Research Prioritization Topic Brief

Topic 8: “Gestational Diabetes”

Comparative effectiveness of medical, surgical and lifestyle treatment options in the prevention and treatment of gestational diabetes.

PCORI Scientific Program Area: Assessment of Prevention, Diagnosis and Treatment Options

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### Introduction

**Overview/definition of topic**

**DESCRIPTION OF CONDITION**
- Normal pregnancy increases the body’s need for insulin, resulting in increases in blood sugar.
- Some women do not produce enough insulin, or their bodies cannot use the insulin well enough.
- As blood sugar rises, the risk of certain adverse outcomes for mother and infant increase.
- Although the association between increasing blood sugar and increasing risk of adverse outcomes is continuous, there are different definitions for the threshold for distinguishing “gestational diabetes” (GDM) from “normal” elevations in blood sugar.

### Relevance to patient-centered outcomes

**SYMPTOMS/OUTCOMES**
- Increased blood sugar → more sugar available to the baby → larger baby than normal (relative proportions of different parts of baby’s body also different, affecting labor and delivery)
- Most common adverse outcomes of GDM related to larger babies
- Outcomes for babies
  - Short term
    - Shoulder dystocia
      - During labor, the head delivers but the baby’s shoulders get stuck—this is potentially fatal. However, the most common adverse outcome is injury to the nerves around the baby’s neck/shoulders, which can result in permanent disability to the baby.
    - Postdelivery hypoglycemia (low blood sugar)
    - Other respiratory and metabolic complications
  - Long term
    - Higher rates of obesity, hyperactivity/attention disorders, diabetes later in life (although unclear if treatment during pregnancy affects these outcomes)
- Outcomes for mothers
  - Short term
    - Association with preeclampsia (high blood pressure and protein in the urine, occasionally leading to seizures); increases risk of death for both mother and baby, sometimes necessitating premature delivery of the baby
    - Increased risk of Cesarean section (C-section), both because of difficult labor due to large baby and lower physician threshold regarding performing C-sections because of concerns about shoulder dystocia
    - Injury to the vagina, bladder, and/or rectum from large baby, which may lead to problems with incontinence, prolapse
    - NIH Consensus Panel noted paucity of data on quality of life, particularly anxiety
  - Long term
    - 5-10% of women diagnosed with GDM have overt diabetes, usually type 2, diagnosed immediately after pregnancy
    - 35-60% chance of developing overt diabetes in next 10-20 years
## Burden on Society

### Recent incidence and prevalence in populations and subpopulations

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<thead>
<tr>
<th>INCIDENCE (NEW CASES) &amp; PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)</th>
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<tr>
<td>• Rates of GDM vary across studies (in part due to varying definitions for GDM)</td>
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<td>• Using older definitions, rates of GDM range from 2-10% of pregnancies in the United States (of the approximately four million deliveries, 80,000-400,000 women, annually)²</td>
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<td>• New proposed definition would increase proportion of women diagnosed with GDM to 15-20% of pregnancies (600,000-800,000 women annually)³</td>
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<td>• Risk increased in some ethnic populations</td>
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<td>o African American</td>
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<td>o Hispanic/Latino American</td>
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<td>o Native American</td>
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<td>o Pacific Islander</td>
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<tr>
<td>• Risk increased in older women, obese women, and women with family history of diabetes</td>
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<td>o Incidence increasing over time as average age of pregnancy increases and prevalence of obesity in population increases</td>
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### Effects on patients’ quality of life, productivity, functional capacity, mortality, use of health care services

