescent girls after an overnight fast at the end of the first and beginning of the third trimester of pregnancy. Our results show that, although whole-body glucose production increased significantly (P < 0.01) in both groups by

TABLE 3
Weight-specific (μmol · kg⁻¹ · min⁻¹) and whole-body (μmol · min⁻¹) glucose kinetics during pregnancy in adult women and adolescent girls¹

Kinetic variable	Adults (n = 8)			Adolescents (n = 8)		
	Trimester 1	Trimester 3	Percentage change	Trimester 1	Trimester 3	Percentage change
Glucose R _a (μmol · kg ⁻¹ · min ⁻¹) ²	9.3 ± 0.3 ³	11 ± 0.3	18.3	9.8 ± 0.7	11.2 ± 0.3	14.3
Whole-body glucose R _a (μmol · min ⁻¹)	579 ± 29	730 ± 31 ⁴	26	537 ± 32	695 ± 20 ⁴	29
Gluconeogenesis (μmol · kg ⁻¹ · min ⁻¹)	5.6 ± 0.2	6.7 ± 0.6	20	6.0 ± 0.8	5.3 ± 0.6	-11.7
Whole-body gluconeogenesis (μmol · min ⁻¹)	343 ± 13.6	441 ± 35.6 ⁴	28.6	325 ± 42	327 ± 38	1
Glycogenolysis (μmol · kg ⁻¹ · min ⁻¹) ²	3.8 ± 0.3	4.3 ± 0.7	13	3.9 ± 0.8	6.0 ± 0.5	53.8
Whole-body glycogenolysis (μmol · min ⁻¹)	236 ± 20.6	289 ± 54	22	189 ± 26.7	368 ± 31.8 ⁴	95
Gluconeogenesis/glucose R _a	0.60 ± 0.02	0.61 ± 0.06	1.6	0.61 ± 0.07	0.47 ± 0.05	-23.0
Glycogenolysis/glucose R _a	0.40 ± 0.02	0.39 ± 0.06	-2.5	0.39 ± 0.07	0.53 ± 0.05	36.0

¹ R_a, production. All weight-specific kinetic data were analyzed by mixed-model analysis of repeated measures with 2 fixed effects (age group and time of pregnancy) and one random effect (subject). All whole-body kinetic data were analyzed by paired Student's t test.

² Significant main effect of pregnancy time: trimester 3 compared with trimester 1, P < 0.05 (mixed-model analysis of repeated measures).

³ Mean ± SE (all such values).

⁴ Significantly different from trimester 1, P < 0.01 (paired Student's t test).

TABLE 4
Glucose concentration and clearance and insulin resistance in pregnancy¹

Variables	Adults (<i>n</i> = 8)		Adolescents (<i>n</i> = 8)	
	Trimester 1	Trimester 3	Trimester 1	Trimester 3
Glucose concentration (mmol/L) ²	4.0 ± 0.1	3.6 ± 0.1	3.8 ± 0.1	3.7 ± 0.05
Glucose clearance (mL · kg ⁻¹ · min ⁻¹) ²	2.5 ± 0.1	3.2 ± 0.1	2.8 ± 0.2	3.3 ± 0.1
Insulin (μU/mL) ²	3.9 ± 0.5	6.5 ± 1.2	5.8 ± 1.4	9.6 ± 1.4
HOMA ²	0.7 ± 0.1	1.1 ± 0.2	1.0 ± 0.2	1.6 ± 0.2

¹ All values are means ± SEs. All data were analyzed by mixed-model analysis of repeated measures with 2 fixed effects (age group and time of pregnancy) and one random effect (subject). HOMA, homeostatic model assessment.

² Significant main effect of pregnancy time: trimester 3 compared with trimester 1, *P* < 0.05 (mixed-model analysis of repeated measures).

almost the same extent, the weight-specific glucose production rate of the adolescents did not increase by the same magnitude as in the adult group because adolescents gained 53% more body weight than adults. Whereas in adults the increase in glucose production was largely accounted for by a significant increase in the rate of gluconeogenesis, in adolescents there was no change in the rate of whole-body gluconeogenesis and weight-specific gluconeogenesis actually decreased by 11.7%. On the other hand, the increase in glucose production in the adolescents was exclusively accounted for by a significant increase in the rate of glycogenolysis. These findings suggest that, when in the fasted state, pregnant adolescents cannot increase weight-specific glucose production by the same magnitude as their adult counterparts in late pregnancy. Furthermore, whereas adult women increase glucose production primarily through an increased rate of gluconeogenesis, adolescents do so exclusively through an increased rate of glycogenolysis.

