HHS Public Access

Author manuscript

Obstet Gynecol. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

Obstet Gynecol. 2018 August ; 132(2): 496–505. doi:10.1097/AOG.0000000000002726.

Research Gaps in Gestational Diabetes Mellitus: Executive Summary of an National Institute of Diabetes and Digestive and Kidney Workshop

Deborah J. Wexler, MD, MSc[1], **Camille E. Powe, MD**[1], **Linda A. Barbour, MD, MSPH**[2], **Thomas Buchanan, MD**[3], **Donald R. Coustan, MD**[4], **Rosa Corcoy, MD**[5], **Peter Damm, MD, DMSc**[6], **Fidelma Dunne, MD, PhD**[7], **Denice S. Feig, MD, FRCPC**[8], **Assiamira Ferrara, MD, PhD**[9], **Lorie M. Harper, MD**[10], **Mark B. Landon, MD**[11], **Sara J. Meltzer, MD, FRCPC, FACP**[12], **Boyd E. Metzger, MD**[13], **Hilary Roeder, MD**[14], **Janet A. Rowan, MD**[15], **David A. Sacks, MD**[16], **David Simmons, FRACP, MD**[17], **Jason G. Umans, MD, PhD**[18], and **Patrick M. Catalano, MD**[19]

[1]Diabetes Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA [2]Divisions of Endocrinology, Metabolism, and Diabetes and Maternal-Fetal Medicine, University of Colorado School of Medicine and Anschutz Medical Campus, Aurora, CO [3]Division of Endocrinology and Diabetes, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA [4]Women & Infants Hospital of Rhode Island and Warren Alpert Medical School of Brown University, Providence, RI [5]Diabetes Unit, Hospital de la Santa Creu I Sant Pau, Universitat Autonoma de Barcelona, Bellaterra, Barcelona, CIBER-BBN [6]Center for Pregnant Women with Diabetes, Department of Obstretrics, Rigshospitalet, Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark [7]College Medicine Nursing and Health Sciences, National University of Ireland Galway (NUIG), Galway, Ireland [8]Diabetes & Endocrine in Pregnancy Program, Mount Sinai Hospital and University of Toronto, Toronto, Canada [9]Division of Research, Kaiser Permanente Northern California; Oakland, CA [10]Department of Maternal-Fetal Medicine, Center for Women's Reproductive Health, University of Alabama at Birmingham, Birmingham, AL [11]Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, OH [12]Departments of Medicine and Obstetrics and Gynecology, McGill University Health Centre, Montreal, QC, Canada [13]Northwestern University Feinberg School of Medicine, Chicago, IL [14]Kaiser Permanente Southern California; San Diego, CA [15]National Women's Health, Auckland, New Zealand [16]Department of Research and Evaluation, Kaiser Permanente Southern California; Pasadena, CA [17]Campbelltown Hospital and Western Sydney University, Australia [18]MedStar Health Research Institute, Hyattsville, Maryland; Georgetown-Howard Universities Center for

Corresponding Author and Request for Reprints: Deborah J. Wexler, MD, MSc, MGH Diabetes Center, 50 Staniford Street, Suite 301, Boston, MA 02114, Tel: 617-726-8767, Fax: 617-726-6781, dwexler@mgh.harvard.edu.

Financial Disclosure

Peter Damm has participated in a multinational study on the use of insulin in pregnancy in collaboration with Novo Nordisk. No personal honorarium was received. Denice Feig led an investigator-initiated trial to which Apotex donated pharmaceuticals; Apotex has had no role in the design or interpretation of the study. Sara J. Meltzer has worked as an advisory board consultant for Astra-Zeneca, Medtronic, Novo-Nordisk, and Sanofi within the last 3 years. The other authors did not report any potential conflicts of interest.

Each author has indicated that he or she has met the journal's requirements for authorship.

Clinical and Translational Science, Washington, DC [19]Center for Reproductive Health, Case Western Reserve University at MetroHealth Medical Center, Cleveland, OH

Abstract

The National Institute of Diabetes and Digestive and Kidney Diseases convened a workshop on research gaps in gestational diabetes mellitus (GDM) with a focus on 1) early pregnancy diagnosis and treatment and 2) pharmacologic treatment strategies. This manuscript summarizes the proceedings of the workshop. In early pregnancy, the appropriate diagnostic criteria for the diagnosis of GDM remain poorly defined, and an effect of early diagnosis and treatment on the risk of adverse outcomes has not been demonstrated. Despite many small randomized controlled trials of glucose-lowering medication treatment in GDM, our understanding of medication management of GDM is incomplete, as evidenced by discrepancies among professional society treatment guidelines. The comparative effectiveness of insulin, metformin, and glyburide remains uncertain, particularly with respect to long-term outcomes. Additional topics in need of further research identified by workshop participants included phenotypic heterogeneity in GDM and novel and individualized treatment approaches. Further research on these topics is likely to improve our understanding of the pathophysiology and treatment of GDM to improve both short- and long-term outcomes for mothers and their children.

Introduction

Gestational diabetes mellitus (GDM), hyperglycemia first recognized in pregnancy, is a public health issue of global import. Its prevalence is increasing with the obesity epidemic and advancing age of motherhood. There has also been greater awareness of the risk associated with mild degrees of hyperglycemia in pregnancy since the Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO) demonstrated a linear relationship between adverse perinatal outcomes and increasing glucose levels at 24–28 weeks gestational age, without a clear inflection point (1).

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened the workshop “Research Gaps in Gestational Diabetes” to identify the major questions in this field. The workshop was held at the National Institutes of Health (NIH) in Bethesda, MD, August 2–3, 2017. NIDDK conveners and workshop co-chairs identified 1) early pregnancy diagnosis of GDM and 2) pharmacologic management of GDM as the two main topic areas for discussion. Participants were invited to give presentations in their areas of expertise, followed by participant discussion and proposal of other high-priority topics. This manuscript summarizes the proceedings of the workshop (Box 1).

