

A Randomized Trial Evaluating a Predominately Fetal Growth-Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

UTE M. SCHAEFER-GRAF, MD^{1,2}
SIRI L. KJOS, MD^{2,5}
OSTARY H. FAUZAN, MD²
KAI J. BÜHLING, MD²
GERDA SIEBERT, PHD³

CHRISTOPH BÜHRER, MD⁴
BARBARA LADENDORF, MD¹
JOACHIM W. DUDENHAUSEN, MD²
KLAUS VETTER, MD¹

OBJECTIVE — To compare the management of Caucasian women with gestational diabetes (GDM) based predominantly on monthly fetal growth ultrasound examinations with an approach based solely on maternal glycemia.

RESEARCH DESIGN AND METHODS — Women with GDM who attained fasting capillary glucose (FCG) <120 mg/dl and 2-h postprandial capillary glucose (2h-CG) <200 mg/dl after 1 week of diet were randomized to management based on maternal glycemia alone (standard) or glycemia plus ultrasound. In the standard group, insulin was initiated if FCG was repeatedly >90 mg/dl or 2h-CG was >120 mg/dl. In the ultrasound group, thresholds were 120 and 200 mg/dl, respectively, or a fetal abdominal circumference >75th percentile (AC>p75). Outcome criteria were rates of C-section, small-for-gestational-age (SGA) or large-for-gestational-age (LGA) infants, neonatal hypoglycemia (<40 mg/dl), and neonatal care admission.

RESULTS — Maternal characteristics and fetal AC>p75 (36.0 vs. 38.4%) at entry did not differ between the standard ($n = 100$) and ultrasound groups ($n = 99$). Assignment to (30.0 vs. 40.4%) and mean duration of insulin treatment (8.3 vs. 8.1 weeks) did not differ between groups. In the ultrasound group, AC>p75 was the sole indication for insulin. The ultrasound-based strategy, as compared with the maternal glycemia-only strategy, resulted in a different treatment assignment in 34% of women. Rates of C-section (19.0 vs. 18.2%), LGA (10.0 vs. 12.1%), SGA (13.0 vs. 12.1%), hypoglycemia (16.0 vs. 17.0%), and admission (15.0 vs. 14.1%) did not differ significantly.

CONCLUSIONS — GDM management based on fetal growth combined with high glycemic criteria provides outcomes equivalent to management based on strict glycemic criteria alone. Inclusion of fetal growth might provide the opportunity to reduce glucose testing in low-risk pregnancies.

Diabetes Care 27:297–302, 2004

From the ¹Department of Obstetrics, Vivantes Medical Center Neukoelln, Berlin, Germany; the ²Department of Obstetrics, Charité, Campus Virchow Klinikum, Humboldt University, Berlin, Germany; the ³Department of Biometry, Charité, Campus Virchow Klinikum, Humboldt University, Berlin, Germany; the ⁴Department of Neonatology, Charité, Campus Virchow Klinikum, Humboldt University, Berlin, Germany; and the ⁵Department of Obstetrics, University Southern California Keck Medical School, Los Angeles, California.

Address correspondence and reprint requests to Ute M. Schaefer-Graf, MD, Department of Obstetrics, Vivantes Medical Center Neukoelln, Mariendorfer Weg 28, 12051 Berlin, Germany. E-mail: ute.schaefer-graf@vivantes.de.

Received for publication 28 April 2003 and accepted in revised form 15 September 2003.

Abbreviations: 2h-CG, 2-h postprandial capillary glucose; AC, abdominal circumference; AC>p75, AC >75th percentile; FCG, fasting capillary glucose; GDM, gestational diabetes; LGA, large for gestational age; SGA, small for gestational age.

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

© 2004 by the American Diabetes Association.

See accompanying editorial, p. 610.

