A Randomized Controlled Trial Using Glycemic Plus Fetal Ultrasound Parameters Versus Glycemic Parameters to Determine Insulin Therapy in Gestational Diabetes With Fasting Hyperglycemia

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OBJECTIVE — To compare management based on maternal glycemic criteria with management based on relaxed glycemic criteria and fetal abdominal circumference (AC) measurements in order to select patients for insulin treatment of gestational diabetes mellitus (GDM) with fasting hyperglycemia.

RESEARCH DESIGN AND METHODS — In a pilot study, 98 women with fasting plasma glucose (FPG) concentrations of 105–120 mg/dl were randomized. The standard group received insulin treatment. The experimental group received insulin if the AC, measured monthly, was ≥70th percentile and/or if any venous FPG measurement was >120 mg/dl. Power was projected to detect a 250-g difference in birth weights.

RESULTS — Gestational ages, maternal glycemia, and AC percentiles were similar at randomization. After initiation of protocol, venous FPG ($P = 0.003$) and capillary blood glucose levels ($P = 0.049$) were significantly lower in the standard group. Birth weights (3,271 ± 458 vs. 3,369 ± 461 g), frequencies of birth weights >90th percentile (6.3 vs 8.3%), and neonatal morbidity (25 vs. 25%) did not differ significantly between the standard and experimental groups, respectively. The cesarean delivery rate was significantly lower (14.6 vs. 33.3%, $P = 0.03$) in the standard group; this difference was not explained by birth weights. In the experimental group, infants of women who did not receive insulin had lower birth weights than infants of mothers treated with insulin (3,180 ± 425 vs. 3,482 ± 451 g, $P = 0.03$).

CONCLUSIONS — In women with GDM and fasting hyperglycemia, glucose plus fetal AC measurements identified pregnancies at low risk for macrosomia and resulted in the avoidance of insulin therapy in 38% of patients without increasing rates of neonatal morbidity.

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Gestational diabetes mellitus (GDM) has been linked to a variety of perinatal complications, the most common being fetal hyperinsulinism and accelerated fetal growth (1–3). Because maternal glucose levels have been directly correlated with risk of accelerated fetal growth and neonatal morbidity (3–6), recommendations for the medical management of women with GDM have focused on prevention of perinatal complications by maintaining pre- and postmeal blood glucose concentrations in a low-risk range in all patients (7). The approach of achieving strict glycemia to eliminate excess macrosomia has, in some studies (5,8), resulted in the requirment of insulin therapy for the majority of patients. However, because only a minority of infants are at risk for perinatal complications in pregnancies complicated by GDM (3–6,9–11), normalizing glucose levels in all patients may result in unnecessary use of insulin treatment in many pregnancies not at risk for fetal complications; in some cases, this may lead to intrauterine growth restriction (5).

In a previous study (12), we used a single measurement of the fetal abdominal circumference (AC) early in the third trimester to identify a large proportion of pregnancies at low risk for neonatal macrosomia when maternal fasting plasma glucose (FPG) concentrations remained <105 mg/dl during diet therapy. The present study was designed to test whether ultrasound can identify fetuses at low risk for macrosomia and related perinatal complications in women who pre-

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Abbreviations: AC, abdominal circumference; FPG, fasting plasma glucose; FSG, fasting serum glucose; GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age; VBAC, vaginal birth after cesarean.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

