

Modified Therapy for Gestational Diabetes Using High-Risk and Low-Risk Fetal Abdominal Circumference Growth to Select Strict Versus Relaxed Maternal Glycemic Targets

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The traditional treatment goal for gestational diabetes mellitus (GDM) has been to achieve “normal” range values for maternal glucose by diet and or insulin therapy, adapting a strategy successful in treating pregestational diabetes during pregnancy. Intensive insulin therapy to achieve strict euglycemia in GDM pregnancies has improved perinatal morbidity; however, it has not eliminated the excess rate of macrosomia compared with the reference populations (1). Increasing evidence suggests that disturbances in the intrauterine metabolic environment produced by GDM appear to increase the risk in offspring for obesity and diabetes. The obesity risk in early childhood in offspring born to mothers with GDM has been correlated with the birth weight and parental obesity, and those children who were large-for-gestational-age (LGA) at birth had obesity rates close to 40% compared with 25% in those born with normal weight (2). Studies that have attempted to reduce macrosomia rates by setting very strict glycemic targets during pregnancy have required insulin therapy in two-thirds of the women (3). However, only a minority of offspring of GDM mothers appear to be at risk for fetal overgrowth and newborn morbidity, even when GDM is untreated in blinded controlled trials (4,5). The Toronto Tri-

Hospital Gestational Diabetes Project demonstrated a modest association of newborn morbidity with antenatal maternal glucose concentrations, adjusting for other risk factors (6). However, no threshold values that would suggest treatment were found.

These facts led Buchanan et al. (7) to advocate using fetal ultrasound measurements of growth in addition to maternal glycemia to identify which fetuses in utero are at increased and decreased risk for complications. This approach relaxes glycemic targets in women whose fetuses are at low risk for LGA growth and intensifies therapy by using stricter glycemic targets for those at high risk.

FETAL GROWTH MEASUREMENTS

Amniotic fluid insulin levels

Fetal hyperinsulinism is believed to play a central role in the development of diabetic fetopathy (8,9) and can be indirectly determined by the measurement of insulin levels in the amniotic fluid, which reflects the urinary excretion of insulin in the fetus (10,11). Weiss has used third trimester amniotic fluid insulin concentration to adjust insulin treatment, demonstrating that diabetic fetopathy was found predominantly in pregnancies with

amniotic fluid insulin levels two- to threefold above those in nondiabetic pregnancy (12). Weiss found that “biochemical diabetic fetopathy,” defined as hypoglycemia and biochemical dysregulation in the newborn, occurred when third trimester amniotic fluid insulin levels were $>17 \mu\text{U/ml}$, while “somatic fetopathy,” or LGA newborns, was found only in pregnancies in which amniotic fluid insulin concentrations were $>20 \mu\text{U/ml}$. In nonrandomized patient treatment assignment, instituting insulin therapy when elevated amniotic fluid insulin levels were detected reduced the risk of both complications compared with those not treated. Other researchers have confirmed that only markedly elevated amniotic fluid insulin levels ($>18 \mu\text{U/ml}$) were associated with somatic overgrowth at birth (13), whereas others found that elevated levels can be found early in pregnancy before 20 weeks and were associated with later glucose intolerance and macrosomia (14). Metzger and Freinkel (9) found long-term effects into childhood, namely obesity and impaired glucose tolerance, were associated with third trimester elevated amniotic fluid insulin levels of $>150 \text{ pmol/l}$ ($\sim 20 \mu\text{U/ml}$) and $>100 \text{ pmol/l}$ ($\sim 14 \mu\text{U/ml}$), respectively. Despite the physiological rationale for aggressively treated diabetic pregnancies identified by elevated amniotic fluid insulin, this clinical approach has not been widely adopted, presumably because it requires an invasive diagnostic procedure.

Fetal abdominal circumference measurements

Electrical impedance measurement demonstrates that infants of GDM pregnancy have normal fat-free body mass but increased adiposity compared with matched offspring from nondiabetic pregnancies (15). Compared with normal birth weight offspring of GDM mothers, anthropometric measures of newborns weighing more than the 90th percentile

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Abbreviations: AC, abdominal circumference; GDM, gestational diabetes mellitus; 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.