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<th>QUALITY OF LIFE</th>
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<td>• Diagnosis of GDM carries significant self-management burden for mothers (checking sugar levels multiple times a day)</td>
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<td>• Having a larger baby can cause birth trauma or more C-sections, which impact mother’s quality of life and recovery from birth</td>
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<td>• History of GDM is linked to a greater risk of the mother developing type 2 diabetes, type 1 diabetes, and cardiovascular disease later in life</td>
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<td>• Diagnosis of GDM may cause significant anxiety/concern over and above normal concerns about pregnancy</td>
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<th>PRODUCTIVITY</th>
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<td>• In the short term, C-sections have longer recovery than vaginal delivery and may interfere with mother-infant interaction in the delivery room.</td>
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<td>• In the longer term, a history of GDM increases the risk of other chronic illnesses (diabetes, cardiovascular disease). Developing these chronic conditions may impact mother’s future productivity.</td>
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<th>FUNCTIONAL CAPACITY</th>
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<td>• C-sections is associated with a higher rate of injury to some organs (bladder, bowel, blood vessels), infections (wound, uterus, urinary tract), and blood clotting complications (although absolute risks are low).</td>
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<td>• Children of mothers with GDM have higher rates of childhood obesity, hyperactivity/inattention disorders, and higher rates of developing diabetes later in life.</td>
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<th>MORTALITY</th>
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<td>• For fetus, greater risk of death near time of delivery</td>
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<tr>
<td>• For mothers, greater risk life-threatening preeclampsia</td>
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<td>• Absolute risk for death in both mother and infant low</td>
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How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?

- GDM is relatively common, and new definitions may make it even more common
- Short- and long-term effects on mother and infant
  - Significant impact on C-section utilization alone
- Major source of uncertainty is effect of changing screening practices/definitions, with two- to three-fold increase in number of women diagnosed with GDM and relative lack of data on benefits and harms in this broader population

Options for Addressing the Issue

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?

SYSTEMATIC REVIEWS/AVAILABLE DATA
- Ample systematic review data available regarding screening/diagnosis, prevention, and treatment of GDM
- However, available data based on studies conducted using different screening/diagnostic criteria—unclear how they would apply if criteria change

SCREENING/EARLY DIAGNOSIS
- Two main options for screening (usually between 24-28 weeks gestation, earlier for high-risk women)
  - “Two-step” approach traditional in the United States, recommended by American Congress of Obstetricians and Gynecologists (ACOG)^4-5
    - 50 grams of glucose taken orally without regard to whether woman has recently eaten
    - Blood glucose (sugar) measured 1 hour later
      - If less than cutoff, patient is “negative” and no further testing
      - If above cutoff, a second step (on another day) is performed, using 100 grams of glucose while patient is fasting; blood glucose measured before the dose and 1, 2, and 3 hours after and compared to cutoffs to make diagnosis.
    - This approach was originally developed to identify women at risk for developing diabetes later in life, not to identify women at high risk for GDM-related complications during pregnancy
    - Minimizes the number of women needed to fast for testing (can be difficulty/inconvenient during pregnancy)
  - “One-step” approach used internationally, recommended by International Association of Diabetes and Pregnancy Study Group (IADPSG) and American Diabetes Association (ADA)^3,6
    - 75 grams of glucose given while fasting
    - Fasting, 1-, and 2-hour levels compared against criteria
    - Some minor differences in definitions between two groups
    - IADPSG cutoffs based on pregnancy outcomes (glucose values associated with 1.75-fold increase in selected adverse outcomes)
  - Adoption of “one-step” approach would make US practice consistent with rest of world, but would increase number of women with diagnosis of GDM two- to three-fold
  - Recent NIH Consensus Conference (March 2013) concluded too little data about relative benefits and harms to recommend change^1

PREVENTION OF GDM
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<th>Lack of clear evidence on weight loss, diet, or physical activity before or during pregnancy to prevent GDM</th>
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<td><strong>TREATMENT</strong></td>
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<td>According to a recent AHRQ-sponsored systematic review, there is moderate evidence for reduction of preeclampsia, macrosomia (big baby), and shoulder dystocia with receipt of treatment for GDM (defined as treatments reducing maternal blood sugar levels)7</td>
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<td>o Diet/activity may be sufficient</td>
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<td>o If no response, insulin is standard of care, but uncertainty about safety of some preparations</td>
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<td>o Limited data on oral agents in the United States, none FDA-approved</td>
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<td>o Limited data on harms/benefits of different delivery management strategies (e.g., induction of labor)</td>
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<td><strong>PREVENTION OF LONG-TERM MATERNAL DIABETES</strong></td>
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<td>No data on effectiveness of strategies aimed at preventing long-term development of diabetes in women</td>
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What could new research contribute to achieving better patient-centered outcomes?