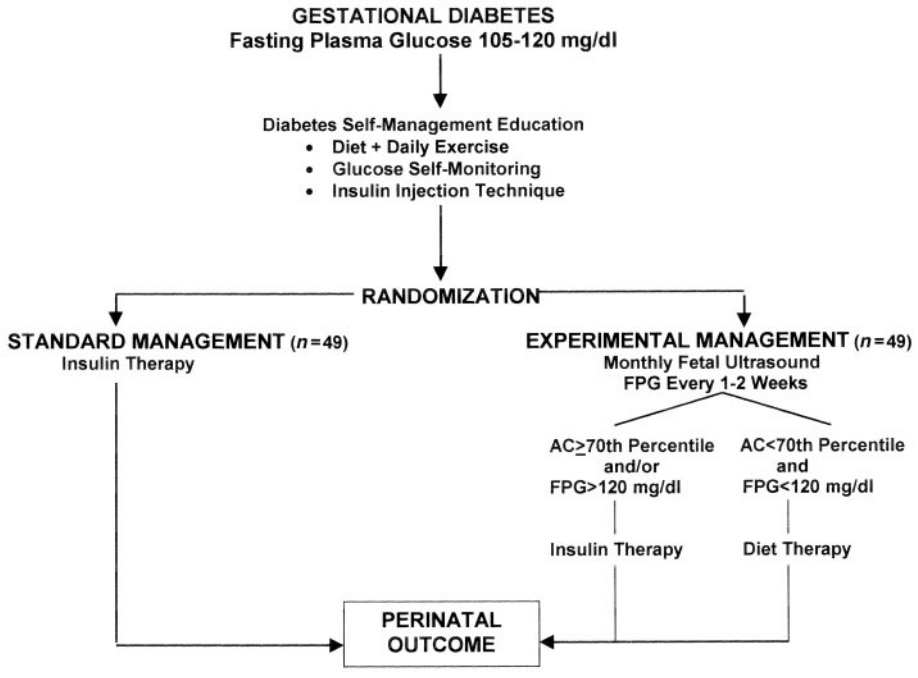

Figure 1—*Overview of the study design. The interventions listed in the figure were used for patient management. All subjects received individualized diabetic diet plans and instruction for daily exercise, performed glucose self-monitoring, and underwent monthly fetal AC measurements expressed as a percentile for gestational age. The glucose self-monitoring results were used to guide therapy only in insulin-treated subjects, using the glucose targets described in the text. Monthly fetal AC measurements and weekly or biweekly venous FPG levels were used to guide therapy only in the experimental management group.*

sented with fasting hyperglycemia in the range of 105–120 mg/dl. Our study protocol combined higher glycemic thresholds, to initiate insulin therapy, with monthly ultrasound assessments of fetal growth. Pregnancies that continued to demonstrate growth at low risk for macrosomia, i.e., normal fetal AC growth, were permitted more relaxed glycemic targets. In contrast, for pregnancies that had or developed a pattern of growth associated with a greater risk of macrosomia, i.e., accelerated fetal AC growth, intensive insulin therapy was initiated and titrated to achieve strict euglycemic control (12).

RESEARCH DESIGN AND METHODS

The study was conducted at the Los Angeles County and University of Southern California Medical Center and at the Good Samaritan Hospital, both in Los Angeles. From October 1995 through November 1997, pregnant women attending the prenatal clinics at these two institutions were asked to participate in the present study if they met the following criteria: *1*) GDM (1); 2) FPG concentrations >105 and <120 mg/dl; *3*) gestational age >14 and <34 weeks at time of study entry; *4*) singleton pregnancy; *5*) no medical complications, e.g., hypertension or vascular disease, except GDM known to affect fetal growth or neonatal morbidity; *6*) reliable estimation of gestational age, with either the first clinical examination <12 weeks or the first ultrasound examination <20 weeks; *6*) no use of tobacco, alcohol, or illicit drugs during pregnancy; and *7*) literacy. Subjects were enrolled after giving written informed consent for participation in the study, which was approved by the human research committees of the participating institutions.

Randomization and metabolic management

Before randomization (Fig. 1), all subjects had a complete fetal ultrasound examination by one of the investigators (S.L.K., U.S.G., or J.D.B.). The average of three measurements of the AC was taken at the level of the stomach and umbilical vein within the liver (13). The raw AC measurements were given to the study coordinator (C.S.), who calculated the percentile AC by gestational age (14). We used AC percentile measurements (based on a Los Angeles population [14]) that were not substantially different from those determined by Hadlock et al. (13). Subjects were then educated in diabetes self-care by a certified diabetes educator and a licensed dietitian. The education consisted of *1*) self-monitoring of blood glucose 4–7 times per day using a reflectance meter with electronic memory (Advantage glucose meter; Boehringer-Mannheim, Gaithersburg, MD); *2*) techniques for self-administration of insulin, which were to be used in the event that insulin therapy was prescribed; *3*) diabetic dietary instruction; and *4*) exercise advise. Dietary prescription was based on body weight at study entry, with a provision of 30 kcal · kg^{-1} · day^{-1} for women whose prepregnancy weight was <120% of the ideal and 25 kcal · kg^{-1} · day^{-1} for other women. Calories were distributed as 50–55% carbohydrate and <30% fat, to be ingested as three meals and three snacks. No woman was prescribed <1,800 or >2,500 kcal/day, regardless of her prepregnancy weight. All subjects were instructed to walk three times a day for 20–30 min after each meal.