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for gestational age demonstrated higher ponderal indexes, increased skinfold thickness, and decreased head to abdominal circumference ratios. Before birth, sonographic measurement of the fetal abdominal circumference (AC) can be used as a proxy for the development of in utero somatic fetopathy. Third trimester fetal AC measurements less than the 90th percentile for gestational age have been associated with a birth macrosomia risk <5% in term diet-controlled GDM pregnancies (16). Landon et al. (17) demonstrated that LGA infants of diabetic mothers had a significantly accelerated rate of fetal AC growth identifiable in the early third trimester, in contrast to normal rates of head circumference and femur length growth. AC growth at 18–20 weeks in pregestational diabetic pregnancies also predicts subsequent relative macrosomia at birth, suggesting that significant hyperglycemia earlier in gestation may produce recognizable fetal overgrowth earlier in development (18,19).

In a retrospective study by Schaefer-Graf et al. (20), third trimester amniotic fluid insulin levels in diabetic pregnancies positively correlated with increasing AC percentiles determined by ultrasound examination at time of amniocentesis. An upper quartile AC percentile (≥ 75 th for gestational age), occurring in 21% of the study cohort, identified all cases of severe hyperinsulinism (amniotic fluid insulin $>16 \mu\text{U/ml}$). These studies suggest that fetal AC growth or single observation relative AC dimensions in mid-pregnancy may be used to modify pregnancy intervention and provide a simple assessment of the effect of maternal diabetes on the fetus (Fig. 1).

RANDOMIZED INTERVENTION TRIALS UTILIZING FETAL ABDOMINAL CIRCUMFERENCE

To date, four randomized controlled clinical trials in diverse populations have used fetal AC measurements to identify fetuses at high and low risk for LGA growth and to stratify medical therapy based on that risk. Pregnancies at low risk for LGA growth, the majority, are permitted more relaxed pre- and postprandial glycemic targets. Those at high risk for LGA growth require lower glycemic goals below the conventional glycemic targets. The rationale for using lower glycemic targets in high-risk pregnancies was based on the findings of Langer et al. (3) who demonstrated that

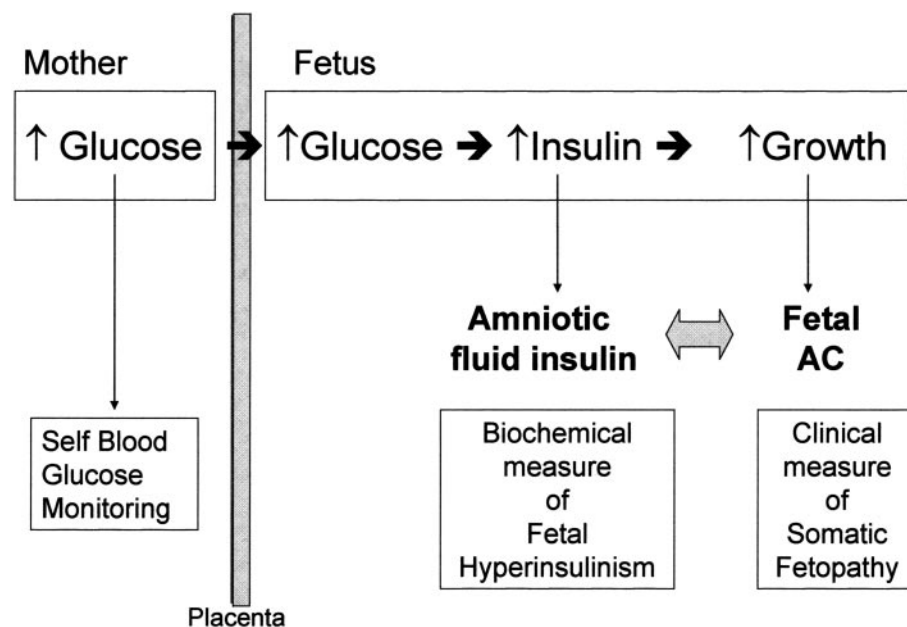


Figure 1—The relationship of pathophysiology (e.g., Pederson Hypothesis) and clinical assessment of diabetic effects on the fetus.