Box 1

Research Gaps in GDM

I. Early pregnancy diagnosis and treatment
A. Diagnostic criteria and definitions

B. Alternative markers for diagnosis
C. Effect of early diagnosis and treatment on outcomes
II. Pharmacologic management
A. Pharmacokinetics and placental transfer of oral glucose-lowering medications
B. Effects of glucose-lowering medications on perinatal outcomes
C. Effects of glucose-lowering medications on long-term outcomes
III. Additional gaps
A. Phenotypic heterogeneity
B. Novel and individualized treatment

Session I: Research Gaps in Early Diagnosis of GDM

The question of early diagnosis of GDM is pressing because women diagnosed with diabetes earlier in gestation, as compared to typical diagnosis at 24–28 weeks, may be more likely to have adverse outcomes and a need for insulin or other glucose-lowering medications (2, 3). In fact, women with GDM diagnosis prior to 12 weeks gestation may have similar pregnancy outcomes to women with preexisting or “overt” type 1 or type 2 diabetes (4). Hyperglycemia early in pregnancy may also result in unfavorable fetal metabolic imprinting (5). However, data showing benefit of early treatment of GDM are lacking: a 2014 United States Preventive Services Task Force review concluded that there was insufficient evidence to recommend for or against screening for GDM prior to 24 weeks given lack of evidence for effect on maternal or infant health outcomes (6). During the workshop, three key areas regarding early diagnosis and treatment in GDM were identified as priorities for further investigation: A) Diagnostic criteria and definitions; B) Alternative markers for diagnosis; and C) Effects of early diagnosis and treatment on outcomes.

IA. Diagnostic criteria and definitions

The conference used the Fifth International Workshop Conference on Gestational Diabetes Mellitus definition: glucose intolerance with onset or first recognition during pregnancy (7). Based on the initial studies of O’Sullivan and Mahan, GDM has been diagnosed primarily in the second and third trimesters (8). The criteria for the 2-step method (50 g glucose challenge test followed by the 100 g 3-hour oral glucose tolerance test (OGTT)) derived from the work of Carpenter and Coustan (9) are currently accepted by both the American College of Obstetricians and Gynecologists (ACOG) and the American Diabetes Association (ADA), though ACOG also accepts the National Diabetes Data Group (NDDG) Criteria (10) rather than the old O’Sullivan and Mahan criteria. The HAPO Study also assessed glucose tolerance in late second and early third trimester, using the single step (75 g 2-hour OGTT), leading to the adoption of this approach by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and World Health Organization. There continues to be extensive debate regarding the criteria used to make the diagnosis of GDM and whether the criteria used, which have been derived in late pregnancy, apply to early pregnancy. Moreover, there is interest in establishing diagnostic criteria for GDM in early pregnancy

and determining whether early pregnancy GDM diagnosis and treatment could improve outcomes.

The physiologic changes in glucose metabolism across gestation have implications for early pregnancy diagnosis of GDM (7). In one of the few studies examining longitudinal changes in results of oral glucose tolerance tests (OGTTs) across trimesters of pregnancy, post-load glucose levels increased with each trimester (8). Continuous glucose monitoring (CGM) studies confirm the rise in mean glucose with advancing gestation: post-prandial glucose levels as well as duration of time per day spent above selected thresholds increase as pregnancy progresses (9). Some studies have shown that fasting glucose falls during the early first trimester of pregnancy, though this has not been a consistent finding, especially in women with pre-pregnancy BMI > 30 kg/m^2 (8, 10). These longitudinal changes in glucose metabolism complicate interpretation of glucose levels measured in early pregnancy for GDM diagnosis. Two crucial issues relevant to early vs. late diagnosis of GDM are whether glucose levels are already elevated in early pregnancy, which would allow early testing and diagnosis, and whether they rise more in women with GDM than in normal women, which would favor later testing and diagnosis.

The major professional organization guidelines differ on the definition of GDM in **early** pregnancy, with most applying the usual criteria regardless of the timing of detection of glucose intolerance. (11–17). Importantly, it is uncertain whether current diagnostic criteria are valid prior to 24 weeks. ACOG accepts either the 24-week Carpenter-Coustan or NDDG criteria applied to a 100 g oral glucose tolerance test (OGTT) in early pregnancy, but there are few data supporting this practice (13). The IADPSG recommends screening for “overt” diabetes in early pregnancy using American Diabetes Association (ADA) criteria for the diagnosis of type 1 or type 2 diabetes outside of pregnancy (11). When IADPSG criteria for GDM, rather than those for “overt” diabetes, are applied in early pregnancy, they may fail to detect metabolic abnormalities that can impact fetal development. In addition, early elevations in glucose levels may not portend persistent hyperglycemia (18). Indeed, studies have shown that diagnoses of GDM in early pregnancy were not always confirmed by 24–28 week testing (19, 20). In women with a diagnosis of GDM in early pregnancy, up to 60% may have a normal OGTT in later gestation because of several potential factors, including the glycemic physiology changes (7, 8, 10), the fetal glucose steal phenomenon (21), and the well-known poor reproducibility of oral glucose tolerance testing (22).

Finally, women may not present for prenatal care before 12 weeks gestation. Therefore, in practice, early diagnosis and treatment may include evaluation as late as 16 or 20 weeks gestation. This may be several weeks after the onset of maternal hyperglycemia which starts as early as 11 to 15 weeks.(23).