After completing their education, subjects were stratified into one of five blocks according to their gestational age (≤20 weeks + 6 days, 21–23 weeks + 6 days, 24–26 weeks + 6 days, 27–29 weeks + 6 days, or 29–33 weeks + 6 days) and then randomized within the blocks to one of two study groups using a computer-generated numerical randomization scheme. Women randomized to standard management were prescribed NPH and regular insulin before breakfast and dinner. The initial daily dose (0.8, 0.9, 1.0, 1.1, or 1.2 units/kg body wt, respectively) was assigned according to the gestational age at entry according to the five randomization blocks above. Insulin doses were adjusted to achieve preprandial capillary blood glucose concentrations ≤90 mg/dl and 2-h postprandial concentrations ≤120 mg/dl (7). Women randomized to experimental management were prescribed insulin immediately only if the fetal AC was ≥70th percentile for gestational age. Initial doses were assigned as in the standard management group, but glycemic targets were ≤80 mg/dl before meals and ≤110 mg/dl 2 h after meals (12).

All subjects were seen in the clinic every other week until 34 weeks of gestation and weekly thereafter. At each visit, subjects were counseled to adhere to the prescribed program of diet, exercise, and glucose monitoring. Venous FPG was measured after an overnight fast. Glycemic control was evaluated by review of glucose levels using a computer program for glycemic management (Boehringer Mannheim), which calculated the number and mean of self-monitored capillary glucose levels since the last visit. The information was reviewed with each patient to assess and encourage daily dietary and exercise compliance and to adjust insulin doses in insulin-treated patients.

After the baseline ultrasound, additional fetal AC measurements were made at 20, 24, 28, 32, and 36 weeks of gestation (Fig. 1). For subjects in the standard group, this information was not used in patient management. For subjects randomized to the experimental group, insulin therapy was prescribed using the initial doses and glycemic targets described above if *1*) the fetal AC at entry or any subsequent ultrasound examination was ≥70th percentile for gestational age, *2*) any FPG concentration measured during a clinic visit exceeded 120 mg/dl or, *3*) the subject failed to perform ≥50% of the recommended capillary glucose measurements (see below).

Obstetrical management

Beginning at 34 weeks of gestation, all subjects were scheduled for antepartum fetal testing twice weekly. Elective delivery via labor induction or cesarean was scheduled between 38.5 and 39 weeks gestation, unless spontaneous labor at term ensued or a medical or obstetrical indication prompted an earlier delivery. All subjects with prior low transverse cesarean deliveries were offered a trial of vaginal birth unless they desired repeat cesarean delivery, had more than one prior cesarean delivery, or showed a contraindication to labor. Women undergoing labor induction with a Bishop's score >4 received intravenous oxytocin. Women with a Bishop's score ≤4 received prostaglandin cervical ripening before labor induction. Capillary blood glucose levels were monitored every 4 h during the latent phase and every 1–2 h during the active phase of labor. Insulin was administered intravenously if maternal capillary glucose concentrations exceeded 120 mg/dl, regardless of the mother's antepartum therapy.

Neonatal management and assessment

All neonates were observed in the neonatal intensive care unit for 4–6 h. Capillary blood glucose concentrations were measured immediately after birth, then at 1, 2, and 4 h of life. On the first day of life, Hb, total serum bilirubin, and serum calcium concentrations were measured, and a newborn physical examination, including anthropometric measurements (head, chest, upper arm, and thigh circumferences; body length; and skinfold thickness), was performed by the neonatologist (S.S.), who was blinded to the study group. Skinfold thickness was measured in triplicate at four sites on the newborn's right side (triceps, biceps, subscapular, and iliac crest), and the means of triplicate measures were used in data analysis. Other neonatal care was prescribed as clinically indicated. At discharge from the hospital, each neonatal record was reviewed for clinical outcomes by one of two investigators (S.S. or S.K.).