lower mean capillary glucose levels during pregnancy were associated with progressively lower rates of LGA infants and a corresponding increase in small-for-gestational-age (SGA) infants. The four trials were completed over the last decade and used slightly different diagnostic criteria to define GDM: the first two trials dealing primarily with Latinas in the U.S. (21,22) used the older National Diabetes Data Group criteria; the third trial (23) used German criteria based on a 75-g glucose tolerance test with thresholds below those of Carpenter and Coustan (23a); while the fourth trial in Italy (24) used the newer Carpenter and Coustan criteria. All studies used fetal AC ≥ 75 th percentile as a threshold for high risk, except the study by Kjos et al. (22), which used AC ≥ 70 th percentile and included only subjects with moderate fasting hyperglycemia. All four of the trials had control groups in whom insulin was prescribed according to “conventional” criteria. These criteria varied somewhat in the glycemic criteria used to start insulin therapy, with the older U.S. trials using fasting glucose levels of $\geq 105 \text{ mg/dl}$ and the more recent European trials using fasting/2-h postprandial levels of 90/120 mg/dl. In all four trials, the intervention groups where insulin prescription was “modified” based on accelerated AC growth, the therapeutic fasting/2-h postprandial glycemic targets were set lower (80/100–110 mg/dl). All four trials used regional or national standards to define LGA (≥ 90 th percen-

tile) and SGA (≤ 10 th percentile) neonatal growth.

The first trial by Buchanan et al. (21) enrolled 59 women in the early third trimester with mild fasting hyperglycemia controlled by diet alone ($<105 \text{ mg/dl}$) with high-risk fetal AC (≥ 75 th percentile) to conventional therapy, e.g., maintained on diet alone or modified therapy, e.g., diet plus insulin therapy with strict glucose targets (80/110 mg/dl). A third group of 171 women, excluded from randomization based on low-risk fetal AC (<75 th percentile) were also followed on diet therapy without self-monitoring of glucose. In the group receiving modified therapy, the LGA rate was reduced to 13% compared with the 45% rate in the group receiving conventional therapy, and it was similar to the 14% rate in the nonrandomized group with low-risk fetal AC. Neonatal skinfold thickness measures were also significantly lower in the modified group. A post hoc analysis of the LGA rates for each decile of fetal AC between 29 and 33 weeks of gestation found the 70th percentile to be the best threshold: the LGA rate in two-thirds of the infants with fetal AC <70 th percentile was 11% compared with a rate of 37% with a fetal AC ≥ 70 th percentile. This study demonstrated that in pregnancies complicated by mild GDM, fetal AC measurements could be used to identify a low-risk group requiring minimal intervention (conventional therapy) and a high-risk group whose pregnancies were at sub-

stantial risk for LGA group, despite acceptable glucose levels. Second, the LGA risk could be reduced by intensive therapy to achieve lower glycemic targets.

The second trial, which included 98 women with pregnancies from 14–34 weeks of gestation (22), examined an opposite subgroup, those with moderate fasting hyperglycemia (105–120 mg/dl). Women randomized to “conventional” therapy were managed with diet, exercise, and insulin with conventional glucose targets (90/120 mg/dl). Those randomized to modified therapy underwent monthly fetal growth evaluations. Relaxed glycemic targets (120/200 mg/dl) were permitted and insulin was not initiated if fetal AC growth remained under the 70th percentile. These criteria were met in 38% of the modified group. Strict glycemic targets (80/110 mg/dl) and insulin therapy were instituted if high-risk fetal AC growth (≥ 70 th percentile) or overt hyperglycemia (120/200 mg/dl) developed. Despite higher mean daily glucose levels with modified therapy, the neonatal birth weight, LGA rate, and morbidity rates were not significantly different from the conventional group. In the modified group, 44% maintained normal growth by monthly measures of fetal AC < 70 th percentile, and none of these subjects were LGA. All newborns that were LGA had an initial fetal AC ≥ 70 th percentile. In the conventional group, three newborns were SGA, including one stillborn at 36 weeks. Although not statistically significant, this is consistent with prior observations that intensive glycemic management of GDM pregnancies without attention to fetal growth can increase the risk of SGA infants (3).

The two later European trials compared an overall management protocol for GDM using conventional therapy based solely on maternal glycemia with modified therapy incorporating both maternal glycemia and periodic fetal AC measurements.

The third trial (23) enrolled 199 German women and randomized half to conventional therapy starting insulin if fasting/2-h postprandial glycemic targets exceeded 90/120 mg/dl and half to modified therapy, starting insulin if glucose targets exceeded 120/200 mg/dl or monthly fetal AC ≥ 75 th percentile. When high-risk growth was identified, lower glycemic targets of 80/110 mg/dl were used. The rates of LGA, SGA, or neonatal morbidity did not significantly differ by therapy. In a secondary analysis, all case subjects were categorized by whether

