Diabetes and Pregnancy

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Diabetes and Pregnancy

Overview/Classification
- Physiology of carbohydrate metabolism
- Associated anomalies
- Antepartum & intrapartum management
- Management of DKA
- Diagnosis and management of GDM

Pregestational Diabetes Overview

- Present in 1-2% of all pregnancies
  - 8 million patients in US
- Type II diabetes most common
  - Onset later in life
  - Peripheral insulin resistance
  - Relative insulin deficiency
  - Obesity
- Type I diabetes less common
  - Onset earlier in life
  - Autoimmune destruction of pancreatic beta cells
  - Predisposed to DKA

ACOG Practice Bulletin # 60 Reaffirmed 2016
### Priscilla White’s Classification

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<td>Duration less than 10 years and Age of onset greater than 19</td>
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<td>E</td>
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<td>Proliferative retinopathy</td>
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<td>H</td>
<td>Heart disease</td>
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<td>Renal transplant</td>
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### Carbohydrate metabolism in pregnancy

- Increased insulin resistance
- Reduced sensitivity to insulin
- Mediated by:
  - Placental lactogen
  - Progesterone & Estrogen
  - Prolactin
  - Placental growth hormone
    - Chorionic somatomammotropin
Carbohydrate metabolism in pregnancy

- Relative fasting hypoglycemia
- Caloric requirements increased by 300 kcal
- Insulin requirements increase 30% over course of entire pregnancy
- Glucose transported to fetus via carrier mediated facilitated diffusion
- Placental gradient yields fetal glucose 20-30 mg/dl less than maternal glucose levels

Congenital anomalies associated with pregestational diabetes

- Fourfold increase incidence of major congenital malformations
- Occurs in 6-12% of infants of diabetics
- Risk of anomaly directly related to level of maternal glycemic control
- HbA1C of 10% associated with 20-25% risk
- Underscores critical importance of preconceptional glucose control

Cardiovascular anomalies

- Ventricular septal defects
- Transposition of the great vessels
- Hypoplastic left heart syndrome
- Situs inversus
- Atrial septal defect
- Overall, 5-fold increased risk
Central nervous system malformations

- Anencephaly
- Meningomyelocele
- Encephalocele
- Holoprosencephaly
- Microcephaly
- 10-fold risk increase

Skeletal anomalies

- Spina bifida
- Caudal regression syndrome
  - Most characteristic diabetic embryopathy
  - 200-400 times more common in diabetics
  - Sacral agenesis

Preconceptional counseling

- Focus on importance of glycemic control before pregnancy to minimize morbidity
- Complete history and physical
- Glycosylated hemoglobin
- Ophthalmology consult, neurologic exam, EKG, maternal echo, 24-hour urine, TFT’s
- Clear discussion of fetal, maternal, and perinatal risks associated with diabetes and pregnancy
- Initiate prenatal vitamin with at least 800 mcg folic acid
Maternal Morbidity: Diabetic Retinopathy

- Background
  - Retinal microaneurysms
  - Dot-blot hemorrhages
- Proliferative
  - Neovascularization
  - Best treated with preconceptional laser therapy
  - Rapid institution tight glycemic control associated with acute progression of retinopathy
- Close surveillance warranted

Maternal morbidity: diabetic nephropathy

- Occurs in 5-10% of diabetic pregnancies
- With mild/moderate nephropathy, no permanent deterioration due to pregnancy
- With severe disease, progression to end stage disease more common
- Increased risk for HTN, uteroplacental insufficiency, iatrogenic preterm birth

Maternal morbidity: chronic hypertension

- Occurs in 5-10% of pregnant diabetics
- Increases risk of preeclampsia, uteroplacental insufficiency, IUFD
- Best controlled prior to pregnancy
- ACE inhibitors and angiotensin II receptor blockers contraindicated
- Baby aspirin prophylaxis
Management of diabetes

- Diet is foundation of all therapy
- Caloric requirements increase 300 kcal
- Registered dietitian consultation invaluable
  - 40-50% complex carbohydrates
  - 20% protein
  - 30-40% unsaturated fats
  - Distributed in 2/7, 2/7, 2/7, 1/7 pattern
- Artificial sweeteners safe in moderate amounts

Insulin requirements increase
- 0.7-0.8 U/kg/d first trimester
- 0.8-1 U/kg/d second trimester
- 0.9-1.2 U/kg/d third trimester
- Maternal euglycemia is goal
  - Fasting < 95 mg/dl
  - 2 hr post-prandial < 120 mg/dl
  - Mean glucose of 100 mg/dl
  - Overnight glucose not less than 60 mg/dl

Variety of insulin preparations useful
- Usually biosynthetic human insulin
- Regular, Novolog, Aspart
- Intermediate (NPH) and long acting
- Insulin pump effective for motivated patient
- Frequent self-monitoring critical
- Self-management of hypoglycemia important
  - Glucagon should be available
  - Frequent patient contact helpful
Management of DKA