Data analysis

Neonates were classified as small for gestational age (SGA) (birth weight ≤10th percentile), appropriate for gestational age, or large for gestational age (LGA) (birth weight ≥90th percentile), according to standards derived from sex-specific norms at our institution (15). Neonatal outcomes and growth patterns were compared between standard and experimental groups by intent-to-treat analysis. A sample size of 98 subjects was projected to provide 80% power to detect a difference in birth weight of 250 g between the two groups, assuming a common SD of 425 g, based on a prior study of GDM at our institution ($\alpha = 0.05$, two-sided test) (12). Continuous variables were compared using the Student's *t* test or analysis of variance. Categorical variables were compared using Pearson's χ^2 or Fisher's exact tests. All analyses were carried out on SAS version 6.12 (Cary, NC). Missing data were excluded from analyses of individual variables. Data are presented as means ± SD in the text and tables.

RESULTS — A total of 98 subjects were randomized, 49 to each management arm. Sixty subjects received care at the Women and Children's Hospital (33 and 27 in the standard and experimental groups, respectively), and 38 received care at Good Samaritan Hospital (16 and 22 in the standard and experimental groups, respectively).

At study entry, maternal age, parity, gestational age, and prior history of macrosomia and GDM were not significantly different between the groups (Table 1). The mean BMI before pregnancy was indicative of obesity in both groups but was significantly greater in the standard group. Half of the subjects entered the study before 30 weeks and one-quarter entered before 25 weeks of gestation. The time between GDM diagnosis and study entry was not significantly different between the standard (5.8 weeks, 95% CI 4.5–6.9) and experimental (6.6 weeks, 5.3–7.8) groups. All diagnostic glycemic variables and fetal ACs at entry did not differ significantly between the two groups (Table 1).

At enrollment, 19 (39%) standard group subjects and 22 (45%) experimental group subjects had a fetal AC ≥70th percentile. All standard group subjects were started on insulin therapy immediately, as were 21 experimental group subjects who had a fetal AC ≥70th percentile. Nine additional subjects in the experimental group were started on insulin subsequent to the randomization visit. Five had a fetal AC ≥70th percentile at a subsequent visit (one had an AC ≥70th percentile at randomization but was miscoded until a subsequent ultrasound was taken 4 weeks later), two had a venous FPG values >120 mg/dl, one had both a fetal AC ≥70th percentile and a fasting serum glucose (FSG) value >120 mg/dl, and one failed to comply with the prescribed self-glucose monitoring. Thus, a total of 30 subjects in the experimental group were treated with insulin therapy.

One standard group subject aborted spontaneously at 17 weeks gestation after 2 weeks of insulin therapy. One experimental group subject transferred prenatal care and was lost to follow-up. Meaningful perinatal data were missing from these two subjects, so they were excluded from outcome analyses, which were performed on the remaining 48 subjects in each group (Table 2).

Maternal outcomes

After randomization, the standard group had significantly lower mean venous FPG levels (84.9 ± 15.5 vs. 88.1 ± 15.4

