Three-versus two-dimensional sonographic biometry for predicting birth weight and macrosomia in diabetic pregnancies

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Three-Versus Two-Dimensional Sonographic Biometry for Predicting Birth Weight and Macrosomia in Diabetic Pregnancies

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Objective—The purpose of this study was to test the hypothesis that a formula incorporating 3-dimensional (3D) fractional thigh volume would be superior to the conventional 2-dimensional (2D) formula of Hadlock et al (Am J Obstet Gynecol 1985; 151:333–337) for predicting birth weight and macrosomia.

Methods—We conducted a prospective cohort study of pregnancies complicated by pregestational or gestational diabetes and delivered after 38 weeks. Two-dimensional and 3D sonographic examinations were performed for fetal biometry and factional thigh volumes at 34 to 37 weeks. Fetal weight was estimated by Hadlock’s 2D formula IV, which uses only 2D biometry, and formula 6 from Lee et al (Ultrasound Obstet Gynecol 2009; 34:556–565), which incorporates 3D fractional thigh volume and 2D biometry. The gestation-adjusted projection method was used to estimate predicted birth weights from 2D and 3D estimates. The primary outcome was fetal macrosomia, which was defined as birth weight of 4000 g or higher.

Results—A total of 115 women with diabetes met inclusion criteria, and 17 (14.8%) delivered macrosomic neonates. The mean percentage error was significantly lower for the 2D than the 3D projected estimate (1.0% versus 12.0%; \( P < .01 \)). The standard deviation of the mean percentage error was also significantly lower for the 2D projected estimate (10.2% versus 17.2%; \( P < .01 \)). Two-dimensional biometry was overall superior to 3D biometry for predicting macrosomia (area under the receiver operating characteristic curve, 0.88 versus 0.75; \( P = .03 \)). Specificity was significantly higher for 2D biometry (85% versus 66%; \( P < .01 \)), whereas the difference in sensitivity was not statistically significant (59% versus 71%; \( P = .22 \)).

Conclusions—In this study, the Hadlock 2D formula was superior to the 3D method for predicting birth weight and macrosomia in diabetic women when used approximately 2 weeks before delivery, based on the gestation-adjusted projection method.

Key Words—diabetes; fetal macrosomia; fetal weight; obstetric ultrasound; 3-dimensional sonography

Fetal macrosomia, defined as fetal weight exceeding 4000 or 4500 g regardless of gestational age, is associated with increased risks of neonatal and maternal morbidity, including shoulder dystocia, birth trauma, perineal lacerations, and cesarean delivery.1–4 Diabetes, especially when poorly controlled, is a major risk factor for fetal macrosomia. This association is partially explained by excessive growth from elevated maternal plasma glucose levels, resulting in elevated fetal insulin and insulin-like growth factor levels, which stimulate glycogen synthesis, fat deposition, and fetal growth.5,6
Tuuli et al—3D Versus 2D Sonographic Biometry in Diabetic Pregnancies

Moreover, neonates of diabetic mothers of the same birth weight are at higher risk for shoulder dystocia compared to those of nondiabetic mothers because of different distributions of body fat.7,8 Thus, the American College of Obstetricians and Gynecologists suggests consideration of cesarean delivery for estimated fetal weight higher than 4500 g in women with diabetes and higher than 5000 g for women without diabetes.9 This policy places a premium on prenatal diagnosis of macrosomia, particularly in women with diabetes, to inform obstetric care.

Despite its clinical value, accurate estimation of fetal weight and prediction of macrosomia are challenging, with substantial margins of error for both clinical estimates and routine 2-dimensional (2D) sonographic biometry, especially at the extremes of fetal weight.10-13 Recent advances in 3-dimensional (3D) sonography have shown promise in improving fetal weight estimation over 2D sonography. Lee et al14,15 demonstrated a significant improvement over 2D biometry when fractional thigh volume, a soft tissue parameter based on 50% of the femur diaphysis length from 3D sonography, was incorporated into 2D biometry. Although this finding is promising, there are limited data on the performance of 3D sonography for predicting macrosomia in diabetic pregnancies.16 The objective of this study was to test the hypothesis that incorporating 3D fractional thigh volume would be superior to conventional 2D biometry.