Guidelines for management of pregnancies complicated by gestational diabetes (GDM) generally call for normalizing maternal glucose levels without further individual risk assessment (1,2). This “glucose-only” approach requires frequent glucose monitoring in all women and insulin therapy in a substantial proportion. In contrast, GDM management guided by fetal criteria can identify pregnancies at low risk for neonatal morbidity and limits intensive monitoring and/or therapy to those at high risk. So far, measurements of amniotic fluid insulin (3) and fetal abdominal circumference (AC) growth have been tested as fetal criteria for their utility in GDM management. Two trials testing the fetal growth-based approach in a predominately Latino population demonstrated low rates of large-for-gestational-age (LGA) newborns in infants whose AC remained below the 70–75th percentile during pregnancy (4), although insulin was withheld in women meeting the glycemic criteria for insulin therapy (5). In contrast, institution of insulin therapy in pregnancies with accelerated fetal growth without respect to maternal glycemia has been found to substantially decrease LGA rates (4,5). The aim of the present study was to compare a management based solely on strict glycemic criteria with a strategy based predominantly on fetal AC growth in Caucasian women with GDM.

RESEARCH DESIGN AND METHODS

Study population, GDM, and obstetrical management

The study population was recruited from women referred to two hospital-based diabetic prenatal care clinics (Vivantes Medical Center, Neukoelln, and Charité, Humboldt-University, Berlin) from January 2000 through January 2003. The two

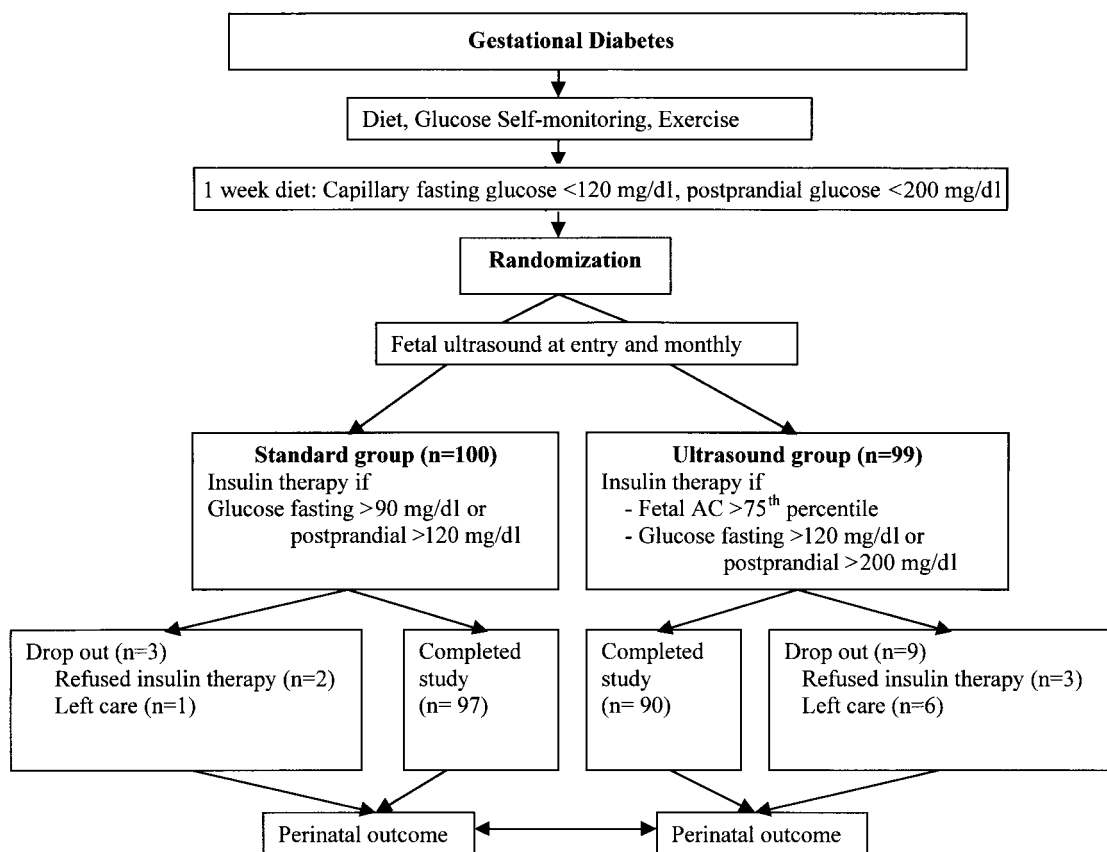


Figure 1—Overview of the study design.