New research could contribute to achieving better patient-centered outcomes in certain key areas:

- **Diagnosis/screening:**
  - Further comparative-effectiveness research (CER) evaluating the timing of assessment for GDM could improve patient-centered outcomes (for both mothers and babies)
  - Further CER evaluating strategies for assessment of GDM (for example one-step vs. two-step strategy, 100 gram vs. 75 gram glucose tolerance tests) could improve patient-centered outcomes for both mothers and babies

- **Prevention**
  - Further CER exploring prevention of GDM through nutritional, exercise, and drug treatment strategies could improve patient-centered outcomes for both mothers and babies

- **Treatment**
  - Further CER exploring treatment of GDM through nutritional, exercise, and different pharmacologic strategies (including insulin, more established medications like glyburide and metformin, and newer medication classes) could improve patient-centered outcomes for both mothers and babies
  - In particular, further CER to identify safe and effective alternatives to insulin could improve patient-centered outcomes such as quality of life (because insulin imposes a greater self-management burden on mothers)

- **Development of GDM and overt diabetes**
  - Research to identify risk factors for GDM and subsequent development of overt diabetes could improve patient-centered outcomes for both mothers and babies
  - Potential risk factors could include maternal health behaviors (such as diet, physical activity, or breastfeeding), maternal metabolic measures (such as glucose tolerance test, insulin levels, or cortisol levels), comorbid conditions (such as advanced maternal age, hypertension, or hyperlipidemia), genetic factors (such as gene mutations, epigenetic factors, and gene-environment interactions)
  - Further CER exploring prevention of subsequent development of overt diabetes following GDM (through behavioral change strategies, lifestyle interventions, or pharmacologic strategies) could improve patient-centered outcomes for both mothers and babies

Have recent innovations made research on this topic especially compelling?

Recent innovations:

- With the availability of new classes of non-insulin-dependent diabetes medications in addition to better-established non-insulin-dependent diabetes medications, research on prevention and non-insulin-dependent treatment of GDM using these therapies is compelling
- As our understanding of the role of genetic factors in development of disease expands, new opportunities exist to explore novel questions about risk factors for the development of GDM and the development of overt diabetes after GDM (including gene mutations, epigenetic factors, and gene-environment interactions)

How widely does care now vary?

VARIABILITY IN CARE

- Widespread variation in delivery practices between types of providers (obstetricians, family practice physicians, nurse midwives) and within different groups
- Variability in postdelivery screening/testing
### What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?

**RECENT PUBLICATIONS**
- MEDLINE search, 1/1/2008 – 4/3/2013: total 575
  - 53 randomized controlled trials (RCTs)
  - 58 meta-analyses or systematic reviews

**ONGOING TRIALS**
- There are at least 125 ongoing studies listed in ClinicalTrials.gov
- NIH Reporter (a database of NIH funded studies) lists:
  - 129 projects
  - 146 publications

### How likely is it that new CER on this topic would provide better information to guide clinical decision making?

**KEY UNCERTAINTIES IN CLINICAL DECISION MAKING**
- What is the optimal timing and mode of GDM screening?
- What are the comparative benefits and harms of different behavioral strategies (diet, exercise) and drug treatments on mother and child outcomes?
- What is the optimal management of women diagnosed with GDM after delivery?
- What is the optimal management of children born to women with GDM?

**LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES**
- While there have been many systematic reviews on GDM, most point to a lack of well-designed, higher-quality studies. New, high-quality CER could contribute significantly to this area and provide needed guidance for clinical decision making.

### Potential for New Information to Improve Care and Patient-Centered Outcomes

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<th>What are the facilitators and barriers that would affect the implementation of new findings in practice?</th>
<th>FACILITATORS</th>
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<td>Common condition with serious outcomes that impact both mother and child.</td>
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<td>Pregnancy is a time of heightened patient activation. Thus, patient may be adherent to new behaviors at this time if prompted by physician.</td>
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<th>BARRIERS</th>
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<td>Variability in screening and diagnostic criteria may lead to differential implementation</td>
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<td>Cost of treatments</td>
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<td>Patient compliance with taking medications during pregnancy</td>
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<td>Uncertain how patients and providers weigh relative benefits/harms to mother vs. infant in event of competing risks; further research on this alone would be critical and have applicability beyond management of GDM</td>
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<tr>
<th>How likely is it that the results of new research on this topic would be implemented in practice right away?</th>
<th>EVIDENCE OF BENEFIT</th>
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<td>Likely to be implemented if clear evidence of better mother-child outcomes</td>
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<tr>
<th>EVIDENCE OF NO BENEFIT OR HARM</th>
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<td>Depending on practice, likelihood of stopping/decreasing practice may be variable. For example, to the extent that C-section rates are driven by provider concern about adverse outcomes and subsequent malpractice litigation, lack of evidence of benefit may still not lead to changes in practice.</td>
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Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?