Table 1—*Baseline characteristics of the two study groups*

	Standard group	Experimental group
n	49	49
Maternal age (years)	31.9 (4.9)	30.9 (7.3)
Parity	2.4 (1.4)	2.2 (1.8)
Prior gestational diabetes	26.5%	20.4%
Prior newborn >4,000 g	40.8%	31.2%
Prepregnancy BMI		
Overweight (from ≥27.0 to <30 kg/m^2)	19.6%	17.4%
Obese (≥30 kg/m^2)	60.8%	50.0%
BMI at entry (kg/m^2)	33.8 (6.5)	31.2 (4.6)*
Gestational age at diagnosis of GDM (weeks)	0.7 (7.5)	20.6 (7.4)
Gestational age at entry (weeks)	26.9 (6.2)	26.9 (6.2)
Area under OGTT glucose curve (min × g/dl)	32.6 (4.2)	32.4 (4.7)
OGTT fasting plasma glucose (mg/dl)	110.1 (11.5)	109.2 (12.3)
OGTT 1-h plasma glucose (mg/dl)	224.3 (25.3)	218.9 (24.1)
OGTT 2-h plasma glucose (mg/dl)	198.7 (31.2)	192.2 (37.9)
Highest fasting plasma glucose (mg/dl)†	117.4 (11.6)	115.5 (6.8)
HbA_{1c} at entry (%)	6.8 (1.2)	6.4 (0.83)
Initial AC percentile‡	64.3 (21.6)	66.9 (26.1)
Initial AC ≥70th percentile‡	19 (39%)	22 (45%)

Data are means (SD) or fraction (%) of women in each treatment group. *P = 0.03 between groups (Student's t test); $P > 0.05$ for all other comparisons; †only values before initiation of insulin therapy are included for women who took insulin; ‡standards from Bochner et al. (14) were used. OGTT, oral glucose tolerance test.

mg/dl, $P = 0.003$) and capillary blood glucose levels (97.0 ± 13.6 vs. 99.0 ± 13.2 mg/dl, $P = 0.049$) than the experimental group. The duration of insulin therapy in subjects treated with insulin (10.0 ± 6.2 vs. 9.1 ± 5.3 weeks) and frequency of pregnancy-induced hypertension (14.6 vs. 8.3%) were not significantly different between standard and experimental groups, respectively.

Labor and delivery

Disparity existed between groups with respect to suitability for a trial of labor. The experimental group had more subjects than the standard group (9 vs. 4) with prior cesarean deliveries without subsequent vaginal birth. Spontaneous onset of labor was infrequent (7 vs. 9), with the majority undergoing elective induction of labor (38 vs. 32). The standard group had twice as many women with favorable cervical exams at the time of induction (21 vs. 10, $P = 0.03$); these women did not require cervical ripening before oxytocin.

Rates of spontaneous vaginal deliveries were not significantly different between the standard and experimental groups (64.6 vs. 57.1%, respectively). The standard group had more vaginal births after cesarean (VBACs) and operative vaginal deliveries (10 vs. 4), whereas the experimental group had more primary (7 vs. 3) and repeat cesarean (9 vs. 4) deliveries. When delivery route was analyzed as either vaginal (i.e., spontaneous, operative, and VBAC deliveries) or abdominal (i.e., primary and repeat cesarean deliveries), the standard group had a significantly lower abdominal delivery rate (14.6 vs. 33.3%, $P = 0.03$). In the experimental group, more subjects were not allowed to labor (7 vs. 5) and more failed labor induction (5 vs. 2). Arrest of labor occurred in only one study subject (experimental group). Four cesareans, all in the experimental group, were performed for fetal distress for the following indications: placental abruption in a normotensive subject, rupture of an unscarred uterus in a grand multiparous subject, fetal tachycardia and febrile chorioamniotis after prolonged induction in a nulliparous subject, and severe fetal bradycardia noted during the 34-week antepartum test. In the latter case, a tight nuchal cord was found at delivery. None appeared to be related to maternal diabetes or fetal macrosomia. Subjects who had cesarean deliveries were similar to those who did not with regard to predelivery maternal weight (189 ± 38 vs. 193 ± 36 lb), maternal venous fasting (87.5 ± 14.8 vs. 87.6 ± 34.1 mg/dl), and capillary blood (100.6 ± 15 vs. 98.1 ± 33.8 mg/dl) glucose levels after randomization; infant birth weights (3,338 ± 475 vs. 3,314 ± 458 g); and all neonatal anthropometric measurements (data not shown).

Neonatal outcome

One subject in the standard group had a intrauterine demise documented at 36 1/2 weeks and delivered 1 week later. Autopsy revealed a 2,280-g SGA male fetus with no abnormalities on autopsy other than a nuchal chord. The mean of maternal capillary glucose levels after randomization was 97.5 mg/dl. Data from this pregnancy were included in the analyses presented below.