IB. Alternative Markers for Diagnosis

Given the poor reproducibility, cost, inconvenience, and diagnostic uncertainty of glucose tolerance testing in early pregnancy, there has been a search for alternate early pregnancy diagnostic markers of GDM. Hemoglobin A1c (HbA1c) is an obvious candidate, but this test would need to be validated against pregnancy outcomes, as would other glycemic measures. Many clinical centers perform an early pregnancy HbA1c to detect previously undiagnosed

overt diabetes. When comparing HbA1c prior to 20 weeks with IADPSG criteria at 24 weeks, women with HbA1c in the 5.7–6.4% range have a 27–29% rate of GDM (24). There is also evidence that a HbA1c of >5.9% at >24 weeks is associated with 2.6–3.6-fold risks of large for gestational age (LGA), macrosomia, caesarean delivery and hypertensive disorders, but its predictive value is less earlier in gestation (25). Newer technologies that may be routine in several years, such as continuous glucose monitoring (CGM), could be tested for diagnostic use, perhaps with both degree and duration of hyperglycemia incorporated into the definition of GDM.

Beyond glucose, other biomarkers may be useful in GDM diagnosis in early pregnancy. For example, potential biomarkers tested later in pregnancy include plasma glycated CD59 (pGCD59) which had high sensitivity and specificity for diagnosis of GDM when measured at 24–28 weeks and was associated with large for gestational age (LGA) birth weight (26). Another is 1,5-anhydroglucitol, which, when measured in the 3rd trimester, also predicted macrosomia with similar predictive value as HbA1c in a study of 82 women with type 1 DM (27).

IC. Effect of Early Diagnosis and Treatment on Outcomes

Participants emphasized that more information is needed about the association of early pregnancy glycemia with pregnancy outcomes. In most GDM prevention trials, in which the intervention usually takes place in early pregnancy or prior to pregnancy, the primary outcome is the diagnosis of GDM by OGTT at 24–28 weeks; less emphasis has been placed on clinical outcomes such as fetal overgrowth (28–32). Since maternal and fetal adverse outcomes are directly related to the degree of hyperglycemia (1, 33, 34), capturing the richness of continuous data relating dysglycemia to adverse outcomes was felt to be of paramount importance.

ID. Research priorities in early diagnosis and treatment

There are many ongoing studies of early GDM diagnosis and treatment GDM; four of these studies were reviewed by the participants to frame the discussion of research priorities (Table 1). Among these studies, there is variation in the criteria by and gestational age at which “early” GDM is diagnosed. All of the studies are examining the effects of early GDM treatment on the risk of maternal or neonatal perinatal outcomes.

Studying early (<20 weeks) versus late (24–28 week) diagnosis and treatment of GDM was of broad interest. Participants felt that emphasis should be placed on whether early screening, diagnosis, and treatment reduce short and long term adverse perinatal outcomes rather than just the subsequent diagnosis of GDM. There was some discussion of ethical concerns about not treating a diagnosis of GDM in early pregnancy in the context of a research study, as it was felt that the detrimental effects of hyperglycemia on fetal development are well known. However, given the lack of evidence supporting benefits of early treatment compared to the current standard of care (treatment later in pregnancy), participants felt that this issue should be addressed in a prospective manner rather than using retrospective analyses which could be subject to bias.

Session II: Research Gaps in Pharmacologic Management of Gestational Diabetes

One clear sign that there are research gaps in the appropriate pharmacologic management of GDM is the variation among professional organization guidelines (Table 2). The 2018 ACOG Practice Bulletin recommends insulin as first-line treatment in women with GDM who require a glucose-lowering medication; ACOG considers metformin to be second-line in those who decline insulin, and both metformin and insulin are preferred to glyburide (12, 35). The 2018 Society for Maternal-Fetal Medicine statement on treatment of GDM states that both metformin and insulin are reasonable first line treatments for GDM when diet and physical activity are not sufficient to achieve adequate glucose control (36). The 2018 American Diabetes Association (ADA) Standards of Care consider insulin to be first-line, but based on trans-placental fetal exposure to metformin being greater than glyburide, the ADA does not suggest a preference of one oral agent over the other (37). These conflicting recent guidelines highlight the need for further research comparing the effectiveness of insulin and oral agents in GDM.

As reflected in the guidelines, insulin is well accepted as a pharmacotherapy for GDM; most of the controversy regarding pharmacologic management relates to the use of oral glucose-lowering medications. Cochrane Reviews on this subject suggest that due to imprecision, risk of bias, and inconsistencies among studies, it is difficult to determine the relative benefits and risks of insulin versus glyburide versus metformin (38, 39). At the same time, use of oral glucose-lowering medications has become widespread (40, 41). For example, glyburide use in the treatment of GDM increased dramatically between 2000 and 2011 in the US, with glyburide use becoming more prevalent than insulin use in 2007 (41, 42).

Workshop participants identified three key areas of uncertainty with respect to pharmacologic treatment of GDM: A) Pharmacokinetics and placental transfer of oral glucose-lowering medications, B) Effects of glucose-lowering medications on perinatal outcomes, and C) Effects of glucose-lowering medications on long-term outcomes.

IIA. Pharmacokinetics and placental transfer of oral glucose-lowering medications

The pharmacokinetics of commonly used oral glucose-lowering medications in pregnancy were reviewed. Glyburide, a drug commonly used in the U.S. for treatment of hyperglycemia in GDM, has different pharmacokinetics in pregnancy than in the non-pregnant state. The dose-response relationship in pregnancy is not clear, with small studies suggesting the possibility of a ceiling effect on insulin secretion. Further, glyburide is often taken before bedtime or immediately before a meal; neither approach is rational since its peak effect on insulin secretion occurs 2–4 hours after dosing (43, 44). Though an older literature using insensitive assays of plasma glyburide suggested trivial placental transfer, more recent studies using sensitive assays reveal significant maternal-to-fetal transfer, which may at times be limited by the combined effects of placental metabolism of glyburide and fetal-to-maternal efflux transporters (45, 46). Recent data suggest that glyburide may also increase the expression of the primary placental glucose transporter, GLUT-1 (47), perhaps contributing to fetal overgrowth by increased nutrient transport.