- GDM is a relatively common condition with multiple uncertainties in diagnosis and treatment. It is likely that high-quality RCT evidence would remain current for several years.
- At current time, greatest controversy in this field is whether to adapt one-step screening, with consequent two- to three-fold increase in number of women diagnosed with GDM
  - Because the likelihood of benefits and harms and the ratio of benefits and harms will vary based on the underlying population, new research on prevention, treatment, and postpregnancy management would all need to be conducted.

REFERENCES:


APPENDIX: TOPIC QUESTIONS

Nominated by AHRQ

1. What are the effectiveness and safety of any of the second generation sulfonylureas compared to any insulin in the treatment of gestational diabetes with regard to the following: short- and long-term maternal outcomes, neonatal outcomes, and long-term offspring outcomes?

2. What are the effectiveness and safety of metformin compared to any insulin in the treatment of gestational diabetes with regard to the following: short- and long-term maternal outcomes, neonatal outcomes, and long-term offspring outcomes?

3. What are the comparative effectiveness and safety of various insulin regimens in terms of type/duration, dosing, and frequency of administration in the treatment of gestational diabetes with regard to the following: short- and long-term maternal outcomes, neonatal outcomes, and long-term offspring outcomes?

4. What are the effectiveness and safety of other hypoglycemic drug classes (eg, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, meglitinides) compared to any insulin or other hypoglycemic drugs in the treatment of gestational diabetes with regard to the following: short- and long-term maternal outcomes, neonatal outcomes, and long-term offspring outcomes?

5. What are the effectiveness and safety of elective labor induction at 40 weeks compared to expectant management in women with gestational diabetes with regard to the following: maternal and neonatal outcomes?

6. What are the effectiveness and safety of elective cesarean delivery at 40 weeks compared to expectant management in women with gestational diabetes with regard to the following: maternal and neonatal outcomes?

7. What is the evidence that maternal health behaviors (such as breastfeeding, physical activity, diet) are associated with the risk of developing type 2 diabetes or glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes?

8. What is the evidence that maternal metabolic measures (eg, fasting insulin levels, OGTT measures, HPA axis stress (subclinical hypercortisolism)) are associated with the risk of developing type 2 diabetes or glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes?

9. What is the evidence that comorbid conditions (eg, advanced maternal age, obesity, hypertension, hypercholesterolemia) are associated with the risk of developing type 2 diabetes or glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes?

10. What is the evidence that family history, gene mutations, genotypes, gene-environment interactions, epigenetic modifications, or other biomarkers are associated with the risk of developing type 2 diabetes or glucose intolerance/impaired fasting glucose among women with gestational diabetes? Are there differences in these associations by race or ethnic group?

11. What is the comparative effectiveness of various lifestyle interventions (eg, diet, physical activity, smoking) for prevention of type 2 diabetes, glucose intolerance/impaired fasting glucose, and obesity in women with a history of gestational diabetes?

12. What is the comparative effectiveness of various educational and behavioral change strategies (eg, patient education about diabetes risk, lactation support, diet, physical activity) for prevention of type 2 diabetes and glucose intolerance/impaired fasting glucose in women with a history of gestational diabetes?

13. What are the performance characteristics (sensitivity, specificity, and reproducibility) of a single fasting blood glucose test compared to the full 2-hour 75-gm OGTT in screening for type 2 diabetes and glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes? Does the accuracy of the fasting blood glucose test compared to the full 2-hour 75-gm OGTT vary with the postpartum testing interval in
screening for type 2 diabetes and glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes?

14. What are the performance characteristics (sensitivity, specificity, and reproducibility) of the HbA1c test compared to the 2-hour 75-gm OGTT in screening for type 2 diabetes and glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes? Does the accuracy of the HbA1c test compared to the full 2 hour 75-gm OGTT vary with the postpartum testing interval in screening for type 2 diabetes and glucose intolerance/impaired fasting glucose following a pregnancy with gestational diabetes?