Materials and Methods

We conducted a prospective cohort study of pregnancies complicated by diabetes from 2005 to 2010 at Washington University Medical Center. This work was part of a primary study aimed at evaluating the ability of novel biomarkers to predict fetal macrosomia in women with diabetes. Approval was obtained from the Washington University School of Medicine Human Research Protection Office before initiation of the study. Informed consent was received from all participants.

Women were eligible if they had pregestational type 2 or gestational diabetes, carried a singleton nonanomalous fetus, and delivered after 38 weeks. Gestational diabetes was diagnosed on the basis of universal 2-step screening using a cutoff of 140 mg/dL on the 1-hour glucose challenge test and the National Diabetes Data Group criteria on the 3-hour glucose tolerance test.17 Pregnancies were dated by the women’s last menstrual periods and confirmed with first- or second-trimester sonography using standard criteria. All patients with diabetes routinely undergo sonography for growth based on routine 2D biometry (head circumference, biparietal diameter, abdominal circumference, and femoral length) at 34 to 37 weeks. We performed sonographic examinations at 34 to 37 weeks because fetal sonographic biometry becomes less accurate nearer the time of delivery, possibly because of descent of the fetal head and a reduction in the amniotic fluid volume. All sonographic examinations were performed by certified registered diagnostic medical sonographers who were credentialed in obstetrics and gynecology. Diagnostic interpretations were made by experienced sonologists and maternal-fetal medicine attending physicians.

Three-dimensional thigh volumes were obtained at the time of 2D biometry by 2 dedicated sonographers using Voluson Expert 730 machines (GE Healthcare, Milwaukee, WI), as previously described by Lee et al.14,15 Briefly, 3D multiplanar imaging was used to obtain thigh volumes centered on the midpoint of the femur. At least 3 thigh volumes were taken per patient. Fractional thigh volume measurements were obtained from the best volume by a single physician, who was blinded to the birth weight, by manually tracing around a central portion of the femoral diaphysis using GE 4D View software. The fractional thigh volumes were acquired twice, and the measurements were averaged.

Fetal weights based on 2D biometry were estimated by using formula IV from Hadlock et al18 (log10 2D estimate = 1.5115 + 0.0436 [abdominal circumference] + 0.1517 [femur length] – 0.00321 [abdominal circumference × femur length] + 0.0006923 [biparietal diameter × head circumference]). Three-dimensional formula 6 from Lee et al14,15 incorporates 3D fractional thigh volume and 2D biometric measurements (ln estimated weight = -0.8297 + 4.0344 [ln biparietal diameter] – 0.7820 [ln abdominal circumference] + 0.0528 [ln fractional thigh volume]) was also used to estimate fetal weight. Since 2D and 3D measurements were obtained a few weeks before delivery, we estimated predicted birth weights from 2D and 3D estimates using the gestation-adjusted projection method described by Mongelli and Gardosi.19 This extrapolation method is based on the assumption that the ratio of fetal weight to median weight for gestational age remains constant within an interval of a few weeks in the third trimester.

The primary outcome measure was macrosomia, defined as birth weight of 4000 g or higher, and the secondary outcome was birth weight of 4500 g or higher. Descriptive characteristics were calculated for the cohort and were compared for the presence or absence of macrosomia by the χ² test, Fisher exact test, Student t test, or...
Mann-Whitney U test as appropriate. The mean percentage error, a measure of systematic bias, was estimated for predicted weight for 2D and 3D methods by using the formula \((\text{projected estimate} - \text{actual birth weight}) \times 100/\text{actual birth weight}\). The standard deviation of the mean percentage error was estimated for each method as a measure of random error. The mean percentage errors and standard deviations for the two methods were compared by the paired t test. Bland-Altman analysis was performed, comparing the projected estimated weight from each method to birth weight. The differences between birth weight and the projected estimates (projected estimate – birth weight) were plotted against birth weight. Systematic bias, random error, and agreement were evaluated by the mean absolute differences, standard deviations of the mean differences, and 95% limits of agreement, respectively.20

