The National Institute of Child Health and Human Development Maternal-Fetal Medicine Unit Network Randomized Clinical Trial in Progress

Standard therapy versus no therapy for mild gestational diabetes

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It is recognized that women with gestational diabetes mellitus (GDM) who have significantly elevated fasting blood glucose levels are at increased risk for fetal macrosomia and perinatal morbidity if treatment is not provided (1,2). The association of milder forms of GDM with perinatal morbidity and mortality remains unclear, primarily because the condition is often confounded with other risk factors such as maternal obesity, age, and parity. Screening for GDM is recommended for most pregnant women, yet it is unknown whether there is a benefit to the identification and treatment of mild carbohydrate intolerance during pregnancy (3,4). The present report is an update of our previous description of a current ongoing randomized treatment trial for mild GDM (5). A randomized clinical trial of women with mild GDM (fasting glucose <95 mg/dl) is being undertaken that compares perinatal outcomes in those receiving diet therapy and insulin as required versus those randomized to no specific treatment. This study aims to clarify whether there is utility in identifying and treating women with a normal fasting glucose level who meet standard criteria for GDM. We plan to compare perinatal outcomes in women who have been randomized to diet and/or insulin therapy with women who have been randomized to no specific treatment. A randomized treatment trial of mild GDM will clarify whether identification and treatment of mild GDM reduce perinatal morbidity. This information will assist in determining appropriate thresholds for the treatment of GDM.

BACKGROUND AND STUDY RATIONALE — Overall, with broader identification and aggressive treatment, perinatal mortality rates associated with GDM appear to be similar to the nondiabetic population (1). Several analyses of 20 years ago did document an increased stillbirth rate for GDM pregnancies that would qualify as preexisting diabetes according to World Health Organization criteria (6–9). Below this threshold, the extent to which untreated GDM is accompanied by excess perinatal mortality is uncertain.

GDM, if untreated or not recognized, may also be associated with an increased risk of several morbidities such as macrosomia, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia, and respiratory distress syndrome (7). The association of GDM with accelerated fetal growth resulting in large infants at risk for birth trauma and long-term metabolic effects of obesity has received the most clinical attention. However, the attributable risk of GDM for excessive fetal growth is not entirely clear (10–12). Race, parity, BMI, and maternal weight gain have all been associated with an increased risk of macrosomia (13). Sacks et al. (13) reported that only a weak relationship exists between maternal glucose levels and birth weight centiles, after controlling for confounding variables. Similarly, Casey et al. (12) found that only 12% of the excess risk for macrosomia in their GDM population could be attributed to maternal carbohydrate intolerance. The relationship between other morbidities such as neonatal hypoglycemia and hyperbilirubinemia with maternal glucose levels in GDM has not been well characterized. Retrospective studies suggest that intensive treatment of GDM may reduce these morbidities (3).

As women with GDM represent a metabolically heterogeneous group, this likely translates into a broad range of perinatal risk. This contributes to the controversy surrounding whether a treatment benefit exists for pregnancies complicated by this disorder. Despite longstanding recognition of this problem, little progress has been made in developing evidence-based guidelines for screening and treatment (4). Nearly 15 years ago, an in-

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Abbreviations: GDM, gestational diabetes mellitus; MFMU, Maternal-Fetal Medicine Unit.