Most commonly occurs in Type I diabetics
- Complicates 5-10% of pregnancies
- In pregnancy, develops more rapidly and at lower glucose values than non-pregnant

Risk factors include
- New onset diabetes
- Infections
- Poor patient compliance
- Insulin pump failure
- Beta mimetics (tocolytic) and corticosteroids

Clinical presentation
- Abdominal pain, nausea, vomiting, headache, malaise, weight loss, dry mouth, shortness of breath, polyuria, polydypsia

Laboratory findings
- Hyperglycemia, ketonemia, acidemia (pH<7.30), prerenal azotemia, anion gap, low serum bicarbonate (<15 mEq/L), severe volume depletion

Vigorous fluid replacement crucial
- 4-6 L in first 12 hours
- 1 L in first hour; 500-1,000 mL/h for 2-4 h

Parenteral insulin therapy
- Add glucose to infusion when glucose 250 mg/dL

Meticulous metabolic surveillance indicated

Monitor potassium; replacement usually needed
- Bicarb not indicated unless pH< 7.10

Diagnose and treat underlying etiology
- Question of fetal surveillance if fetus viable
Fetal management

- Confirmation gestational age: CRL
- MSAFP at 15-20 weeks for ONTD
- Targeted ultrasound at 16-20 weeks
- Fetal echocardiogram at 18-22 weeks
- Serial assessment of EFW

Obstetric complications

- Tied to severity of disease and level of control
- Increased perinatal morbidity/mortality
- Increased risk of preeclampsia
  - 15-20% without nephropathy
  - 50% with nephropathy
  - Baby aspirin prophylaxis (?)
- Underlying vascular disease in 10% diabetics
  - Fetal growth restriction
  - Indicated preterm delivery
  - Variable impact on nephropathy/retinopathy

Obstetric management

- Meticulous maternal glucose control
- Intensive third trimester fetal surveillance
  - NST, BPP, OCT, Doppler velocimetry (if IUGR)
- Women with diabetes are at increased risk for uncontrolled hyperglycemia and cesarean delivery. The optimal timing of delivery in diabetics depends on the severity of the condition, presence of comorbidities, and the occurrence of superimposed obstetric conditions.'
  - The provided recommendations are largely based on consensus expert opinion and extrapolations from relevant articles.
Obstetric Management
Timing of Delivery

- Timing Indicated Late-Preterm and Early-Term Birth
  - Catherine Y. Spong, Brian M. Mercer, et al
  - Obstet Gynecol 2011;118:323–33
- Diabetes—pregestational well controlled
  - LPTB or ETB not recommended
- Diabetes—pregestational with vascular disease
  - 37–39 wk
- Diabetes—pregestational, poorly controlled
  - 34–39 wk (individualized to situation)

Pregestational diabetes

Gestational diabetes

- Risk factors
  - Maternal age > 30
  - Obesity
  - Multiple gestation
  - Prior history of GDM
  - Macrosomia
  - Strong family history of DM
Maternal-Fetal risks with GDM

- Up to 70% lifetime risk Type II DM for mother
- Increased risk preeclampsia (10-20%)
- Fetal macrosomia
- Operative delivery
- Birth trauma including shoulder dystocia
- Neonatal metabolic instability
  - Hypoglycemia, hyperbilirubinemia

Impact of fetal macrosomia

- “Asymmetric” growth acceleration of infants of poorly controlled diabetic mothers
- Excessive fat deposition in shoulders, thorax, upper abdomen (insulin sensitive regions)
- Avoid mid-pelvic forceps with macrosomia
- With diabetes, risk of shoulder dystocia 20% at 4000g and 50% at 4500g
- With shoulder dystocia, 15% risk of fetal damage, of that 15%, 5% of infants have permanent sequelae

Diagnosis of GDM

- 50g 1-hr glucola challenge at 24-28 weeks
  - Cut-off 130-140 mg/dL
- 100g 3-hr oral GTT
  - Preparation diet may decrease false +’s
  - National Diabetes Data v. Carpenter/Coustan
    - FBS: 105  95
    - 1Hr:  190  180
    - 2Hr:  165  155
    - 3Hr:  145  140
Diagnosis of GDM Criteria Revisited

- Retrospective cohort study 1988-2001
  - Grouped patients into 3 categories
    - 3.3% (480) GDM by NDDG criteria
    - 5.1% (753) "GDM" by Carpenter/Coustan criteria
    - 9%: 180/155/140
    - Leaving 1.9% (273) as the study group
    - Received routine care
- Study group patients had statistically significantly higher risk for adverse outcomes compared to patients without GDM
  - Cesarean delivery OR 1.44
  - Operative vaginal delivery OR 1.72
  - Birth weight greater than 4500 g OR 4.47
  - Shoulder dystocia OR 2.24

Further, GDM patients diagnosed by NDDG criteria (treated) had significantly reduced risk (one fifth) for adverse pregnancy outcome compared to study patients (untreated patients by Carpenter/Coustan criteria)

- Birth weight greater than 4500 g OR 0.16
- Shoulder dystocia OR 0.21
- Outcomes due to persistent in utero hyperglycemia?