Receiver operating characteristic (ROC) curves were used to estimate the overall predictive ability of projected 2D and 3D estimates for macrosomia. The areas under the ROC curves for the two groups were compared by using the method described by DeLong et al.21 Predictive characteristics (sensitivity, specificity, accuracy, positive predictive value [PPV], and negative predictive value [NPV]) were estimated for the two methods. Sensitivities and specificities were compared by using an extension of the McNemar test.22

All women meeting inclusion criteria during the study period who provided consent were included; no a priori sample size calculation was performed. All tests were 2 tailed, with \(P < .05\) considered significant. Statistical analyses were completed with the Stata version 11 special edition software package (StataCorp, College Station, TX).

Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire Cohort (n = 115)</th>
<th>Macrosomia (n = 17)</th>
<th>No Macrosomia (n = 98)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td>29.4 ± 6.1</td>
<td>28.8 ± 5.8</td>
<td>29.5 ± 6.1</td>
<td>.67</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>69 (60.0)</td>
<td>9 (52.9)</td>
<td>60 (61.2)</td>
<td>.28</td>
</tr>
<tr>
<td>White</td>
<td>35 (30.4)</td>
<td>5 (29.4)</td>
<td>30 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Latina/Hispanic</td>
<td>9 (7.8)</td>
<td>2 (11.8)</td>
<td>7 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.8)</td>
<td>1 (5.9)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Primiparous, n (%)</td>
<td>36 (31.3)</td>
<td>2 (11.8)</td>
<td>34 (34.7)</td>
<td>.06</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>34.6 ± 9.5</td>
<td>33.6 ± 6.8</td>
<td>34.8 ± 9.9</td>
<td>.63</td>
</tr>
<tr>
<td>Obese (body mass index &gt;30 kg/m²)</td>
<td>75 (65.2)</td>
<td>10 (58.8)</td>
<td>65 (66.3)</td>
<td>.55</td>
</tr>
<tr>
<td>Diabetes type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>.77</td>
</tr>
<tr>
<td>Pregestational</td>
<td>78 (67.8)</td>
<td>11 (64.7)</td>
<td>67 (68.4)</td>
<td></td>
</tr>
<tr>
<td>Gestational</td>
<td>37 (32.2)</td>
<td>6 (35.3)</td>
<td>31 (31.6)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at sonography, wk</td>
<td>37.5 ± 1.3</td>
<td>37.7 ± 1.0</td>
<td>37.5 ± 1.4</td>
<td>.53</td>
</tr>
<tr>
<td>Gestational age at delivery, wk</td>
<td>39.5 ± 0.8</td>
<td>39.6 ± 0.7</td>
<td>39.5 ± 0.8</td>
<td>.95</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD where applicable.

Results

A total of 115 women with diabetes met inclusion criteria and had both 2D and 3D sonographic biometry. Most of the cohort was African American, and two-thirds were obese. One-third had gestational diabetes, and two-thirds had pregestational diabetes. The mean gestational ages at sonographic biometry and delivery were 37.5 and 39.5 weeks, respectively, with a 2-week average interval from biometry to delivery (mean ± SD, 2.0 ± 1.5 weeks). There were no significant differences in baseline characteristics between women with and those without a macrosomic neonate (Table 1).