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

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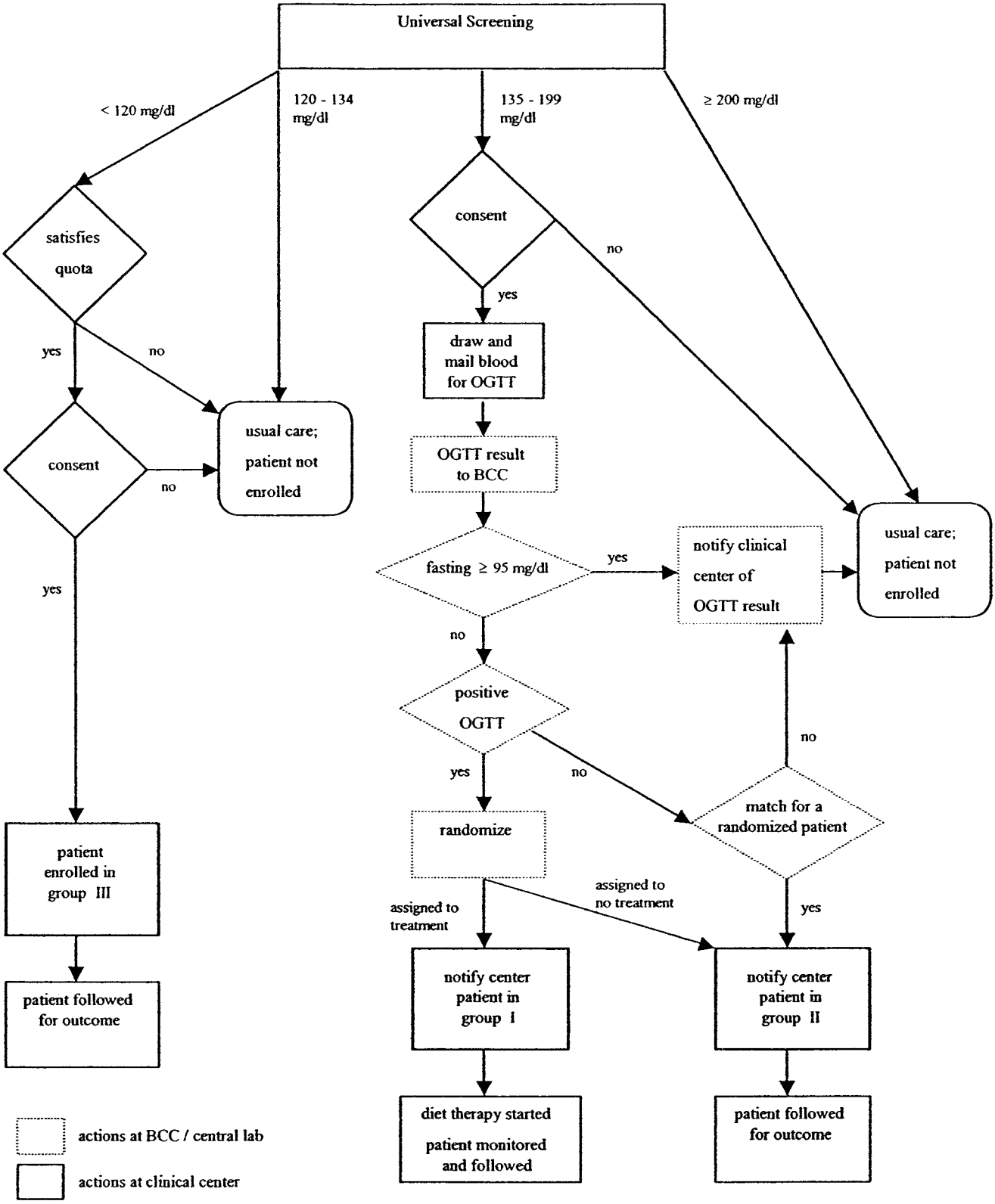

Figure 1—*Reprinted with permission from Landon et al. (5).*

ternational consensus conference on the adverse effects of gestational diabetes co-sponsored by the National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Disease concluded that "the sensitivity, specificity, and cost-effectiveness of efforts to diagnosis and treat gestational diabetes mellitus in order to prevent adverse perinatal effects cannot be resolved without additional carefully designed studies" (14). Similar conclu-

sions have been reached by the Canadian Task Force on periodic health examination and by the U.S. Preventive Services Task Force (15). Most women in the U.S. are subjected to glucose screening during pregnancy followed by formal diagnostic testing in ~15–20% of the population. GDM is being diagnosed with increasing frequency based on the less stringent revised criteria proposed by the Fourth International Workshop-Conference. Most of these additional cases represent mild GDM, which undergo a variety of obstetrical and medical interventions throughout the remainder of their pregnancy. Such interventions for GDM are currently without much scientific justification and, in fact, may present risk to the patient so diagnosed. Studies have demonstrated a consistently higher rate of cesarean section for those women designated as having GDM (16).

The Maternal-Fetal Medicine Unit (MFMU) Network of the National Institute of Child Health and Human Development conducts multicenter clinical studies that address important issues in maternal-fetal medicine and obstetrics. Over a decade ago, the MFMU Network began planning a randomized clinical treatment trial for GDM. Numerous retrospective studies as well as a pilot randomized clinical trial were carefully considered in the planning of our study. Garner et al. (17) conducted a pilot study of strict glycemic control and tertiary care versus routine obstetric care in the management of women with normal fasting glucose levels (diet-controlled GDM). The aim of Garner's pilot study was to prepare for a multicenter trial by assessing patient acceptance, determining realistic accrual rates, and detecting any major adverse outcomes in the control group who received routine obstetric care. Among 300 GDM women randomized, there were no differences in mean birth weight, macrosomia, or birth trauma between the study groups. The mode of delivery was also similar between the two groups, while the treatment group did have lower preprandial and postpartum glucose levels during the third trimester.