hospitals serve a population of similar ethnic and social background. The study protocol was approved by the local institutional review board. Informed written consent was obtained at the first visit. Before entry, all subjects were prescribed a diet based on true body weight ($30 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) with caloric restriction for overweight women ($25 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$). Women were advised to exercise after meals and taught to self-monitor blood glucose using a reflectance meter with memory (Roche Diagnostics, Mannheim, Germany). Glucose profiles consisting of six daily measurements (three preprandial and three 2-h postprandial) were performed twice weekly while on diet and daily on insulin. After 1 week of therapy, women were evaluated for eligibility for the study protocol.

Women meeting the following inclusion criteria were offered to participate: 1) GDM, diagnosed by at least two abnormal values in a 75-g oral glucose tolerance test (fasting $\geq 90 \text{ mg/dl}$ [5.0 mmol/l]; 1 h $\geq 165 \text{ mg/dl}$ [9.1 mmol/l], 2 h $\geq 145 \text{ mg/dl}$ [8.0 mmol/l]); 2) all capillary fast-

ing glucose (FCG) measurements $\leq 120 \text{ mg/dl}$ (6.6 mmol/l) and 2-h postprandial capillary glucose (2h-CG) measurements $\leq 200 \text{ mg/dl}$ (11.1 mmol/l); 3) singleton pregnancy 16–34 completed weeks confirmed by ultrasound performed before 20 weeks; 4) no maternal medical conditions known to affect fetal growth; and 5) no abuse of tobacco (more than five cigarettes/day), alcohol, or illicit drugs during pregnancy. After informed consent, subjects were stratified into one of five blocks based on gestational age and randomized within blocks to standard or ultrasound management following the sequence of allocation generated by a statistician (Fig. 1).

In the standard group, insulin was prescribed before 36 weeks gestation if two glucose profiles had two or more elevated values (FCG $>90 \text{ mg/dl}$ or 2h-CG $>120 \text{ mg/dl}$) or four profiles had at least one elevated value during a 2-week period. In the ultrasound group, insulin was started whenever the AC exceeded the 75th percentile ($\text{AC} > p75$) (6) before 36 completed weeks. In this group, glucose

targets were not discussed with patients, and glucose values were not used to guide management, unless any FCG $>120 \text{ mg/dl}$ and/or any 2h-CG $\geq 200 \text{ mg/dl}$ was measured, at which point insulin was prescribed irrespective of AC measurement. Because of the risk of maternal hypoglycemia, insulin was not prescribed irrespective of fetal AC when FCG was $<80 \text{ mg/dl}$ and/or 2h-CG value was $<100 \text{ mg/dl}$.

Ultrasound examinations were performed at entry and thereafter at 4-week intervals at 20, 24, 28, 32, and 36 weeks of gestation. Complete biometry was performed (Accuson XP 3, 3 and 5 MHz) obtaining three AC measurements taken at the standard cross-sectional view (6). The coefficient of variance for the AC measurements among the ultrasonographers (U.M.S.-G., S.L.K., and B.L.) was $<7\%$. A mean AC measurement was calculated by study assistants and transformed into a percentile for gestational age using Hadlock's formula (6). While periodic ultrasound examinations were performed in all subjects, results in the standard group

Table 1—Maternal characteristics and glycemic and fetal parameters at entry

	Standard group	Ultrasound group	P
n	100*	99†	
Prior pregnancy with (%)			
GDM	14.0	9.1	0.2
Macrosomia (>4,000 g birth weight)	9.0	12.1	0.3
Cesarean delivery	11.0	12.1	0.5
Age (years)	31.3 ± 5.0	31.0 ± 5.6	0.7
Parity	2.1 ± 1.2	2.1 ± 1.3	0.9
Prepregnancy BMI (kg/m ²)	28.4 ± 6.6	26.9 ± 5.9	0.09
Oral glucose tolerance test (mg/dl)			
Fasting	95.7 ± 15.7	94.2 ± 15.1	0.5
1 h	200.6 ± 28.7	202.2 ± 25.5	0.7
2 h	156.8 ± 32.0	155.4 ± 31.9	0.8
HbA _{1c} at entry (%)	5.1 ± 0.6	5.2 ± 1.0	0.3
Gestational age at diagnosis (weeks)	26.1 ± 4.3	26.2 ± 4.3	0.9
Gestational age at study entry	29.0 ± 3.8	29.1 ± 3.4	0.8
Fetal abdominal circumference >75th percentile (%)	36.0	38.4	0.4