The mean percentage error (measure of systematic bias) was significantly lower for the 2D than the 3D projected estimate (1.0% [95% confidence interval (CI), –1.0%, 2.9%] versus 12.0% [95% CI, 8.9%, 15.2%]; \(P < .01\)). The standard deviation of the mean percentage error (measure of random error) was also significantly lower for the 2D projected estimate (10.2% versus 17.2%; \(P < .01\)). Bland-Altman analysis showed a lower mean difference between the projected estimates and birth weight for 2D biometry (14.9 versus 402.33 g; \(P < .01\)), suggesting less systematic bias. The standard deviation of the mean difference was significantly lower for the 2D projected estimates (373.8 versus 624.1 g; \(P < .01\)), indicating lower random error. The 95% limits of agreements were wide for both methods, but relatively narrower for 2D projected estimates (–717.6 to +747.4 versus –820.8 to +1625.5 g), suggesting overall better agreement between the 2D projected estimates and birth weight (Figure 1).
Seventeen of the 115 women (14.8%) delivered macrosomic neonates with birth weights of 4000 g or higher (primary outcome). Two-dimensional biometry was overall superior to 3D biometry for predicting macrosomia (area under the ROC curve, 0.88 [95% CI, 0.80, 0.95] versus 0.75 [95% CI, 0.60, 0.89]; \( P = .03 \); Figure 2). The associated specificity for predicting macrosomia was significantly higher for 2D biometry (85% versus 66%; \( P < .01 \)). Sensitivity was nominally higher for 3D sonography, but the difference was not statistically significant (59% versus 71%; \( P = .22 \); Table 2). The PPVs (40% versus 27%) and NPVs (92% versus 93%) were not significantly different for the two methods in this cohort.

Seven of the 115 women (6.1%) had macrosomic neonates with birth weights of 4500 g or higher (secondary outcome). Two-dimensional biometry appeared nominally superior to 3D biometry for predicting macrosomia of 4500 g or higher, but the difference was not statistically significant (area under the ROC curve, 0.90 [95% CI, 0.81, 0.99] versus 0.83 [95% CI, 0.68, 0.98]; \( P = .44 \); Figure 3). The associated specificity for predicting macrosomia of 4500 g or higher was significantly higher for 2D biometry (99% versus 85%; \( P < .01 \)), whereas sensitivity was nominally higher for 3D biometry, but the difference was not statistically significant (24% versus 53%; \( P = .25 \); Table 3).

**Discussion**

In this study using the gestation-adjusted projection method approximately 2 weeks before delivery, we found that a formula based on 2D biometry was overall superior to a formula incorporating 3D fractional thigh volume for predicting birth weight and fetal macrosomia in women with diabetes. Specificity was significantly higher for 2D biometry, whereas the difference in sensitivity was not statistically significant. Systematic bias and random error were both significantly lower for 2D biometry.

Pagani et al\(^1\) conducted a similar prospective study comparing the accuracy of model 6 from Lee et al\(^1\) which incorporates 3D fractional thigh volume, to the Hadlock formula in 125 Italian women with gestational diabetes. Similar to our study, they found no differences in sensitivity for predicting macrosomia. However, in contrast to our study, they found that the 3D Lee formula (not the 2D Hadlock formula) had lower systematic bias and higher specificity for predicting macrosomia. It is unclear why our results differed from those of Pagani et al with regard to systematic bias and random error for predicting birth weight and specificity for macrosomia. Both studies included only diabetic pregnancies and compared the accuracy predict-
was a key strength of the study. Furthermore, measurement of the fractional thigh volumes, which have been shown to be reproducible among blinded examiners, was performed twice and averaged. We also used rigorous methods to comprehensively assess the systematic bias, random bias, and predictive ability of 2D and 3D biometry for macrosomia. We used Bland-Altman analysis to assess agreement between projected estimates and birth weight, which is important because the mean percentage error alone does not capture the full range of differences between the projected estimates and birth weights. We assessed the predictive accuracy of birth weight of 4500 g or higher in addition to birth weight of 4000 g or higher, which is clinically relevant because 4500 g is the more common fetal weight cutoff at which consideration of cesarean delivery is recommended in women with diabetes. Furthermore, we included only women who delivered after 38 weeks to maximize the occurrence of fetal macrosomia.

There were limitations that should be considered when interpreting our results. We extrapolated estimated birth weight using the gestation-adjusted projection method, which relies on the assumption that the ratio of actual fetal weight to the median fetal weight at the same gestational age is constant in the third trimester. Although this assumption is reasonable within the fairly narrow interval between sonography and delivery and has been used in other studies, it has not been formally validated. In addition, it is plausible that poor glycemic control in our sample, which was made up of both pregestational and gestational diabetics, could have violated this assumption, which may have accounted for the larger systematic bias we observed especially for the 3D method.