A serious shortcoming of Garner's study was that women in the control arm were not blinded to their diagnosis and could have been self-treating by modifying their diet. Moreover, these women actually performed self-monitoring of blood glucose and also could have modified their behavior based on testing results. Nearly all previous studies of GDM have failed to blind practitioners to the diagnosis, which can affect obstetric decision making. Thus, a trial blinding the control group and practitioners to the oral glucose tolerance test results was critical to our study design. In selecting criteria for inclusion, it was apparent that practitioners and institutional review boards would not accept blinding of test results in women with fasting hyperglycemia. Moreover, many women with fasting hyperglycemia might have underlying overt diabetes with associated increased perinatal risk. However, a prospective clinical trial involving women with milder forms of hyperglycemia was acceptable to both the Steering Committee of the MFMU Network and Advisory Board based on the lack of current evidence supporting treatment of this group of women.

STUDY DESIGN — We have previously reported the design of this clinical trial (5). The study aims to address the primary research question, "Do women with a singleton pregnancy diagnosed with mild gestational diabetes between 24 and 29 weeks of gestation receiving diet modification and performing self-monitoring of blood glucose have a reduction in the incidence of neonatal morbidity and mortality, as compared with standard obstetrical care?" Mild GDM is defined as a 3-h oral 100-g glucose tolerance test with normal fasting level (i.e., <95 mg/dl) and two of the three post–glucose load determinations exceeding thresholds established by the Fourth International Workshop-Conference on Gestational Diabetes (17).

The study will also address secondary research questions including whether treatment of mild GDM reduces the risk of a large-for-gestational-age infant and/or macrosomia (birth weight >4,000 g), neonatal intensive care unit admission, and maternal complications including cesarean section and preeclampsia. The study design also permits an analysis of whether mild GDM is associated with an increase in macrosomia and/or large-for-gestational-age infants compared with a similar normal nondiabetic population.

The study represents a combination of a randomized multicenter clinical treatment trial and observational cohort study (Fig. 1). Glucose screening is performed between 24 weeks, 0 days, and 29 weeks, 6 days, followed by a diagnostic 3-h glucose tolerance test. The oral glucose tolerance test is analyzed centrally with results forwarded to the Biostatistical Coordinating Center of George Washington University. Four groups of women are being enrolled. Women with mild GDM are centrally randomized to one of two groups (denoted groups I and IIA, respectively): Group 1: Formal nutritional counseling and diet therapy, along with insulin if required; Group IIA: No specific treatment.

In addition, women with a positive 50-g glucose challenge test, but with a normal subsequent oral glucose tolerance test, will be enrolled centrally in an observational cohort (denoted group IIB) matched by race and BMI (<27 kg/m^2, ≥ 27 kg/m^2) to the women randomized to "no treatment." Participating centers will be notified that a patient has been enrolled in group II and will thus be unaware of whether the individual is a mild GDM subject.

A group of nondiabetic control subjects with a negative 50-g glucose tolerance test (value <120 mg/dl) will also be enrolled by the clinical centers. Recruitment will be controlled by the Biostatistical Coordinating Center for nondiabetic patients in each race/BMI category. The race/BMI categories will be determined individually by center according to the racial distribution among the gestational diabetic women at that center. The nondiabetic control group (group III) will have demographics similar to those patients randomized to treatment (group I) (Table 1).

After central randomization (by the Biostatistical Coordinating Center after verification of eligibility), the clinical center will be notified only that a patient has been randomized to diet therapy (group I) or that she is in group II (no treatment). After enrollment by the Biostatistical Coordinating Center, women in group I receive nutritional counseling and are instructed on the technique of performing self-monitoring of blood glucose in both the fasting and postprandial states. Insulin therapy is reserved for individuals in which the majority of either fasting levels are ≥95 mg/dl or 2-h postprandial glucose levels are >120 mg/dl after 1 week of diet therapy. Oral hypoglycemic agents are not used for treatment.

Women with mild GDM not randomized to treatment (group IIA) are not clinically distinguishable from those with an abnormal screen and normal oral glucose tolerance test results (group IIB). Both of these groups as well as the non-GDM (group III) are not receiving any specific

Table 1—*Study group allocation*

Group	Population	Glucose challenge test	Oral glucose tolerance test: Fasting	Oral glucose tolerance test: 1, 2, 3 h	Treatment	Selection
I	Mild GDM	≥135 mg/dl	Normal	Positive	Yes	Randomized
A	Mild GDM	≥135 mg/dl	Normal	Positive	No	Randomized
II						
B	Non-GDM	≥135 mg/dl	Normal	Normal	No	Matched to I and IIA
	Non-GDM	<120 mg/dl	N/A	Normal	No	Matched to I

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dietary therapy except for general nutritional recommendations for pregnancy.