The National Institute of Child Health and Human Development (NICHD) Obstetric-Fetal Pharmacology Research Unit (OPRU) Network performed a pharmacokinetic-pharmacodynamic (PK-PD) study of glyburide and found that glyburide concentrations were approximately 50% lower in women with GDM compared to non-pregnant women with T2DM for any given dose of glyburide (48). Although higher doses have neither been tested nor recommended in pregnancy, this reduction in glyburide levels during pregnancy suggests the need to explore different glyburide administration and dosing strategies. One possibility is that dosing of glyburide, as well as that of other medications, could be individualized, a strategy that is currently being tested (NCT03029702).

Metformin has dose-dependent absorption and bioavailability. The extended release formulation has not been studied in pregnancy. Metformin is transferred to the fetus with high fetal-to-maternal ratios; there are likely effects of a slowly equilibrating fetal compartment. The OPRU real-world PK study of serum levels in women taking metformin found that metformin clearance increased in mid-to late-pregnancy with increasing GFR, with a wide range of metformin concentrations in umbilical cord plasma and in breast milk post-partum (49). Results have not yet been reported for a completed PK-PD study comparing metformin, glyburide, and their combination in GDM (NCT01329016). Metformin has a wide array of cellular effects including growth inhibition, suppression of mitochondrial respiration, epigenetic modifications on gene expression, potential fetal nutrient restriction, and possibly alteration of postnatal gluconeogenic responses. The fetus (but not the embryo) expresses metformin transporters. These properties raise important questions about developmental programming of metabolic disease in offspring (50).

IIB. Effects of glucose-lowering medications on perinatal outcomes

A meta-analysis of 15 randomized controlled trials of drug treatment in GDM considered 14 primary and 16 secondary outcomes in 2,509 subjects (51). Compared to insulin, treatment with glyburide resulted in higher birthweight and more macrosomia and neonatal hypoglycemia. Compared to insulin, treatment with metformin resulted in less maternal weight gain, lower gestational age at delivery, and a reduction in neonatal hypoglycemia that approached statistical significance. In comparison with glyburide, treatment with metformin was associated with less maternal weight gain, macrosomia, LGA, and lower birth weight, but preterm birth was increased. However, treatment failure was higher for metformin than glyburide. A recent study (N=104) of glyburide vs. metformin and their combination, not included in the meta-analyses, showed relatively high rates of metformin intolerance, but the combination of these two oral medications reduced the need for insulin to 11% (52). One study has tested acarbose, but 42% of acarbose-treated participants ultimately required insulin; furthermore, use of acarbose is limited by gastrointestinal side effects (53–55).

In summary, glyburide appears to have comparable glycemic efficacy to insulin, but there is concern for higher rates of adverse perinatal outcomes and uncertainty regarding the optimal dosing strategy in pregnancy (56). Metformin may improve some perinatal outcomes compared to insulin, while possibly increasing the risk of prematurity, but this has not been consistent in all studies (51, 57, 58). Meta-analyses comparing oral agents with insulin for the treatment of GDM are limited by the methodology of the source trials. Specifically, the

diagnostic criteria for GDM and the target glucose levels are often unclear and not uniform. The severity of hyperglycemia is variable and influences the effectiveness of a given glucose-lowering medication. Most of the trials have been small, with wide confidence intervals around the effect estimates; workshop participants also questioned whether sample sizes from previous studies were large enough to assess short or long-term safety.

IIC. Effects of glucose-lowering medications on long-term outcomes

The relationship between pharmacologic treatment of GDM and long-term outcomes merits further study. Women with GDM have an increased risk of subsequent metabolic syndrome, dysglycemia, type 2 diabetes, and cardiovascular disease. Offspring have risks of obesity, metabolic syndrome, diabetes, and behavioral and neurodevelopmental conditions, potentially related to fetal programming in the intrauterine environment (59). In an observational analysis, hyperglycemia in pregnancy was associated with an increased risk of childhood obesity at 5–7 years, but there was no adjustment for maternal weight (5). By contrast, long-term follow up of a randomized trial of treatment of mild GDM, where insulin was used as pharmacologic treatment if needed, showed no effect on offspring BMI at 7 years, but girls had lower fasting glucose levels (60), suggesting no harm and possible benefit of insulin treatment.

There are some long-term follow-up data for metformin. In studies of metformin use in pregnant women with PCOS, offspring of mothers exposed to metformin weighed 0.5 kg more at 1 year, but their mothers were also heavier in the first trimester (61). In the Metformin in Gestational Diabetes (MiG) trial (62), children of mothers initially assigned to metformin during pregnancy had higher skinfold measurements but no difference in body fat percent by body composition measures or in neurodevelopmental outcomes at age 2 compared to offspring of women randomized to insulin (63). Of note, 46% of the women randomized to metformin also received insulin treatment during the pregnancy. Small subgroups of these children were followed for up to 7 or 9 years. There was no difference in total or abdominal body fat percent or metabolic measures between offspring exposed to metformin compared with those whose mothers were treated with insulin, but metformin offspring were larger by several measures at 9 years, including weight, waist and arm circumference, triceps skin fold, and waist-to-height ratio, with a trend to increased BMI and fat mass and fat-free mass by DXA (64).

There are no long-term maternal or child outcome data for glyburide.

IID. Research priorities in pharmacologic management of GDM

Participants extensively debated inclusion of glyburide in future interventional studies on the treatment of GDM. Some participants voiced concern about continued use of glyburide for GDM based on the current state of knowledge, which suggests potential inferiority. Others felt that strong consideration should be given to further research on glyburide since it is currently the most commonly used glucose-lowering medication for GDM in the United States and has lower placental transfer than metformin (45). Thus, after discussion, consensus emerged that future research of pharmacologic management of GDM should include all three commonly used agents: insulin, glyburide and metformin. Moreover,

optimal dosing of oral medications, with evaluation of pharmacokinetics, maternal blood levels, and cord blood levels, should be evaluated.