Data are means ± SD, unless otherwise noted. *Includes 3 women not completing the study; †includes 9 women not completing the study.

were not discussed with the women and were not used to guide management.

Insulin was titrated to achieve FCG <90 mg/dl and 2h-CG <120 mg/dl in the standard group and FCG <80 mg/dl and 2h-CG <110 mg/dl in the ultrasound group. Four daily injections were administered with regular insulin before meals and NPH at bedtime.

Twice weekly antepartum fetal heart rate testing was started at 32 weeks. Delivery via labor induction or cesarean was scheduled after 40 completed weeks in the absence of spontaneous labor or obstetrical complications prompting an earlier delivery. During delivery, maternal capillary glucose levels were measured every 2 h and intravenous insulin was administered as needed to maintain levels at 90–140 mg/dl. Cord blood was obtained directly after delivery, stored at –80°C and assayed for insulin using a radioimmunoassay (Insulin RIA 100-Pharmacia; Pharmacia, Freiburg, Germany).

Neonatal capillary blood glucose was measured at 1, 3, 6, and 12 h postpartum. Newborn feeding was encouraged soon after birth. Newborns were transferred to the neonatal intensive care unit (NICU) for intravenous glucose therapy, if hypoglycemia (<40 mg/dl) did not respond to oral feeding, or for other neonatal complications as determined by standard clinical practice at the institution. Birth weight and length were obtained right after de-

livery. Skinfold thickness was measured in triplicate at four sites (triceps, subscapular, iliac crest, and thigh) at day 2 of life by study assistants. Intra- and postpartum care was managed by on-call hospital staff physician and midwife services who were blinded to the study arm.

Data analysis

A minimum sample size of 178 women was calculated to detect a difference in birth weight of 225 g between the study groups based on an SD of 530 g in prior studies in our GDM population (7,8)

Table 2—Neonatal outcome in the two study groups

	Standard group	Ultrasound group	P
n	100	99	
Gestational age at delivery (weeks)	39.3 ± 1.3	39.0 ± 1.9	0.2
Induction (%)	23.0	23.2	0.5
Cesarean delivery (%)	19.0	18.2	0.5
Birth weight (g)	3371.2 ± 500	3306.1 ± 558	0.4
SGA (%)	13.0	12.1	0.5
LGA (%)	10.0	12.1	0.4
Neonatal BMI (kg/m ²)	13.1 ± 1.2	12.8 ± 1.5	0.2
Sum of skinfolds (mm)*	13.2 ± 3.2	14.1 ± 3.4	0.07
Hypoglycemia (<40 mg/dl) (%)	16.0	17.0	0.5
Intravenous glucose (%)	11.0	9.1	0.4
Cord blood insulin (μU/ml)†	9.1 ± 6.2	8.8 ± 6.82	0.8
Transfer to NICU (%)‡	15.0	14.1	0.5

Data are means ± SE. *Sum of skinfolds measured at four sites of the body (subscapular, iliac crest, triceps, thigh), missing in three infants of women who did not complete the study; †missing in four infants of women who did not complete the study; ‡neonatal intensive care unit.

(power 80%, $\alpha = 0.05$, two-sided test). Neonatal outcome was compared by intent-to-treat-analysis.

Newborns were classified as SGA if the birth weight was <10th percentile and LGA if birth weight was >90th percentile according to recent sex-specific German growth curves (9).

Differences between the groups were tested for statistical significance by *t* tests or ANOVA (continuous variables) or by χ^2 analysis (categorical variables). Data are presented as means ± 1 SD.

All calculations were performed with the statistic package SPSS 10.0 (Chicago, IL).