Routine antepartum fetal surveillance (nonstress testing) is not undertaken for group I until 40 weeks' gestation unless obstetric indications exist. Women in all study groups are instructed on daily assessment of fetal activity. Similarly, ultrasonography to assess fetal growth is limited to standard obstetrical indications. As ultrasonography may be used in treated individuals to assess fetal growth characteristics, these data will be collected.

Cord blood is being collected for all groups and is forwarded centrally for C-peptide determination. Infant birth weight is collected after delivery along with neonatal anthropometric assessment, including skinfold measurements, length, head circumference, and upper mid-arm circumference. A sample of heel stick blood is obtained for all infants to assess glucose and bilirubin levels.

A composite end point with clinically relevant components has been chosen as the primary outcome. This consists of perinatal mortality and morbidities that have been demonstrated to be associated with maternal hyperglycemia, specifically stillbirth, neonatal mortality, hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma.

Macrosomia was not chosen for the primary outcome, primarily because it represents a secondary result associated with birth trauma and therefore is not a health-based outcome. Comparison of macrosomia rates could also yield a biased result. Because obstetricians may be more likely to proceed with delivery earlier in women with GDM, fetuses destined to reach 4,000 g or a selected weight cutoff in the treated group may never reach this end point. Therefore, it is possible that the treatment could have an effect on the rate of macrosomia as a result of physician practice characteristics.

The secondary outcome measures for this study include fetal/neonatal outcomes such as macrosomia, large for gestational age, neonatal ponderal index, brachial plexus injury, fetal distress, and respiratory distress syndrome. Maternal secondary outcomes include cesarean section or operative delivery, maternal weight gain, preeclampsia, and length of stay.

STATISTICAL CONSIDERATIONS

We conducted a survey of the literature to determine the frequency of each component of the composite outcome in both treated and untreated GDM. The frequency of these morbidities varies widely, due to differences in treatment as well as in the populations studied. The morbidities are unlikely to be independent so that the frequencies cannot be summed for an overall frequency. However, it is assumed that in the untreated mild GDM population, the rate of hypoglycemia, hyperbilirubinemia, hyperinsulinemia (C-peptide >95th percentile), and birth trauma is likely to be 20–30%.

If the composite outcome in the untreated group is 25%, a sample size of 950 (475 per group) would be sufficient to detect a 30% reduction in the composite outcome. An effect size smaller than a 30% reduction would suggest that there is marginal benefit to treatment of mild GDM (type 1 error of 5% and power of 80%).

The primary evaluation of the clinical trial will be an intent-to-treat analysis based on the total cohort of patients randomized or enrolled. Standard statistical methods for rates and proportions will be applied for dichotomous variables, and the Wilcoxon's rank-sum test will be used to compare continuous variables. Statistical analysis will be adjusted for any differences in pretreatment factors among groups. Subgroup analyses will also be conducted if a treatment effect exists.

SUMMARY

There is apparent widespread acceptance of universal laboratory screening for GDM in the U.S., despite both the 2001 ACOG Technical Bulletin on Gestational Diabetes and the Fourth International Workshop-Conference on Gestational Diabetes failing to endorse this practice (4,18). The clinical dilemma of GDM was summarized during the Fourth International Workshop-Conference, which concluded that "although there is a general consensus that prevalence of GDM is increasing globally, there is considerable controversy about the clinical importance of GDM and the magnitude of its impact on mother and offspring" (14,18).

Similarly, the Canadian Task Force on Periodic Health Examination stated that "further research is needed to establish the relative risk of neonatal and perinatal illness in relation to various degrees of sub-diabetic elevations in maternal blood glucose levels. The quality of available evidence cannot support a recommendation to include universal screening for gestational diabetes" (15). Instead, this panel suggested that a decision to proceed with screening for this diagnosis must be made on other nonspecific grounds. This vague recommendation was accompanied by an admission that the Task Force recognized that a proportion of women with various degrees of carbohydrate intolerance during pregnancy will have adverse outcomes and might benefit from screening.

In 2003, the U.S. Preventative Services Task Force acknowledged that no well-conducted randomized controlled trial existed that provided direct evidence for the health benefits of screening for GDM (2). Whereas insulin therapy may decrease the incidence of fetal macrosomia in those pregnancies complicated by significant hyperglycemia, the magnitude of any effect on maternal and neonatal health remains uncertain. Moreover, the

Task Force report noted that insufficient evidence exists to determine if a health benefit accompanies treatment for the large number of women with GDM with milder degrees of hyperglycemia. A randomized controlled trial is necessary to answer this question (2). With mild GDM affecting 1–3% of pregnancies, ~50–100,000 women annually are being identified and treated for this diagnosis, making this an important clinical issue.