during the study they 1) met standard criteria for insulin therapy and 2) met fetal AC criteria for insulin therapy to examine in which subgroups the study protocols changed therapy. The assignment to either conventional or modified therapy would not have changed medical therapy, i.e., whether or not subjects received insulin therapy, in the majority (58%) of subjects. These subjects either received no insulin (40%), because both maternal glucose levels were controlled by diet at or below standard targets (conventional) and low-risk AC growth was maintained throughout the study (modified) or the subjects received insulin (18%) because glucose levels exceeded standard targets (conventional) and fetuses developed high-risk AC growth (modified). The former (normalized glucose and low-risk growth) LGA rate was 2.6% and, in the latter (elevated glucose and accelerated growth), the LGA rate was 26.1%. In 42% of subjects, the therapy (insulin) was changed based on study randomization. When glycemia remained below standard targets on diet but high-risk fetal AC growth was identified (24%), the LGA rates for those on conventional therapy (no insulin) was 21.9% compared with 8.3% on modified therapy. When glycemia was elevated above standard targets but fetal AC remained low risk, the LGA rates in both groups were the same (5.9%), but the SGA rate for those on conventional therapy was 35.3% compared with 16.6% on modified therapy. These differences were not statistically significant, but supported the findings of the first and second studies. The almost two-thirds reduction in LGA rates when strict glycemic targets are initiated for high-risk growth was similar in magnitude to the first trial of Buchanan et al. (21). Conversely, the halving of SGA rates using relaxed glycemic targets for low-risk growth reinforces the suggestion by Kjos et al. (22) that conventional therapy in the face of normal growth might increase the risk of SGA infants.

The fourth trial (24) of 229 Italian women, subjects randomized to conventional therapy, had insulin initiated when fasting/2-h postprandial glucose targets exceeded 90/120 mg/dl. Those randomized to modified therapy had fetal AC growth measured every 2 weeks. When growth remained low-risk (< 75 th percentile) relaxed glycemic targets of 100/140 mg/dl were used to start insulin therapy. When the AC ≥ 75 th, strict glycemic targets (80/100 mg/dl) were used

and insulin therapy was prescribed if these targets were not met by diet therapy. Compared with conventional therapy, this flexible approach resulted in a significantly lower LGA rate in the modified group (7.9 vs. 17.9%) and a nonsignificantly lower SGA rate (6.0 vs. 10.3%). In further analysis, similar to that done by Schaefer-Graf et al. (23), the study groups were dicotomized by the presence or absence of high- and low-risk fetal AC growth before 34 weeks. When high-risk growth was present, the modified group had significant lower LGA rates of 7.9 vs. 30.8% and higher insulin use of 59.7 vs. 15.4% in the conventional group. When low-risk growth was present, the modified group had significantly lower SGA rates of 14.5% compared with 30.3% in the conventional group. Again, these findings are consistent with the findings of the previous three studies. First, glycemic control when accelerated fetal growth was present reduced LGA rates by over two-thirds. Second, relaxed glycemic control when low-risk growth was present reduced SGA rates by approximately half. The significant differences found in this study may be in part explained by the larger study size and by the more frequent assessment of AC growth (every 2 weeks) leading to earlier adjustments to set strict or relaxed glycemic goals in the modified group. The conventional group only had ultrasound examinations performed at entry and 34 weeks and thus may avoid the “study effect” bias of serial AC measurements, which in the prior studies (22,23) were performed but not used for management in the conventional groups. Such frequent measures may have unknowingly influenced therapy.

More frequent assessment of AC growth would permit earlier therapeutic intervention and provide more time to normalize fetal growth by adjusting glycemic targets. The benefit of earlier identification and intervention for accelerated fetal growth was demonstrated in a randomized trial by Rossi et al. (25) who randomized the fetal AC measurements to early (28 and 32 weeks of gestation) or late (32 weeks) evaluation in diet-controlled GDM pregnancies. In both groups, when high-risk fetal AC growth (≥ 75 th) was identified, insulin therapy was initiated to achieve lower glycemic targets. The rate of LGA growth was significantly lower in the early evaluation group (33.3%) compared with the late evaluation group (71%). The lower rate was explained by reduction of LGA

Table 1—Combined results from four randomized trials comparing conventional with modified therapy on rates of LGA and SGA infants when low-risk and high-risk fetal abdominal growth is detected before 34 weeks