RESULTS

Maternal data

A total of 199 women were randomized, 100 to standard and 99 to ultrasound-guided care. Twelve women did not complete the assigned treatment protocol—three in the standard group (two refused insulin therapy, and one left care) and nine in the ultrasound group (three refused insulin for large AC measurements, and six left care). Except for skinfold measurements in three infants and cord blood insulin in four newborns of women who did not complete the study, neonatal outcome data were available in all subjects.

Maternal and fetal characteristics at entry did not differ significantly between the two groups (Table 1). In the standard group, 30 (30%) subjects met the criteria for insulin. Of these women, 27 received insulin, 2 refused, and 1 woman assigned

Table 3—Outcome of GDM pregnancies who were managed either identically or differentially based on the occurrence of maternal hyperglycemia and a fetal AC>p75 before 36 completed weeks of gestation

Maternal hyperglycemia meeting criteria for insulin therapy in the standard group							
		No		Yes			
AC always ≤75th percentile during study	A	No insulin in both groups N = 75 (ST = 38, US = 37*)		B	ST group (n = 17)	US group (n = 18†)	
					Insulin	No insulin	
		LGA	2.7% (2)		LGA	5.9% (1)	5.9% (1)
		SGA	20.0% (15)		SGA	35.3% (6)	16.6% (3)
		Hypoglycemia	18.7% (14)		Hypoglycemia	11.8% (2)	11.8% (2)
		NICU	17.3% (13)		NICU	5.9% (1)	5.9% (1)
		Cesarean	14.7% (11)		Cesarean	17.6% (3)	23.5% (4)
AC ever >75th percentile during study	C	ST group (n = 32)	US group (n = 13)	D	Insulin in both groups N = 33 (ST = 10, US = 23)		
		No insulin	Insulin				
		LGA	21.9%		LGA	26.1% (6)	
		SGA	0%		SGA	4.3% (1)	
		Hypoglycemia	15.6% (5)		Hypoglycemia	18.2% (6)	
		NICU	12.5% (4)		NICU	24.2% (8)	
		Cesarean	25.0% (8)		Cesarean	24.2% (8)	

In the standard group (ST), hyperglycemia prompted insulin therapy; in the ultrasound group (US), it prompted an AC>p75. All P values for panel B and C >0.05. *Three women with AC>p75 who were not treated with insulin because of low glucose values were included; †one woman with AC>p75 who was not treated with insulin because of AC misclassification was included.

to insulin left care. In the ultrasound group, 40 (40.4%) women met the criteria for insulin, all with AC>p75 ($P = 0.1$ vs. standard). No subject qualified for insulin based on FCG >120 mg/dl or 2h-CG >200 mg/dl. Five subjects had AC>p75 but FCG <80 mg/dl and/or any 2h-CG <100 mg/dl precluded insulin by protocol. Of the 40 women who met study requirements for insulin therapy, 3 refused therapy and 1 subject who should have received therapy did not due to an erroneous AC calculation. The fraction of women receiving insulin did not differ between the groups (27.0 vs. 36.4%, standard vs. ultrasound, $P = 0.1$). FCG and 2h-CG during pregnancy were 85.9 ± 10.5 mg/dl and 111.0 ± 11.3 mg/dl, respectively, for the standard group and 85.1 ± 8.2 mg/dl and 110.3 ± 10.6 mg/dl for the ultrasound group (FCG: $P = 0.5$; 2h-CG: $P = 0.6$). In women who received insulin in the standard and ultrasound groups, means for duration of insulin therapy (8.3 ± 2.8 vs. 8.1 ± 3.5 weeks, respectively, $P = 0.8$) and maximum individual insulin doses (67.2 ± 38.2 vs. 78.2 ± 39.4 units, respectively, $P = 0.3$) were also similar. However, average FCG (85.2 ± 8.5 vs. 80.6 ± 5.2 mg/dl, $P = 0.01$) and 2h-CG (113.0 ± 12.0 vs. 106.6 ± 6.7 mg/dl, $P = 0.01$) during in-

sulin treatment were significantly higher in the standard compared with the ultrasound group, consistent with protocol goals.