Most recently, Crowther et al. (19) reported results on a 10-year multicenter randomized trial designed to determine whether treatment of GDM reduces the risk of perinatal complications. The primary outcome of this study was a composite of perinatal morbidity and mortality (stillbirth, shoulder dystocia, bone fractures, nerve palsy, neonatal intensive care unit admission, and jaundice). The authors found the composite rate of "serious" perinatal complications was lower among the infants of the 490 treated women compared with the 510 infants in the routine care group (1 vs. 4%). This study represents the first large-scale randomized treatment trial for GDM. The sample size is remarkably similar to the ongoing MFMU trial; however, the Crowther study is different with respect to design and analysis of outcome data. Most importantly, the criteria used for the Crowther study include women with more significant hyperglycemia than the MFMU trial. Thus, our study should provide additional information regarding the effect of treatment of women with milder GDM.

The perinatal outcome composite in Crowther's study includes shoulder dystocia, a subjective diagnosis, which in turn weighed heavily on the composite difference observed among study groups. An increased rate of admission to the neonatal intensive care unit was observed in the treatment group; however, no difference was observed in the rate of hypoglycemia (secondary outcome) requiring intravenous therapy. Finally, details regarding several antepartum stillbirths suggest these may not have been related to untreated GDM such that the overall conclusion of a reduction in "serious" perinatal complications in treated GDM must be interpreted with caution. In contrast to the Crowther study, the MFMU Network trial primary outcome includes two markers of fetal response to maternal hyperglycemia: neonatal hypoglycemia and cord C-peptide levels. These outcomes should allow for a meaningful interpretation of any treatment effect in the subset of GDM with mild disease.

To date, few additional studies have examined the effectiveness of intensive treatment among women with mild GDM. A summary of four trials including 612 women with mild GDM found no benefit in dietary treatment in preventing adverse health outcomes (20). The ongoing population-based Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study is designed to determine levels of carbohydrate intolerance during pregnancy associated with adverse perinatal outcomes. Specifically, at what level of maternal glycemia is there fetal and/or maternal risk? A continuum of risk is anticipated as a likely result in the Hyperglycemia and Adverse Pregnancy Outcome study. The previously cited Crowther study and the ongoing MFMU trial address whether treatment of GDM is effective at reducing perinatal risk. Given that the MFMU Network trial considers only women with normal fasting glucose levels, it should help clarify whether a benefit exists to treatment of mild GDM. The trial should also complement the Hyperglycemia and Adverse Pregnancy Outcome study data in arriving at some consensus for selecting thresholds for diagnosis and treatment of carbohydrate intolerance during pregnancy.

APPENDIX — Other members of the National Institute of Child Health and Human Development MFMU Network are as follows: *Ohio State University*: J. Iams, C. Latimer; *University of Alabama at Birmingham*: D. Rouse, W. Andrews, A. Northen, J. Sheppard; *University of Texas Southwestern Medical Center*: B. Casey, K. Leveno, J. McCampbell, L. Moseley, D. Bradford; *University of Utah*: M. Varner, M. Belfort, B. Oshiro, K. Anderson, J. Parsons; *University of Pittsburgh*: S. Caritis, M. Cotroneo, M. Bickus; *Wake Forest University*: M. Harper, P. Meis. M. Swain, K. Lanier; *Drexel University*: A. Sciscione, M. DiVito, M. Talucci; *Wayne State University*: Y. Sorokin, S. Blackwell, G. Norman, P. Lockhardt; *Columbia University*: R. Wapner, R. Berkowitz, S. Bouseleiman, V. Carmona; *Brown University*: E. Chien, D. Catlow; *Northwestern University*: A. Peaceman, W. Grobman, G. Mallett. P. Simon; *University of North Carolina*: J. Thorp, K. Moise, K. Dorman, S. Brody, S. Timlin; *University of Texas at Houston*: S. Ramin, L. Gilstrap, D. Cross-Soebbing, J. Martinez; *Case Western Reserve University*: B. Mercer, P. Catalano, C. Milluzzi, C. Santori; *Vanderbilt University*: S. Gabbe; *The George Washington University Biostatistics Center*: C. Cobb, L. Leuchtenburg; *National Institute of Child Health and Human Development*: S. Pagliaro.

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