At birth, gestational age, infant weight and length, and the frequency of infants who were >4,000 g or LGA were similar between groups (Table 2). All LGA infants (three in the standard and four in the study-guided group) had had a fetal AC ≥70th percentile at randomization, and all mothers were treated with insulin from that time onward. Three infants, all in the standard group, were SGA. Their initial AC measurements ranged between the 30th and 50th percentiles. One was stillborn (see above), and another required phototherapy for hyperbilirubinemia; in both cases, the AC measurement had decreased to the 10th percentile by gestational weeks 31 and 35, respectively. No maternal risk factors for growth restriction were identified, and the means of maternal capillary glucose levels ranged from 82 to 97.5 mg/dl.

The newborn head, chest, upper arm, and thigh circumferences were not significantly different between groups (Table 2). Skinfold thickness was also similar, except at the subscapular site, where the thickness was significantly greater in the experimental group. Neonatal capillary glucose concentrations during the first 4 h of life were neither significantly nor importantly different between study groups.

There were three cases of birth trauma (Table 2). In the standard group, a 2,790 g 36-week-old female infant developed an Erb's palsy after emergency vacuum extraction for fetal bradycardia, with a resultant shoulder dystocia requiring the delivery of the posterior arm. The infant had symmetric and appropriate growth for gestational age. The Erb's palsy was resolved with physical therapy by the

Table 2—*Neonatal outcomes in two study groups and in the experimental subgroups*

			Experimental subgroups	
	Standard group	Experimental group	Diet only	Diet plus insulin
n	48	48	18	30
Gestational weeks at delivery	38.2 (0.9)	38.3 (1.2)	38.1 (1.0)	38.3 (0.9)
Birth weight (g)	3,271 (458)	3,369 (461)	3,180 (425)	3,482 (451)*
Birth weight ≥4,000 g	2.0 (4.2%)	3.03 (6.3%)	0	3.0 (10%)
Birth length (cm)	50.0 (2.1)	50.4 (2.6)	50.0 (2.6)	50.7 (2.7)
Birthweight ≥90th percentile†	3.0 (6.3%)	4.0 (8.3%)	0	4.0 (13.3%)
Birthweight <10th percentile†	3.0 (6.3%)	0	0	0
Circumference (cm)				
Head	34.2 (1.6)	34.6 (1.3)	34.1 (1.5)	34.9 (1.1)*
Chest	33.1 (1.8)	33.6 (1.8)	32.7 (1.5)	34.2 (1.7)‡
Arm	10.5 (0.9)	10.7 (1.0)	10.3 (0.8)	11.0 (1.0)*
Thigh	14.9 (1.6)	15.1 (1.7)	14.6 (1.3)	15.3 (1.8)
Skinfold thickness (mm)				
Triceps	3.6 (0.9)	3.8 (0.9)	3.6 (1.0)	3.9 (0.8)
Biceps	3.2 (1.1)	3.3 (0.8)	3.1 (0.6)	3.4 (0.9)
Subscapular	3.9 (0.7)	4.3 (0.8)§	4.1 (0.5)	4.5 (1.0)
Iliac	3.2 (0.8)	3.5 (0.8)	3.4 (0.9)	3.5 (0.8)
Capillary glucose§ (mg/dl)				
Mean of first 4 h of life	65.6 (24.7)	59.6 (12.5)	59.4 (12.3)	59.8 (12.8)
Lowest in first 4 h of life	47.2 (11)	46.0 (13)	47.3 (11.8)	47.4 (10.8)
Newborn hematocrit	55.2 (6.3)	55.6 (7.9)	55.8 (4.8)	55.6 (7.5)
Any neonatal morbidity‖	12 (25%)	12 (25%)	4 (22.2%)	8 (26.7%)
Birth trauma¶	1	2	0	2
Sepsis, including presumed	7	8	3	5
Transient tachypnea	4	4	1	3
Hypoglycemia (intravenous glucose)	5	5	1	4
Jaundice with phototherapy	1	2	1	1
Partial exchange transfusion	1	0	0	0
Poor feeding	1	0	0	0