We did not perform a sample size estimation a priori, since our sample size was limited by the enrollment in the primary study. Our sample size of 115 was comparable to prior studies, but it was still relatively small, which may have contributed to the relatively wide CIs around our estimates. The associated low statistical power may also have been the reason for our inability to show statistically significant differences even for some estimates that were nominally vastly different. Although the random error of 10.2% for the 2D method was consistent with what has been published in the literature for the Hadlock model, the random prediction error of 17.2% for the 3D method is much higher than that reported in other studies. The study by Pagani et al., using the gestation-adjusted projection method for macrosomia estimation, did not show statistically significant differences for any of the estimates.

Table 2. Predictive Characteristics of 2D and 3D Sonography for Macrosomia of Greater Than 4000 g in Diabetic Pregnancies (n = 115)

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Projected 2D Estimate</th>
<th>Projected 3D Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI), %</td>
<td>59 (33, 82)</td>
<td>71 (44, 90)</td>
</tr>
<tr>
<td>Specificity (95% CI), %</td>
<td>85 (76, 91)</td>
<td>66 (56, 76)</td>
</tr>
<tr>
<td>Accuracy (95% CI), %</td>
<td>72 (59, 84)</td>
<td>69 (56, 81)</td>
</tr>
<tr>
<td>PPV (95% CI), %</td>
<td>40 (21, 61)</td>
<td>27 (15, 42)</td>
</tr>
<tr>
<td>NPV (95% CI), %</td>
<td>92 (85, 97)</td>
<td>93 (84, 98)</td>
</tr>
</tbody>
</table>

Table 3. Predictive Characteristics of 2D and 3D Sonography for Macrosomia of Greater Than 4500 g in Diabetic Pregnancies (n = 115)

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Projected 2D Estimate</th>
<th>Projected 3D Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI), %</td>
<td>24 (7, 50)</td>
<td>53 (28, 77)</td>
</tr>
<tr>
<td>Specificity (95% CI), %</td>
<td>99 (94, 100)</td>
<td>85 (76, 91)</td>
</tr>
<tr>
<td>Accuracy (95% CI), %</td>
<td>61 (56, 62)</td>
<td>69 (56, 82)</td>
</tr>
<tr>
<td>PPV (95% CI), %</td>
<td>80 (28, 100)</td>
<td>38 (19, 59)</td>
</tr>
<tr>
<td>NPV (95% CI), %</td>
<td>88 (81, 94)</td>
<td>91 (83, 96)</td>
</tr>
</tbody>
</table>
method about 3 weeks before delivery, reported a 5.0% random error in gestational diabetics. Similarly, Lee et al.\textsuperscript{15} reported random error values of 6.6% and 5.8% for all neonates and macrosomic neonates weighing 4000 g or higher, respectively, in a study estimating fetal weight within 4 days of delivery based on the 3D method without gestation-adjusted projection. It is unlikely that the use of the gestation-adjusted projection method is an explanation for this observation, since lower random errors were observed in one study that employed it and another study that did not. On the other hand, because random error is a reflection of variability in measurements, the larger random error in our study suggests overall larger measurement errors, which may have been attributable, at least in part, to the high prevalence of obesity (65.2%) in our cohort.

Prediction of fetal macrosomia in women with diabetes remains challenging.\textsuperscript{23} Although the fetal fat mass constitutes only 14% of birth weight, it accounts for as much as 46% of the variance in birth weight.\textsuperscript{24} Moreover, adipose tissue is subject to major changes when conditions associated with accelerated growth such as diabetes are present. Thus, it is likely that better quantification of specific fetal soft tissue such as fat would allow for improved estimation of birth weight and prediction of macrosomia.

In conclusion, the results of this prospective study show that Hadlock’s 2D formula was superior to the 3D method for predicting birth weight and macrosomia in diabetic women when used approximately 2 weeks before delivery, based on the gestation-adjusted projection method. Further studies should include a larger sample size and determine whether quantification of specific fetal soft tissue such as fat and addition of patient characteristics will improve prediction of macrosomia. Until then, our data suggest that 2D sonography should remain the standard of care for predicting birth weight and macrosomia in diabetic pregnancies.

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