Authors recommend that Carpenter/Coustan criteria should be adopted to identify women at risk for adverse outcomes related to fetal hyperglycemia and to improve perinatal outcomes
International Association of Diabetes and Pregnancy

- Conference in June 2008; published 2010
  - 225 experts; 40 countries
  - To identify maternal glucose concentration resulting in an increased risk of 1.75 for adverse outcomes
- Diagnose GDM with ANY one of:
  - FBS > 92 but < 126
  - Overt DM if > 126
  - 1-hour 75-g oral glucose > 180
  - 2-hour 75-g oral glucose > 153
- Would increase rate of GDM to at least 18%

International Association of Diabetes and Pregnancy

- Recommended at 1st prenatal visit
  - Measure either hemoglobin A1c or random glucose or fasting glucose
    - If overt DM diagnosed, treat accordingly
      - FBS > 126, Hgb A1c > 6.5%; random glucose > 200
    - If FBS > 92 but < 126, GDM diagnosed
    - If FBS < 92, re-screen at 24-28 weeks
  - At 24-28 weeks
    - 2-hour 75-g OGTT after overnight fast
      - If FBS > 126, DM diagnosed
      - GDM diagnosed if 1-hour > 180 or 2-hour > 153

ACOG Committee Opinion #504 September 2011

- International Association of Diabetes in Pregnancy Study Group recommended a simplified “one-step” approach to the screening and diagnosis of GDM with a 75-g, 2-hour glucose tolerance test. Notably, adoption of these guidelines would result in GDM being diagnosed in approximately 18% of all pregnant women. Furthermore, despite recent randomized clinical trials demonstrating that the treatment of mild GDM reduces neonatal morbidity, there is no evidence that the identification and treatment of women based on the new International Association of Diabetes in Pregnancy Study Group recommendations will lead to clinically significant improvements in maternal and neonatal outcomes and it would lead to a significant increase in health care costs.
ACOG Committee Opinion #504
September 2011

- All pregnant women should be screened for GDM, whether by patient history, clinical risk factors, or a 50-g, 1-hour loading test to determine blood glucose levels.
- The diagnosis of GDM can be made based on the result of the 100-g, 3-hour oral glucose tolerance test, for which there is evidence that treatment improves outcome. Either the plasma or serum glucose level established by Carpenter and Coustan or the plasma level designated by the National Diabetes Data Group are appropriate.
- Diagnosis of GDM based on the one-step screening & diagnosis test outlined in the International Association of Diabetes in Pregnancy Study Group guidelines is not recommended at this time because there is no evidence that diagnosis using these criteria leads to clinically significant improvements in maternal or newborn outcomes and it would lead to a significant increase in health care costs.

Management of GDM

- Diet is foundation of effective therapy
  - 30 kcal/kg + 300 kcal for pregnancy
  - Carbohydrates 40%
  - Protein 20%
  - Fats 40%
  - Calories distributed 2/7, 2/7, 2/7, 1/7
- 70-80% of GDM patients maintain euglycemia with diet and moderate exercise
- Exercise too frequently not included
  - 30 minutes 5 times/week

Goals of therapy
- FBS less than 95
- 2hr post prandial less than 120
  - < 140 if 1hr post prandial is used

Intensity of glucose surveillance varies
- Random finger sticks in clinic
- 4 times (or more) daily self-monitoring
- Evidence suggests aggressive approach improves compliance, decreases macrosomia
Management of GDM

- Daily compared with weekly blood glucose monitoring in women with GDM A1
  - Reduced rates macrosomic infants
    - 29.5% vs 21.9%
  - Fewer LGA infants; 34.4% vs 23.1%
  - Reduced maternal weight gain
  - No change in cesarean birth rate
- Concluded that “Daily glucose self-monitoring, when compared to weekly office-based testing, is associated with lower risk of oversized neonate.”