Data are means (SD) or *n* (%) of women in each group and in the experimental subgroups, divided according to maternal therapy. Perinatal outcome was available in 48 subjects (see text). *$P < 0.05$ between subgroups; †standards in Aguilar et al. (15) were used. $P = 0.006$ vs. standard therapy group; $P > 0.05$ for all other comparisons between the experimental and standard groups; ‡$P < 0.01$ between subgroups; §mean of glucose levels, and the lowest glucose obtained immediately after birth and at 1, 2, and 4 h of life; ‖six infants in the standard group and seven infants in the experimental group had more than one morbidity, so the sum of individual morbidities does not equal "any morbidity"; ¶Erb's palsy and/or clavicular fracture.

third month of life. In the experimental group, one infant had Erb's palsy with a clavicular fracture, and another had a clavicular fracture only. The mothers of both infants were started on insulin at the time of randomization for the fetal AC measurements (>90th percentile). Both infants were delivered vaginally after spontaneous onset of labor, without recognized shoulder dystocia. They were both LGA, with birth weights of 4,230 and 4,225 g at 39 and 38 weeks of gestation, respectively. The case of Erb's palsy was mild and had resolved by the time of discharge from the hospital at 4 days of life. Frequencies of other neonatal morbidity did not differ significantly differ between the study groups (Table 2). The mean concentrations of Hb, bilirubin, and calcium were not significantly different between groups on the first day of life (data not shown).

Experimental management group: secondary analysis by final maternal therapy

To examine the possible effects of withholding insulin therapy from some patients, we divided the experimental group into patients treated with diet alone ($n = 18$) and patients treated with diet plus insulin therapy ($n = 30$). Women treated by diet alone had significantly lower prepregnancy BMI (27.8 ± 3.2 vs. 31.1 ± 4.6 kg/m^2, $P = 0.01$) and significantly lower borderline HbA_{1c} levels (6.07 ± 0.65 vs. 6.55 ± 0.89% of Hb, $P = 0.05$) compared with the diet plus insulin subgroup. They also had similar FPG levels on the diagnostic oral glucose tolerance test (110.3 ± 10.5 vs. 110.0 ± 12.4 mg/dl) and significantly higher mean capillary glucose levels during the trial (101.5 ± 10.5 vs. 97.6 ± 14.4 mg/dl, $P = 0.003$) compared with the diet plus insulin subgroup. The rate of cesarean deliveries was 33.3% in both subgroups, despite a significantly lower mean birth weight in the diet-only subgroup (Table 2). Neonates in the diet-alone subgroup had smaller head, chest, and upper arm circumferences compared with those treated with diet plus insulin. Skinfold thickness measurements and newborn

capillary glucose concentrations did not differ significantly between the diet-alone and diet plus insulin subgroups. Neonatal morbidity was slightly but not significantly more frequent in the diet plus insulin subgroup.

Irrespective of insulin therapy, none of the 26 subjects in the experimental group with an initial fetal AC <70th percentile at randomization gave birth to an LGA infant. By contrast, 4 (18.2%) of the 22 subjects with a fetal AC ≥70th percentile at randomization gave birth to an LGA infant (21 at randomization and one 4 weeks later), despite all mothers receiving intensive insulin therapy.

CONCLUSIONS — Our study had two important findings in pregnancies complicated by GDM with fasting glycemia of 105–120 mg/dl at diagnosis. First, measurement of the fetal AC with ultrasound identified fetuses at low risk for accelerated somatic growth in utero. This finding expands prior work by Landon et al. (16), Bochner et al. (14), and our own group (12). In our prior study (12) of gestational diabetic patients with fasting glucose levels <105 mg/dl, 65% of pregnancies had a fetal AC <70th percentile early in the third trimester. Those pregnancies had no excess of LGA newborns when mothers were treated with diet therapy alone. In the present study, 21 pregnancies (44%) in the experimental group had a fetal AC <70th percentile, and 18 (38%) were treated with diet plus moderate physical activity. None of these subjects gave birth to an LGA infant. Taken together, the two studies reveal the lesser tendency for low-risk fetal ACs to occur in the presence of greater maternal hyperglycemia (44% with FSG ≥105 mg/dl vs. 65% with FSG <105 mg/dl). The studies also reveal the utility of ultrasound for detecting pregnancies that do not need insulin therapy to prevent macrosomia at term.