	Conventional therapy	Modified therapy	Odds ratio (95% CI)*
			<i>P</i>
Low-risk fetal Abdominal Circumference*	LGA rates (1) Not randomized (2) 0/29 (3) 2/55 (4) 2/39 Total: 4/123 (3.3%)	LGA rates (1) Not evaluated (2) 0/21 (3) 2/55 (4) 4/89 Total: 6/165 (3.6%)	<i>P</i> = 0.86 (Fisher's exact)
High-risk Fetal Abdominal Circumference	(1) 13/29 (2) 3/19 (3) 10/42 (4) 12/39 Total: 38/129 (29.6%)	(1) 4/30 (2) 4/27 (3) 7/36 (4) 5/62 Total: 20/155 (12.9%)	OR 0.41 (0.22–0.78) <i>P</i> = 0.003
Combined LGA rates	42/252 = 16.7%	26/320 = 8.1%	OR 0.44 (0.25–0.77) <i>P</i> = 0.0017
Low-risk fetal Abdominal Circumference*	SGA rates (1) not evaluated (2) 3/29 (3) 14/55 (4) 6/39 Total: 23/123 = 18.7%	SGA rates (1) not evaluated (2) 0/21 (3) 10/55 (4) 0/89 Total: 19/165 = 11.5%	OR 0.57 (0.28–1.15) <i>P</i> = 0.087
High-risk fetal Abdominal Circumference	(1) NA (2) 0/19 (3) 0/42 (4) 2/39 Total: 2/100 (2.0%)	(1) NA (2) 0/27 (3) 1/36 (4) 0/62 Total: 1/125 = (0.8%)	<i>P</i> = 0.41 (Fisher's exact)
Combined SGA rates	25/223 = 11.2%	20/290 = 6.9%	OR 0.59 (0.30–1.13) <i>P</i> = 0.087

The results of four randomized trials are designated (1), (2), (3), and (4), from references 21, 22, 23, and 24, respectively. *Odds ratio (95% CIs) and *P* values were calculated by χ^2 test unless otherwise indicated.

growth (11%) in those identified and treated with insulin by 28 weeks. This study demonstrates the importance of early recognition of high-risk AC growth to permit earlier intensive therapy.

The rates for the LGA and SGA infants are summarized in Table 1 from four randomized controlled intervention trials (21–24) that compared conventional therapy, based on maternal glycemic levels, with modified therapy using different maternal glycemic targets based on high- and low-risk fetal AC measurements. Whereas there were variations between the study designs, all were randomized and controlled, and all used similar threshold cut points (70th to 75th percentile) to define high- and low-risk fetuses, and all used similar lower glycemic targets (80/100–110 mg/dl) for intensive therapy. During the 10-year period in which the trials were published, more refined management protocols have evolved based on each preceding study. This can be seen when comparing the first trial, which based all subsequent therapy on one ultrasound exam between 29 and 33 weeks, to the last trial, which used a

flexible approach using biweekly fetal AC from time of diagnosis and setting strict and relaxed glycemic targets, adding insulin when glycemic targets were not reached. The four trials are designated one through four in order of publication. All of the studies reported the assignment of each subject to a high- or low-risk AC threshold determined before 34 weeks. The total number randomized cases/exposed for LGA and SGA infants were totaled for the AC subgroups and for the overall rates according to conventional and modified therapy. Overall, compared with conventional therapy, the use of modified therapy resulted in a reduction of LGA growth by over 50% (odds ratio 0.44, 95% CI 0.25–0.77; *P* = 0.0017), from 16.7 to 8.1%. Modified therapy also decreased the overall SGA rate from 11.2 to 6.9%; however, this did not reach statistical significance (odds ratio 0.59, 95% CI 0.3–1.13; *P* = 0.087). This result would not be unexpected, since the first three trials were powered to detect a difference in LGA rates, and SGA growth was not considered. The fourth trial considered both LGA and SGA rates and was

powered to detect an 18% difference in appropriate-for-gestational age infants (>10th and <90th percentile birth weight) (24).

SUMMARY— In the last decade, level I evidence from 484 pregnancies in four clinical trials supports modified therapy to reduce newborn somatic growth disturbances related to GDM and demonstrates three consistent findings. First, fetal AC measurements during the second and third trimester discriminate low risk and high risk for LGA newborns using fetal AC thresholds <75th and \geq 75th percentile for gestational age. The fetal AC is a standard component of the basic fetal ultrasound examination. Its reproducibility in determining weights and growth patterns has been long established by studies and daily clinical use. Newer ultrasound machines calculate fetal AC percentiles using standard growth curves. Thus, the fetal AC is ideal as a simple and practical measurement for determining low- and high-risk fetal growth.