Primary neonatal outcome

There were no significant differences between treatment groups with respect to mode of delivery or indexes of newborn growth (Table 2). Neonatal cord blood insulin, rates of transfer to NICU, hypoglycemia, or intravenous supplemental glucose were also similar between the groups. Of the standard group, three women did not complete the study, and no infant was born SGA or LGA or was transferred to NICU. In the ultrasound group, two of the three newborns of mothers refusing insulin were born LGA. Of the newborns of the six women who left care without being assigned to insulin therapy, one infant was born LGA and one was born SGA.

The diagnostic criteria of Carpenter and Coustan (10) were fulfilled by 161 (80.9%) women equally distributed to standard and ultrasound groups. The primary analysis was repeated for this subset. Again, there was no significant difference in outcome between the study groups. The rate of insulin use in the standard group in this subset was 32.1%.

In the majority of the fetuses who presented accelerated growth during the study, the diagnosis AC>p75 was made by the first ultrasound at entry (69.1%). Additionally 20% were diagnosed by the second scan. Of fetuses with AC>p75, 14.3% were born LGA to mothers with insulin therapy in contrast to 23.1% when the mother stayed on diet only. In the standard group, all LGA infants besides one were born to mothers on diet.

Secondary analysis

To evaluate the outcome of the women who were treated differently by the standard therapy (based on glycemia alone) or by the ultrasound-guided therapy (based on fetal growth), we separated the subjects who completed the assigned therapy according to glycemic values and AC growth. Of all subjects who completed the study (standard, $n = 97$; ultrasound, $n = 90$), the glucose profiles during the study period were evaluated to see if they met glycemic targets for insulin according to the standard protocol. Likewise, AC measured in all subjects was evaluated to see if they met criteria for insulin according to the ultrasound protocol. A 2×2 table was constructed to evaluate outcome differences (Table 3). In two of the four groups, women received identical

therapy ($n = 108$ of 187, 58%)—either no insulin (box A) or insulin (box D). In box B, all subjects met criteria for insulin based on standard protocol but not by fetal AC growth and were treated differently by the study group assignment. The 2h-CG was significantly lower in the standard compared with the ultrasound group (114.0 ± 10.3 vs. 121.7 ± 9.1 , $P = 0.02$). Except for the higher prevalence of SGA infants in the standard (35%, 6 of 17) compared with the ultrasound group (17%, 3 of 18, $P = 0.13$), there was no difference in outcome between the two groups. In box C, all women met criteria for insulin based on fetal AC $> p75$, but not by glucose profiles, and were treated differently. Here, 2h-CG was higher in the standard compared with the ultrasound group (108.2 ± 10.2 vs. 102.0 ± 7.0 mg/dl, $P = 0.04$). Almost three times as many infants were LGA or delivered by C-section in the standard (22%, 7 of 32) compared with the ultrasound group (8%, 1 of 12, $P = 0.28$).

CONCLUSIONS— There are two major findings of this study. First, GDM management predominantly based on fetal growth provided the same perinatal outcome as management based on strict glycemic control. Second, fetal ultrasound-based strategy resulted in a treatment assignment in 34% of the women (31 of 90 subjects in the ultrasound group) that would have been different had a maternal glycemia-only strategy been applied.

Fetal growth–based treatment assignment appears safe for both the infant and the mother. Various primary outcome parameters used to gauge the quality of GDM management did not differ between fetal ultrasound- and maternal glycemia-only–guided strategies. In addition, none of the women in the ultrasound group treated with insulin for AC $> p75$ without hyperglycemia experienced severe hypoglycemia. While there is no agreement in regard to the diagnostic criteria for GDM, results of this study were virtually identical when switching to the Carpenter and Coustan criteria for GDM (10). For comparability with the pilot studies (4,5), this study had used the Hadlock growth curves created in 1984. As the difference of fetal AC is only 0.3–0.6 mm, compared with more recent growth curves (11), only a minute fraction might have been

assigned differently when using the recent curves.

The LGA rate in the standard group was much lower than in our prior observational studies in women with GDM (18 or 24%, respectively) (7,12). A similar low rate of LGA was observed in our pilot study in a hyperglycemic Latino population known to have high macrosomia rates (5). Intensive attention under study conditions may enhance compliance of pregnant GDM women.