The second major finding was that a management protocol in which the need for insulin therapy was determined by a combination of fetal AC measurements and maternal FPG measurements did not increase neonatal macrosomia or morbidity compared with a protocol in which all women were given insulin because of fasting hyperglycemia. Despite slightly higher glucose levels in the experimental group, there were only tiny differences compared with the standard group in mean birth weights (4% higher in experimental group) and frequencies of macrosomic (6.3 vs. 4.2%) or LGA (8.3 vs. 6.3%) infants. Likewise, there were no significant intergroup differences in neonatal anthropometric measures, with the exception of subscapular skinfold thickness (10% thicker in the experimental group), or in overall rates of perinatal morbidity, which were identical in the two groups. All of the cases of SGA infants occurred in the group randomized to conventional therapy with insulin. Although not statistically significant, this finding is consistent with prior observations that intensive glycemic management of GDM without attention to fetal growth can increase the risk of SGA infants (5,17) and related morbidities (17). The addition of ultrasound to the management regimen allows the practitioner to withhold insulin when there is no evidence of increased somatic growth, thereby limiting the risk of iatrogenic growth restriction.

One difference observed between treatment groups was the significantly lower rate of cesarean deliveries in the standard group. Randomization was designed to detect a difference in birthweights and done without regard to the risk for cesarean delivery. The experimental group ended up with a larger proportion of women with previous cesareans without successful VBACs, with less women undergoing a trial of labor and more failing to enter active labor after induction. There were also more emergency cesareans performed, but the clinical histories, e.g., uterine rupture, placenta abruption, and nonreassuring fetal heart rates, did not suggest distress related to maternal diabetes. Based on these considerations, it is unlikely that the higher rate of cesareans in the experimental group was related to the withholding of insulin therapy from some patients.

Keller et al. (18) previously reported that a subset of pregnancies complicated by pre-GDM exhibited accelerated growth of the fetal AC before 24 weeks gestation. Those infants also had elevated amniotic fluid insulin levels, suggesting that the pathophysiology of diabetic fetopathy proposed by Pedersen (19) was operative relatively early in gestation in a subset of infants. We also observed the relatively early presence of at-risk fetal ACs in the present study. On average, initial ultrasound examinations were done at 27 weeks gestation. Of the women, 42% had a fetal AC ≥70th percentile at 27 weeks gestation, which was greater than the expected 30%. Moreover, the frequencies of ACs ≥70th percentile were the same in women who entered before, as compared with after, 28 weeks gestation (data not shown). These findings suggest that in pregnancies complicated by GDM with fasting glycemia ≥105 mg/dl, programming of excessive fetal growth may begin before the time that GDM is diagnosed. Fortunately, our results demonstrate that in selected cases, intensive management of maternal diabetes with diet, moderate exercise, and insulin can mitigate the neonatal implications of such an early acceleration of fetal growth. Whether the long-term risks of obesity and diabetes (20,21) can also be mitigated remains to be determined.

In summary, ultrasound measurement of the fetal AC identified fetuses at low risk for neonatal macrosomia as well as morbidity in women with GDM and moderate fasting hyperglycemia. A management protocol, in which insulin was withheld unless the fetal AC was ≥70th percentile for gestational age or the maternal fasting glucose was >120 mg/dl, allowed 38% of patients to be managed without insulin therapy, with no increase in neonatal morbidity compared with patients managed with insulin therapy based on fasting hyperglycemia alone. However, this approach to management was associated with a higher cesarean delivery rate, a secondary outcome that was not readily explained by a failure to mitigate accelerated fetal growth. Our findings indicate that a large-scale randomized trial that compares the clinical efficacy and cost-effectiveness of a management strategy based on ultrasound plus relaxed glycemic criteria (compared with a more traditional management approach based solely on maternal glycemic criteria) is warranted.

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