Second, when high-risk fetal AC growth is identified, modified therapy us-

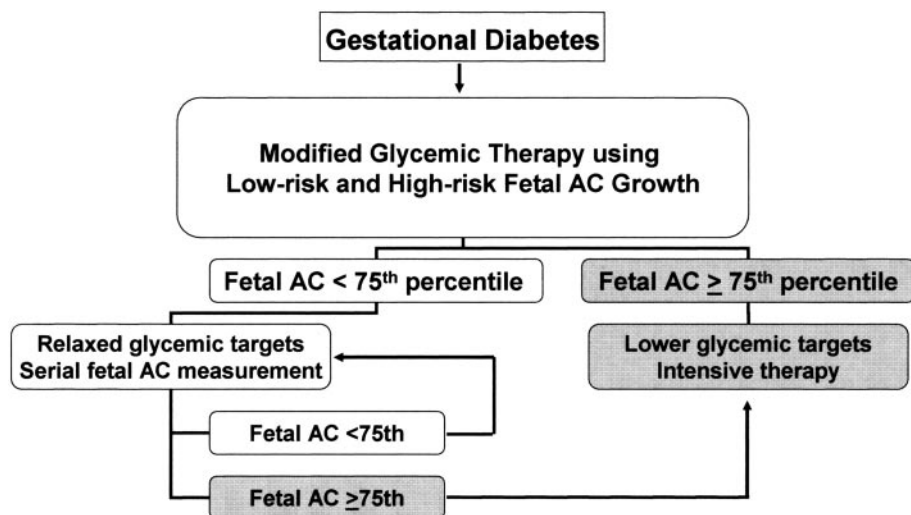


Figure 2—Flow chart of “modified” treatment of GDM-based serial ultrasound measurement of fetal AC. Fetal AC measurement is categorized as low-risk (<75th percentile for gestational age) or high-risk (\geq 75th percentile for gestational age). When low-risk fetal growth is maintained, glycemic targets can be relaxed. When high-risk fetal growth is identified, lower glycemic thresholds are used (fasting glucose <80 mg/dl, 2-h postprandial <100–110 mg/dl), instituting intensive medical therapy as needed.

ing lower fasting/2-h postprandial glucose targets of 80/100–110 mg/dl has been shown to significantly reduce LGA growth by over 50%. The key intervention strategy is lowering glucose levels below the standard levels considered to be “normal range” and can be accomplished by either diet or insulin therapy. Modified therapy may be most effective in pregnancies with mild initial hyperglycemia and excessive growth. When both moderate maternal glycemia and excessive growth are present, and insulin is prescribed regardless of therapy protocol, the LGA rates appear less responsive to glycemic therapy, possibly because high-risk growth may be well established before the traditional time of diagnosis of GDM.

Third, when low-risk growth is identified, relaxing glycemic targets can decrease the risk of SGA infants (24). Larger studies are needed to address how best to reduce SGA risk, whether it is by lowering fetal AC percentiles or deciding which relaxed glucose targets should be used. Preventing SGA growth should be an equally important therapeutic goal as preventing LGA growth, since low birth weight and growth restriction have also been strongly associated with later life increased risk of hypertension and type 2 diabetes (26–28).

From these four trials has emerged a modified therapy approach that is illustrated in Fig. 2. Shortly after the diagnosis of GDM, ultrasound measurement of fetal

AC percentile should be performed. In pregnancies manifesting high-risk fetal growth, lower glycemic targets (80/100–110 mg/dl) should be used, starting insulin as needed. In pregnancies manifesting low-risk fetal growth, relaxed glycemic targets can be used. Currently, there is not a clear basis for recommending either 100/140 or 120/200 mg/dl. However, in the three trials where serial AC measures were performed, insulin therapy was started primarily for high-risk AC growth, not for exceeding either relaxed glycemic target. Current studies do not examine how frequently fetal AC measures should be evaluated. Bonomo et al. (24) attributed their success in reducing both LGA and SGA rates to their protocol of assessing fetal AC growth every 2 weeks and modulating therapy in “real-time.” This permitted early and flexible therapy to reduce excessive growth or unnecessarily lowering glucose levels to avoid fetal undergrowth.

More studies comparing management strategies that address optimal timing, frequency of ultrasound examinations, and glycemic targets will continue to improve modified therapy. Future studies are needed that examine whether other ultrasonic growth parameters (e.g., head-abdomen ratios or subcutaneous fat) are better able to discriminate between accelerated or restricted growth due to maternal, genetic, fetal, or diabetic mediated factors. However, by far, the most impor-

tant outcome of all future therapeutic trials involving GDM pregnancies will be to examine the effects of in utero treatment on childhood and lifetime risks for developing obesity or impaired glucose tolerance.

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