The fetal ultrasound-guided strategy led to a redistribution of assignment to insulin therapy. Insulin was withheld in women with normal fetal growth; even their glucose levels would have qualified them for insulin under standard care. There was no adverse outcome, but the ultrasound approach reduced the SGA rate by more than half in this subgroup. Moderate maternal hyperglycemia might be important for ensuring the nutritional supply of the fetus, just as maternal pregnancy-induced hypertension compensating for poor placental vasculature. Insulin was applied in cases with fetal overgrowth despite glucose values that would not have led to insulin therapy by standard management. In this subgroup, the ultrasound approach reduced LGA and C-section rates by $>50\%$. Similar effects have been observed before with protocols aimed at strict glycemic control in all GDM women that ultimately assigned insulin to the majority of the women (13,14). However, identification of fetal macrosomia by ultrasound (4) allowed for the assignment of insulin to only those women at high risk for LGA and cesarean. The small subgroup sample size resulting from the subanalysis precluded to show the beneficial effects of the fetal growth–based strategy in a statistically significant fashion. To test whether these effects are real, further studies would be needed. Based on the effects in this study, the approximate number of women to be included would be 99 to demonstrate a significant reduction of the SGA rate and 121 to show a significant decrease in the LGA rate.

What are the clinical implications of our findings? Inclusion of fetal growth to direct metabolic therapy in GDM may help to optimize the allocation of resources. Due to the rapid rise of obesity in women of child-bearing age and the growing awareness of the implications of GDM, an increasing number of patients

will require treatment. Without additional tools for antenatal risk assessment, attainment of strict glucose control in all women may cause unnecessary financial and emotional burdens in pregnancies at low risk for morbidity while consuming resources needed for intensive intervention in those at high risk. In most health care systems, fetal ultrasound is part of the routine surveillance and is well accepted by patients. Undoubtedly, availability of personnel trained in performing obstetrical ultrasound is necessary to make any ultrasound-based approach work on a broader base; however, any physician certified for obstetrical ultrasound may be expected to also produce reliable fetal AC measurements by using standard equipment. The decades-long discussion about the diagnostic criteria for GDM and glycemic targets reflects the difficulty to assess the risk for adverse outcome solely based on maternal glycemia. Rather, the relation between maternal glycemia and neonatal and maternal outcome behaves as a continuum (7,15). In addition, other maternal factors besides glucose metabolism have an influence on fetal growth (11,16). Risk assessment by fetal growth might be used to adjust the intensity of glucose monitoring. AC $< p75$ reliably excludes amniotic fluid insulin concentrations $> 16 \mu\text{U/ml}$, which are known to be associated with short- and long-term morbidity (17).

Both intrauterine growth restriction and fetal overgrowth are known to be associated with neonatal complications and long-term sequelae (18–20). The reduced rate of abnormal growth (SGA and LGA) of this study awaits confirmation in larger cohorts.

In addition, management based on fetal criteria might offer an opportunity to act more cost-effectively. Based on an average gestational age of 28 weeks at diagnosis of GDM, the actual total cost of self-glucose monitoring with two profiles per week is approximately €125. The cost of a proposed management based on the reimbursement for two ultrasound examinations (€34) combined with glucose monitoring (two profiles per month, €18) would amount to €52. However, the minimum number of ultrasound examinations needed to reliably identify low-risk GDM pregnancies, as well as the reduction of glucose monitoring possible, remain to be determined. However, our data indicate that more relaxed glycemic

control is justified when fetal assessment is included to target pregnancies for intensive intervention.

Acknowledgments—The authors thank Tom A. Buchanan for his thoughtful comments and helpful criticism during the preparation of the manuscript. We thank the midwives of the Diabetic Prenatal Care Clinic of Vivantes Medical Center and of the Charité for their support in care of the study patients.