It has been reported that maternal glucose is the most important substrate for the growing fetus and placental tissues (15, 16). In overnight-fasted adult women, this increased glucose requirement is met by an increased production of glucose (9, 10). For example, Catalano et al (9) reported a 20% increase in weight-specific glucose production and a 29% increase in whole-body glucose production, and Kalhan et al (10) reported a 21% increase in whole-body glucose production as pregnancy advances from trimester 1 to late trimester 3. Our current findings of an 18% increase in weight-specific glucose production and a 26% increase in whole-body glucose production in adult women are in close agreement with these earlier reports. In the only other study to use a comparable tracer isotope model to estimate rate of gluconeogenesis during pregnancy, Kalhan et al (10) reported that the whole-body rate of gluconeogenesis increased by 29% in overnight-fasted adult women, which, although not statistically significant, fully accounted for the faster whole-body glucose production in the third trimester. Our current finding of a 28.6% increase in whole-body gluconeogenesis in adult women is almost identical to that reported by Kalhan et al (10). One difference between the 2 studies is that, whereas in this study the proportion of glucose derived from gluconeogenesis was 60% at trimester 1 and remained unchanged at trimester 3, it was 72% in trimester 1 and increased to 76% in trimester 3 in the study reported by Kalhan et al (10). These differences are likely due to the fact that 2 different stable isotope approaches were used to estimate the fractional rate of gluconeogenesis in the 2 studies.

Although whole-body glucose production increased significantly (*P* < 0.01) from trimesters 1 to 3 in the adolescent group,

their weight-specific glucose production increased by a lesser magnitude (14%) compared with the 18.3% of the adults. This was due to the fact that, whereas both groups increased their whole-body glucose production by ≈150 μmol · min⁻¹, the adolescent girls had a >54% gain in body weight compared with their adult counterparts from the trimester 1 study to the trimester 3 study. A surprising finding is that the faster glucose production of the adolescent group was not due to a faster rate of gluconeogenesis as seen in the adults but rather to a markedly faster rate of glycogenolysis. This finding suggests that in the fasted state the adolescent adapts to maintain glucose supply during pregnancy by increasing the rate of glycogenolysis rather than the rate of gluconeogenesis. That is, in short-term food deprivation such as an overnight fast, adolescents can supply both the glucose and amino acids needed to grow their fetus by using their hepatic glycogen stores to maintain glucose supply. Our finding that trimester 3 plasma insulin correlated negatively with the fraction of glucose derived from gluconeogenesis and positively with glycogenolysis strongly suggests that this adaptation by adolescents to maintain glucose supply by increasing the rate of glycogenolysis is modulated through insulin.

Although whole-body glucose production increased significantly (*P* < 0.01) from trimester 1 to trimester 3 in both adults and adolescents, plasma glucose concentration was modestly but significantly lower (*P* < 0.05) in trimester 3 compared with trimester 1. Not surprisingly, glucose clearance increased such that in the third trimester clearance was significantly faster (*P* < 0.05) compared with the first trimester. It is interesting that, although glucose clearance was similar in both groups at trimester 1, it was associated with a 66% higher plasma insulin in the adolescents, suggesting that their insulin sensitivity started decreasing very early in pregnancy. This is reflected in their higher HOMA values (an index of insulin resistance) at trimester 1. On the basis of the work of Kalhan et al (17) and Catalano et al (9, 18, 19) that showed that insulin sensitivity decreases significantly with advancing gestation in healthy adult women, the increase in plasma insulin and HOMA from trimesters 1 to 3 is not unexpected. Although, possibly due to the small sample size, the effect of age on insulin concentration was not found to be significant (*P* = 0.087), both insulin concentration and HOMA values were higher by 48% and 45%, respectively, in the adolescent group compared with the adult group at trimester 3, indicating that their insulin resistance became more pronounced in late pregnancy. For example, although glucose clearance was almost identical in the 2 groups in trimester 3, plasma insulin was higher (by 3.1 μU/mL) in the adolescent group, indicating

that insulin sensitivity had decreased to a greater extent in the adolescents than in the adults. Although these normal-weight adolescents still had excellent insulin sensitivity (ie, HOMA value at the 10th centile), it is possible that overweight and obese adolescents will be more prone to gestational diabetes.

Our finding of a positive correlation between HOMA and placental weight corroborates the earlier findings of Catalano et al (20) that placental weight increased as insulin sensitivity decreased in late pregnancy. These authors also reported strong correlations between trimester 3 insulin sensitivity, neonatal birth weight, and fat-free mass, which led them to conclude that maternal insulin sensitivity in late pregnancy is involved in the regulation of nutrient availability to the placenta and fetus. Because placental glucose uptake is independent of insulin (21), it is possible that the insulin resistance of maternal tissues during pregnancy is a metabolic adaptation designed to ensure that an adequate supply of circulating glucose is always readily available for fetoplacental uptake. Although we did not observe any correlation with birth weight, such an adaptation may explain the negative correlation we observed between trimester 3 maternal glucose clearance and infants' birth length.

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