Since there are inadequate comparative data on perinatal outcomes associated with the use of each medication and scant data on long-term maternal and offspring outcomes related to oral medications, further study is warranted to evaluate the effect of pharmacologic interventions for GDM on both perinatal and long-term outcomes. Perinatal outcomes of interest include birth weight, preterm delivery, preeclampsia, gestational hypertension, neonatal adiposity, birth injury, C-peptide, hyperbilirubinemia, and hypoglycemia. Childhood long-term outcomes of interest include measures of childhood adiposity, metabolic dysfunction and cardiometabolic physiology. Maternal long-term outcomes of interest include post-partum development of T2DM, deterioration of beta cell function and postpartum weight retention and insulin resistance.

To accomplish these research goals, sample sizes in future research should to be large enough to examine safety endpoints, and study durations should ideally be long enough to evaluate long-term maternal and offspring outcomes.

Session III: Additional Research Gaps

The last session focused on topics in need of further research raised by workshop participants. Two areas emerged: A) Phenotypic heterogeneity and B) Novel and individualized treatment targets.

IIIA. Phenotypic heterogeneity

There is substantial metabolic heterogeneity in GDM. Although insulin secretion and sensitivity must be interpreted in tandem, some women with GDM may have a predominant defect in insulin resistance associated with inadequate beta-cell compensation, while others have a predominant defect in insulin secretion without excessive insulin resistance (65). The variable contribution of maternal obesity to GDM is another, related, source of heterogeneity (66, 67). Finally, many prior studies of GDM treatment have not been conducted in multi-ethnic U.S. populations, which may be especially heterogeneous in underlying pathophysiology and response to treatment. An understanding of sources of maternal and fetal heterogeneity could inform risk stratification of women with GDM, allowing for treatment intensification in high-risk GDM and while minimizing overtreatment of low-risk GDM.

IIIB. Novel and individualized treatment

Participants questioned whether we know the optimal glycemic targets for GDM treatment among various phenotypes of GDM and whether there are alternative non-glycemic targets. Recognition of the role of phenotypic heterogeneity in GDM suggests that treatment targets may need to be individualized. For example, glucose targets may need to be lower in pregnancies at higher risk for LGA. In line with this, glycemic risk thresholds might vary across different BMI categories and in different racial and ethnic populations. Alternative treatment targets may also be useful. Recent data suggest that maternal hyperlipidemia in GDM and obesity may contribute to fetal fat accretion (68). In a study of both obese and

normal weight women in whom diet was controlled, early fasting triglycerides and free fatty acids were a stronger predictor of neonatal adiposity than 24-hour glycemic measures (67, 69, 70).

Fetal growth, as estimated by ultrasound measurements, was also considered as a potential treatment target to be used clinically. A GDM treatment strategy based on fetal abdominal circumference at 28 weeks has been successful in several previous interventional studies but has not been recommended in ACOG or ADA guidelines (71–77).

Conclusion

Currently, it remains unclear whether diagnosis and treatment of GDM before 20 weeks gestation improves perinatal outcomes. The workshop participants concluded that potential diagnostic criteria using glycemic or other measures before 20 weeks but ideally at 12–14 weeks should be evaluated for association with GDM-associated adverse perinatal outcomes. In addition, prior to recommending widespread screening and or treatment of GDM prior to 24 weeks, such a practice should be demonstrated to improve clinical outcomes. Further, there is uncertainty regarding criteria that should be used to diagnose GDM early in gestation.

The relative effectiveness, safety, acceptability, and long-term outcomes associated with use of insulin versus metformin versus glyburide remain unclear. Future research should compare all three medications and focus on both perinatal and long-term maternal and child outcomes. Optimal dosing strategies should also be evaluated for each of these agents.

Further research on the topics outlined herein are likely to improve our understanding of the pathophysiology and treatment of GDM to improve both short- and long-term outcomes for mothers and their children. Research in this area would be facilitated by collaboration between maternal-fetal medicine specialists, endocrinologists, and pediatricians given the unpredictable timing of early pregnancy care and life course implications of GDM.

Acknowledgments

The authors thank the NIDDK and NICHD for convening the workshop, and Barbara Linder, Andrew Bremer, and Judith Fradkin for comments on earlier drafts of this manuscript. Deborah J. Wexler and Patrick M. Catalano were co-chairs and members of the planning committee. Camille E. Powe was a member of the planning committee.

The conference was funded by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health. Camille E. Powe is supported by career development awards from the NIDDK K23DK113218) and the Robert Wood Johnson Foundation’s Harold Amos Medical Faculty Development Program (74256).

References

1. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008 May 8; 358(19):1991–2002. [PubMed: 18463375]
2. Immanuel J, Simmons D. Screening and Treatment for Early-Onset Gestational Diabetes Mellitus: a Systematic Review and Meta-analysis. Curr Diab Rep. 2017 Oct 2.17(11):115. [PubMed: 28971305]

3. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications. Eur J Obstet Gynecol Reprod Biol. 2003 Jul 01; 109(1):41–4. [PubMed: 12818441]
4. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Constantino M, Harding AJ, et al. Gestational Diabetes Mellitus in Early Pregnancy: Evidence for Poor Pregnancy Outcomes Despite Treatment. Diabetes Care. 2016 Jan; 39(1):75–81. [PubMed: 26645084]
5. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care. 2007 Sep; 30(9):2287–92. [PubMed: 17519427]
6. Moyer VA. Force USPST. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014 Mar 18; 160(6):414–20. [PubMed: 24424622]
7. Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? Diabetes Care. 2007 Jul; 30(Suppl 2):S105–11. [PubMed: 17596457]
8. O'Sullivan JB, Mahan CM. Criteria for the Oral Glucose Tolerance Test in Pregnancy. Diabetes. 1964 May-Jun;13:278–85. [PubMed: 14166677]
9. Coustan DR, Carpenter MW. Detection and treatment of gestational diabetes. Clin Obstet Gynecol. 1985 Sep; 28(3):507–15. [PubMed: 3902304]
10. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018 Feb; 131(2):e49–e64. [PubMed: 29370047]
11. Catalano PM. Trying to understand gestational diabetes. Diabet Med. 2014 Mar; 31(3):273–81. [PubMed: 24341419]
12. Forest JC, Garrido-Russo M, Lemay A, Carrier R, Dube JL. Reference values for the oral glucose tolerance test at each trimester of pregnancy. Am J Clin Pathol. 1983 Dec; 80(6):828–31. [PubMed: 6356879]
13. Siegmund T, Rad NT, Ritterath C, Siebert G, Henrich W, Buhling KJ. Longitudinal changes in the continuous glucose profile measured by the CGMS in healthy pregnant women and determination of cut-off values. Eur J Obstet Gynecol Reprod Biol. 2008 Jul; 139(1):46–52. [PubMed: 18262325]
14. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, et al. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the diabetes in early pregnancy study. Metabolism. 1998 Sep; 47(9):1140–4. [PubMed: 9751245]
15. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010 Mar; 33(3):676–82. [PubMed: 20190296]
16. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018 Jan; 41(Suppl 1):S13–S27. [PubMed: 29222373]
17. Nankervis A, McIntyre HD, Moses RG, Ross GP, Callaway LK. Testing for gestational diabetes mellitus in Australia. Diabetes Care. 2013 May.36(5):e64. [PubMed: 23613605]
18. Thompson D, Berger H, Feig D, Gagnon R, Kader T, et al. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Diabetes and pregnancy. Can J Diabetes. 2013 Apr; 37(Suppl 1):S168–83. [PubMed: 24070943]
19. National Institutes of Clinical Excellence. Diabetes in Pregnancy. 2015.
20. World Health Organization. Diagnostic Criteria and Classification of Hyperglycaemia first Detected in Pregnancy. 2013.
21. McIntyre HD, Sacks DA, Barbour LA, Feig DS, Catalano PM, Damm P, et al. Issues With the Diagnosis and Classification of Hyperglycemia in Early Pregnancy. Diabetes Care. 2016 Jan; 39(1):53–4. [PubMed: 26519336]
22. Corrado F, D'Anna R, Cannata ML, Interdonato ML, Pintaudi B, Di Benedetto A. Correspondence between first-trimester fasting glycaemia, and oral glucose tolerance test in gestational diabetes diagnosis. Diabetes Metab. 2012 Nov; 38(5):458–61. [PubMed: 22595470]

23. Zhu WW, Yang HX, Wei YM, Yan J, Wang ZL, Li XL, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in china. Diabetes Care. 2013 Mar; 36(3):586–90. [PubMed: 23193214]
24. Desoye G, Nolan CJ. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. Diabetologia. 2016 Jun; 59(6):1089–94. [PubMed: 26995651]
25. Bonongwe P, Lindow SW, Coetzee EJ. Reproducibility of a 75g oral glucose tolerance test in pregnant women. J Perinat Med. 2015 May; 43(3):333–8. [PubMed: 25405716]
26. Carpenter MW, Canick JA, Hogan JW, Shellum C, Somers M, Star JA. Amniotic fluid insulin at 14–20 weeks' gestation: association with later maternal glucose intolerance and birth macrosomia. Diabetes Care. 2001 Jul; 24(7):1259–63. [PubMed: 11423512]
27. Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c >/=5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. Diabetes Care. 2014 Nov; 37(11):2953–9. [PubMed: 25190675]
28. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Tan K, Constantino M, et al. Baseline HbA1c to Identify High-Risk Gestational Diabetes: Utility in Early vs Standard Gestational Diabetes. J Clin Endocrinol Metab. 2017 Jan 1; 102(1):150–6. [PubMed: 27797673]
29. Ghosh P, Luque-Fernandez MA, Vaidya A, Ma D, Sahoo R, Chorev M, et al. Plasma Glycated CD59, a Novel Biomarker for Detection of Pregnancy-Induced Glucose Intolerance. Diabetes Care. 2017 Jul; 40(7):981–4. [PubMed: 28450368]
30. Nowak N, Skupien J, Cyganek K, Matejko B, Malecki MT. 1,5-Anhydroglucitol as a marker of maternal glycaemic control and predictor of neonatal birthweight in pregnancies complicated by type 1 diabetes mellitus. Diabetologia. 2013 Apr; 56(4):709–13. [PubMed: 23377619]
31. Rono K, Stach-Lempinen B, Klemetti MM, Kaaja RJ, Poyhonen-Alho M, Eriksson JG, et al. Prevention of gestational diabetes through lifestyle intervention: study design and methods of a Finnish randomized controlled multicenter trial (RADIEL). BMC Pregnancy Childbirth. 2014; 14:70. [PubMed: 24524674]
32. D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, et al. myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care. 2013 Apr; 36(4):854–7. [PubMed: 23340885]
33. D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, et al. Myo-inositol Supplementation for Prevention of Gestational Diabetes in Obese Pregnant Women: A Randomized Controlled Trial. Obstet Gynecol. 2015 Aug; 126(2):310–5. [PubMed: 26241420]
34. Simmons D. Prevention of gestational diabetes mellitus: Where are we now? Diabetes Obes Metab. 2015 Sep; 17(9):824–34. [PubMed: 25974384]
35. Dodd JM, McPhee AJ, Turnbull D, Yelland LN, Deussen AR, Grivell RM, et al. The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on neonatal health outcomes: the LIMIT randomised trial. BMC Med. 2014 Oct 13.12:163. [PubMed: 25315325]
36. Ferrara A, Weiss NS, Hedderson MM, Quesenberry CP Jr, Selby JV, Ergas IJ, et al. Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycaemia and hyperbilirubinaemia. Diabetologia. 2007 Feb; 50(2): 298–306. [PubMed: 17103140]
37. Ehrlich SF, Crites YM, Hedderson MM, Darbinian JA, Ferrara A. The risk of large for gestational age across increasing categories of pregnancy glycemia. Am J Obstet Gynecol. 2011 Mar; 204(3): 240 e1–6. [PubMed: 21247550]
38. Committee on Practice B-O. Practice Bulletin No. 180: Gestational Diabetes Mellitus. Obstet Gynecol. 2017 Jul; 130(1):e17–e37. [PubMed: 28644336]
39. SMFM Publications Committee. SMFM Statement: Pharmacological treatment of gestational diabetes. Am J Obstet Gynecol. 2018 Jan 31.
40. American Diabetes Association. 13. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018 Jan; 41(Suppl 1):S137–S43. [PubMed: 29222384]