Medical Management of GDM

When diet and exercise are not enough

- Three pharmacologic therapies used to treat GDM
  - Insulin, metformin, and glyburide
  - Despite decades of oral agent use, 2017 ACOG Practice Bulletin more strongly endorsed insulin as preferred first-line therapy
  - “Sparks flew”
    - No new evidence became available prompting change
    - 2015 and 2017 meta-analyses supported safety/efficacy of oral agents
- Insulin
  - 100 years of experience in pregnancy
  - Does not cross placenta
  - Requires multiple daily injections
  - Patient compliance and satisfaction issues

SMFM Statement: Pharmacologic treatment of gestational diabetes January 2018

Medical Management of GDM

When diet and exercise are not enough

- Metformin
  - Biguanide that decreases hepatic glucose production, increases peripheral tissue glucose uptake, and decreases glucose absorption
  - Associated with less maternal weight gain, less gHTN, less neonatal hypoglycemia
  - Readily crosses placenta, available data regarding offspring outcomes reassuring
- Glyburide
  - Sulfonylurea that increases pancreatic insulin secretion
  - Crosses placenta, no long term offspring outcome data available
  - Use increased from 7% to 65% in US from 2001 to 2011
  - Lower cost, better compliance, improved patient satisfaction
  - Comparisons based on meta-analyses
    - Most randomized trials of oral agents versus insulin relatively small and underpowered
    - 2015 Balsells et al (BMJ)
      - Glyburide: higher birth weight, more macrosomia, more neonatal hypoglycemia
      - Metformin: less maternal weight gain, fewer LGA infants, higher rate preterm birth
      - Conclusion: glyburide inferior to insulin and metformin; metformin superior to insulin.
Medical Management of GDM
When diet and exercise are not enough

- 2017 Farrar et al. (BMJ)
  - Metformin: lowest risk of neonatal hypoglycemia, macrosomia, LGA, preeclampsia, and NICU admission with comparable preterm birth risk
  - Conclusion: general trend favoring metformin over insulin and glyburide
- 2017 Bloon et al. (2 Cochrane reviews)
  - Insufficient quality evidence to assess whether one oral agent is superior to another or insulin
  - Choice to use one or the other reasonably based on physician/patient preference
- SMFM Publications Committee (January 2018) conclusion:
  - Metformin is a reasonable and safe first-line alternative to insulin
  - While concerns regarding glyburide (macrosomia/hypoglycemia) exist, the evidence of benefit of one oral agent over the other remains limited

ACOG Practice Bulletin February 2018
- When pharmacologic treatment of GDM is indicated, insulin is considered the preferred treatment for diabetes in pregnancy
- Metformin is a reasonable alternative choice for patients who decline insulin therapy or who the provider believes will be unable to safely administer insulin
- Glyburide should not be recommended as a first-choice treatment because, in most studies, it does not yield equivalent outcomes to insulin
- Providers should counsel patients of the limitations in safety data when recommending oral agents for treatment of GDM A2

Obstetric Management

- Challenging issues
  - Frequency and timing of EFW’s
    - Recognized inaccuracy of measurements
    - ‘Reasonable to assess fetal growth by ultrasound or clinical exam late in 3rd trimester to identify macrosomia’
  - How to appropriately interpret data to patient
  - May prompt ‘unnecessary’ intervention
  - Antenatal fetal surveillance
  - Good data demonstrating benefits don’t exist
  - GDM A1’s not at increased risk for IUFD
  - ‘No consensus regarding testing well controlled GDM A1s’
Obstetric Management
Timing of Delivery

- Timing Indicated Late-Preterm and Early-Term Birth
  - Obstet Gynecol 2011;118:323–33
- Diabetes—gestational well controlled on diet
  - LPTB or ETB not recommended
- Diabetes—gestational well controlled on medication
  - LPTB or ETB not recommended
- Diabetes—gestational poorly controlled on medication
  - 34–39 wk (individualized to situation)
- ACOG 2018 Recommendations
  - GDM A1: expectant management up to 40w weeks
  - GDM A2: delivery at 39-39w weeks

Postpartum evaluation

- 15-45% lifetime risk of developing overt DM

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Gaps in Antepartum GDM Screening and Postpartum Follow Up

- Quest Diagnostics data set
  - 68% of 924,873 pregnant pts screened
  - 19% of 23,299 GDM pts screened postpartum
  - Nationally based study demonstrates poor compliance with ACOG/ADA guidelines
Gaps in Antepartum GDM Screening and Postpartum Follow Up

- Literature documents low compliance with postpartum screening
- Failure to screen GDM patients postpartum results in at least 30% of patients with overt DM remaining undiagnosed
- Postal reminders sent to GDM patients and/or their physicians significantly increased rate of postpartum screening
  - Both received reminder: 60.5% screened
  - One received reminder: 55.3% (pt); 51.6% (MD) screened
  - No reminder: 14.3% screened

Diabetes and Perinatal Depression

- Retrospective cohort study (2004-2006)
  - 657 diabetics (gestational & pregestational)
  - 10367 non-diabetics
- Multivariate logistic regression
  - Adjusted for age, race, delivery year, gest age
- Women with diabetes had significantly greater risk of experiencing depression antenatal/postpartum
  - Odds ratio 1.85 (95% CI, 1.45-2.36)

Gestational Diabetes