References

1. American Diabetes Association: Gestational diabetes (Position Statement). *Diabetes Care* 22 (Suppl. 1):S74–S76, 1999
2. Metzger BE, Coustan DR: Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes. *Diabetes Care* 21 (Suppl. 2):B161–B167, 1998
3. Weiss P, Hofmann H: Diagnosis and treatment of gestational diabetes according to amniotic fluid insulin levels. *Arch Gynecol* 239:81–91, 1986
4. Buchanan TA, Kjos SL, Montoro MN, Wu P, Madrilejo NG, Gonzalez M, Nunez V, Pantoja PM, Xiang A: Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. *Diabetes Care* 17:275–283, 1994
5. Kjos S, Schaefer-Graf U, Sardesi S, Peters R, Buley A, Xiang A, Bryne JD, Sutherland C, Montoro MN, Buchanan TA: A randomized controlled trial using glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. *Diabetes Care* 24: 1904–1910, 2001
6. Hadlock FP, Deter RL, Harrist RB, Park SK: Estimated fetal age: computer-assisted analysis of multiple fetal growth parameters. *Radiology* 152:497–501, 1984
7. Schaefer-Graf UM, Dupak J, Vogel M, Dudenhausen JW, Kjos SL, Buchanan TA, et al: Hyperinsulinism, neonatal adiposity and placental immaturity in infants born to women with one abnormal glucose tolerance test value. *J Perinatal Med* 26:27–36, 1998
8. Schaefer-Graf UM, Kjos S, Kilavuz Ö, Plagemann A, Brauer M, Dudenhausen JW, Vetter K: Determinants of fetal growth at different periods of pregnancies complicated by gestational diabetes or impaired glucose tolerance. *Diabetes Care* 26:193–198, 2003
9. Voigt M, Schneider K, Jährig K: Analysis of the total number of births in 1992 in the Federal Republik of Germany. *Geburth Frauenheilk* 56:550–558, 1996
10. Carpenter M, Coustan D: Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 144:768–773, 1982
11. Snijders R, Nicolaides KH: Fetal biometry at 14–40 weeks of gestation. *Ultras Obstet Gynecol* 4:34–48, 1993
12. Schaefer-Graf UM, Heuer R, Kilavuz Ö, Pandura A, Henrich W, Vetter K: Maternal obesity not maternal glucose values correlates best with high rates of fetal macrosomia in pregnancies complicated by gestational diabetes. *J Perinat Med* 30: 313–321, 2002
13. Langer O, Levy J, Brustmann L, Anyaegbunam A, Merkat R, Divon M: Glycemic control in gestational diabetes mellitus: how tight is enough? Small for gestational age versus large for gestational age. *Am J Obstet Gynecol* 161:646–653, 1989
14. Coustan DR, Imarah J: Prophylactic insulin therapy treatment of gestational diabetes reduces the incidence of macrosomia, operative delivery and birth trauma. *Am J Obstet Gynecol* 150:836–842, 1984
15. Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JW, Farine D, Cohen HR, McArthur K, Holzapfel S, Biringer A: Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without diabetes. *Am J Obstet Gynecol* 173:146–156, 1995
16. Knopp RH, Magee MS, Walden CE, Bonet B, Benedetti TJ: Prediction of infant birth weight by GDM screening: importance of plasma triglyceride. *Diabetes Care* 15: 1605–1613, 1992
17. Schaefer-Graf U, Kjos S, Buehling K, Henrich W, Brauer M, Heinze T, Dudenhausen JW, Vetter K: Amniotic fluid insulin levels and fetal abdominal circumference at time of amniocentesis in pregnancies with diabetes. *Diabet Med* 20:349–354, 2003
18. Garcia-Patterson A, Corcoy R, Balsells M, Altirriba O, Adalantado J, Cabero L, de Levia A: In pregnancies with gestational diabetes and intensive therapy, perinatal outcome is worse for small-for-gestational-age newborns. *Am J Obstet Gynecol* 179:481–485, 1998
19. Nesbitt TS, Gilbert WM, Herrchen B: Shoulder dystocia and associated risk factors with macrosomic infants born in California. *Am J Obstet Gynecol* 179:476–480, 1998
20. Dabelea D, Pettitt D, Hanson R, Imperatore G, Bennett P, Knowler W: Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. *Diabetes Care* 22:944–950, 1999