41. Brown J, Grzeskowiak L, Williamson K, Downie MR, Crowther CA. Insulin for the treatment of women with gestational diabetes. Cochrane Database Syst Rev. 2017 Nov 05.11:CD012037. [PubMed: 29103210]
42. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. Cochrane Database Syst Rev. 2017 Jan 25.1:CD011967. [PubMed: 28120427]
43. Goh JE, Sadler L, Rowan J. Metformin for gestational diabetes in routine clinical practice. Diabet Med. 2011 Sep; 28(9):1082–7. [PubMed: 21679232]
44. Camelo Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK Jr, Jonsson Funk M. Trends in glyburide compared with insulin use for gestational diabetes treatment in the United States, 2000–2011. Obstet Gynecol. 2014 Jun; 123(6):1177–84. [PubMed: 24807336]
45. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med. 2000 Oct 19; 343(16):1134–8. [PubMed: 11036118]
46. Barbour LA, Davies JK. Comment on Nachum et al. Glyburide Versus Metformin and Their Combination for the Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Study. Diabetes Care. 2017; 40:332–337. [PubMed: 28077460] Diabetes Care. 2017 Aug.40(8):e115. [PubMed: 28733384]
47. Caritis SN, Hebert MF. A pharmacologic approach to the use of glyburide in pregnancy. Obstet Gynecol. 2013 Jun; 121(6):1309–12. [PubMed: 23812467]
48. Schwartz RA, Rosenn B, Aleksa K, Koren G. Glyburide transport across the human placenta. Obstet Gynecol. 2015 Mar; 125(3):583–8. [PubMed: 25730219]
49. Hebert MF, Ma X, Naraharisetti SB, Krudys KM, Umans JG, Hankins GD, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther. 2009 Jun; 85(6):607–14. [PubMed: 19295505]
50. Diaz P, Dimasuay KG, Koele-Schmidt L, Jang B, Barbour LA, Jansson T, et al. Glyburide treatment in gestational diabetes is associated with increased placental glucose transporter 1 expression and higher birth weight. Placenta. 2017 Sep.57:52–9. [PubMed: 28864019]
51. Hebert MF, Ma X, Naraharisetti SB, Krudys KM, Umans JG, Hankins GD, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther. 2009 Jun; 85(6):607–14. [PubMed: 19295505]
52. Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GD, et al. Pharmacokinetics of metformin during pregnancy. Drug Metab Dispos. 2010 May; 38(5):833–40. [PubMed: 20118196]
53. Lindsay RS, Loeken MR. Metformin use in pregnancy: promises and uncertainties. Diabetologia. 2017 Sep; 60(9):1612–9. [PubMed: 28770325]
54. Balsells M, Garcia-Patterson A, Sola I, Roque M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: A systematic review and meta-analysis. BMJ. 2015; 350:h102. [PubMed: 25609400]
55. Nachum Z, Zafran N, Salim R, Hissin N, Hasanein J, Gam Ze Letova Y, et al. Glyburide Versus Metformin and Their Combination for the Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Study. Diabetes Care. 2017 Mar; 40(3):332–7. [PubMed: 28077460]
56. Bertini AM, Silva JC, Taborda W, Becker F, Lemos Bebber FR, Zucco Viesi JM, et al. Perinatal outcomes and the use of oral hypoglycemic agents. J Perinat Med. 2005; 33(6):519–23. [PubMed: 16318615]
57. Zarate A, Ochoa R, Hernandez M, Basurto L. Effectiveness of acarbose in the control of glucose tolerance worsening in pregnancy. Ginecol Obstet Mex. 2000 Jan.68:42–5. [PubMed: 10774102]
58. Liang HL, Ma SJ, Xiao YN, Tan HZ. Comparative efficacy and safety of oral antidiabetic drugs and insulin in treating gestational diabetes mellitus: An updated PRISMA-compliant network meta-analysis. Medicine (Baltimore). 2017 Sep.96(38):e7939. [PubMed: 28930827]
59. Camelo Castillo W, Boggess K, Sturmer T, Brookhart MA, Benjamin DK Jr, Jonsson Funk M. Association of Adverse Pregnancy Outcomes With Glyburide vs Insulin in Women With Gestational Diabetes. JAMA Pediatr. 2015 May; 169(5):452–8. [PubMed: 25822253]

60. Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy:A systematic review and meta-analysis. Diabet Med. 2017 Jan; 34(1):27–36. [PubMed: 27150509]
61. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, et al. Treatments for gestational diabetes: a systematic review and meta-analysis. BMJ Open. 2017 Jun 24.7(6):e015557.
62. Gunderson EP, Chiang V, Pletcher MJ, Jacobs DR, Quesenberry CP, Sidney S, et al. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the Coronary Artery Risk Development in Young Adults study. J Am Heart Assoc. 2014; 3(2):e000490. [PubMed: 24622610]
63. Landon MB, Rice MM, Varner MW, Casey BM, Reddy UM, Wapner RJ, et al. Mild gestational diabetes mellitus and long-term child health. Diabetes Care. 2015 Mar; 38(3):445–52. [PubMed: 25414152]
64. Carlsen SM, Martinussen MP, Vanky E. Metformin's effect on first-year weight gain: a follow-up study. Pediatrics. 2012 Nov; 130(5):e1222–6. [PubMed: 23071212]
65. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008 May 8; 358(19):2003–15. [PubMed: 18463376]
66. Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. Diabetes Care. 2011 Oct; 34(10):2279–84. [PubMed: 21949222]
67. Rowan JA, Rush EC, Plank LD, Lu J, Obolonkin V, Coat S, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age. BMJ Open Diab Res Care. 2018 in press.
68. Powe CE, Allard C, Battista MC, Doyon M, Bouchard L, Ecker JL, et al. Heterogeneous Contribution of Insulin Sensitivity and Secretion Defects to Gestational Diabetes Mellitus. Diabetes Care. 2016 Jun; 39(6):1052–5. [PubMed: 27208340]
69. Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care. 2012 Apr; 35(4):780–6. [PubMed: 22357187]
70. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. BMJ. 2017 Feb 08.356:j1. [PubMed: 28179267]
71. Barrett HL, Dekker Nitert M, McIntyre HD, Callaway LK. Normalizing metabolism in diabetic pregnancy: is it time to target lipids? Diabetes Care. 2014 May; 37(5):1484–93. [PubMed: 24757231]
72. Harmon KA, Gerard L, Jensen DR, Kealey EH, Hernandez TL, Reece MS, et al. Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. Diabetes Care. 2011 Oct; 34(10):2198–204. [PubMed: 21775754]
73. Barbour LA, Hernandez TL, Hirsch NM, Reece MS, Chartier-Logan C, Friedman JE, et al. 211-OR/211 - Lipid Predictors of Infant Adiposity in Early and Late Pregnancy, Fasting and Fed. American Diabetes Association Scientific Sessions. 2017
74. Kjos SL, Schaefer-Graf U, Sardesi S, Peters RK, Buley A, Xiang AH, et al. 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. 2001 Nov; 24(11):1904–10. [PubMed: 11679455]
75. Schaefer-Graf UM, Kjos SL, Fauzan OH, Buhling KJ, Siebert G, Buhrer C, et al. A randomized trial evaluating a predominantly fetal growth-based strategy to guide management of gestational diabetes in Caucasian women. Diabetes Care. 2004 Feb; 27(2):297–302. [PubMed: 14747203]
76. Bonomo M, Cetin I, Pisoni MP, Faden D, Mion E, Taricco E, et al. Flexible treatment of gestational diabetes modulated on ultrasound evaluation of intrauterine growth: a controlled randomized clinical trial. Diabetes Metab. 2004 Jun; 30(3):237–44. [PubMed: 15223975]
77. Quevedo SF, Bovbjerg ML, Kington RL. Translation of fetal abdominal circumference-guided therapy of gestational diabetes complicated by maternal obesity to a clinical outpatient setting. J Matern Fetal Neonatal Med. 2017 Jun; 30(12):1450–5. [PubMed: 27554188]

78. Balsells M, Garcia-Patterson A, Gich I, Corcoy R. Ultrasound-guided compared to conventional treatment in gestational diabetes leads to improved birthweight but more insulin treatment: systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2014 Feb; 93(2):144–51. [PubMed: 24372329]

79. Buchanan TA, Kjos SL, Schafer U, Peters RK, Xiang A, Byrne J, et al. Utility of fetal measurements in the management of gestational diabetes mellitus. Diabetes Care. 1998 Aug; 21(Suppl 2):B99–106. [PubMed: 9704235]

80. Buchanan TA, Kjos SL, Montoro MN, Wu PY, Madrilejo NG, Gonzalez M, et al. Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. Diabetes Care. 1994 Apr; 17(4):275–83. [PubMed: 8026282]

Table 1

Select Ongoing Studies of Early Diagnosis and/or Treatment of GDM

Study Name	Principal Investigator/Institution	Target Sample Size	Key Inclusion Criteria	Intervention	Primary Outcome(s)
Early Screen and Treatment for Gestational Diabetes NCT02377531	Alejandro R. Rodriguez/University of South Florida	1020	BMI [†]>30 kg/m^2, 12–18 weeks gestation	2-step screening* and diagnosis at 12–18 weeks gestation followed by treatment if diagnosed	Composite perinatal morbidity
Pre-diabetes: can early INTervention improve pregnancy Outcome (PINTO) ACTRN12615000904572	Ruth Hughes/University of Otago	150	HbA1c [+] at <14 weeks gestation of 5.9–6.4%	Blood sugar monitoring beginning at <14 weeks gestation and medication as required	Preeclampsia; neonatal composite outcome
Early Gestational Diabetes Screening in the Gravid Obese Woman (EGGO) NCT01864564	Lori M. Harper/University of Alabama at Birmingham	960	BMI [†]≥30 kg/m^2, 14–18 weeks gestation, no prior cesarean-section	2-step screening* at 14–18 weeks gestation followed by treatment if diagnosed	Composite perinatal outcome
Treatment of Booking GDM (TOBOGM) ACTRN12616000924459	David Simmons/Western Sydney University	800	GDM by IADPSG criteria at <20 weeks gestation	Delayed GDM treatment (24–28 weeks); blinded	Pregnancy-induced hypertension; neonatal composite outcome

[†]BMI=body mass index.

[+]HbA1c=hemoglobin A1c *2-step screening: 50 gram non-fasting glucose load screening test followed by a 100 gram oral glucose tolerance test for diagnosis. (1)

Table 2

2018 Pharmacologic Treatment Guidelines for Gestational Diabetes Mellitus Not Responding to Nutrition Therapy

	Preferred and/or first choice	Alternative
American College of Obstetricians and Gynecologists (10)	Insulin	Metformin
American Diabetes Association (40)	Insulin	Metformin or Glyburide
The Society for Maternal Fetal Medicine (39)	Insulin or Metformin	Glyburide