A Healthy Beginning: Diabetes and Preconception Health

Erin C. Raney, Pharm.D., BCPS, BC-ADM
Professor of Pharmacy Practice
Midwestern University
College of Pharmacy-Glendale
Glendale, Arizona

Learning Objectives

• Describe the importance of preconception health to maternal and infant morbidity and mortality
• Discuss preconception lifestyle recommendations for reproductive age women with diabetes
• List recommended preconception assessments for microvascular and macrovascular disease for women with diabetes
• Describe preconception medication strategies to optimize glycemic control and medication safety during pregnancy

Diabetes in Pregnancy

Pre-gestational type 1 DM
Pre-gestational type 2 DM
Gestational diabetes

Approximately 2% of U.S. births
Am J Obstet Gynecol 2015;212:74.e1-9
Pregnancy-Related Risks

- Spontaneous abortion
- Macrosomia
- Fetal anomalies
- Type 2 diabetes in offspring
- Neonatal hypoglycemia
- Preterm labor
- Preeclampsia

Diabetes Management

- **During pregnancy**
  - Tight glycemic control
  - Fasting ≤ 90 mg/dL, 1-hr postprandial ≤ 130-140 mg/dL, 2-hr postprandial ≤ 120 mg/dL
  - Medical nutrition therapy
  - Pharmacologic agents
    - Sulfonylureas, metformin, insulin for GDM
    - Insulin for pre-gestational type 1 and type 2 DM

Preconception Care

"Preconception care is the provision of biomedical, behavioural and social health interventions to women and couples before conception occurs, aimed at improving their health status, and reducing behaviours and individual and environmental factors that could contribute to poor maternal and child health outcomes. Its ultimate aim is improved maternal and child health outcomes, in both the short and long term."  
[World Health Organization]  

Preconception Health Indicators

- 18.4% of women 18-44 reported receiving preconception counseling
- 54.2% reported drinking alcohol during the 3 months prior to pregnancy
- 25.1% reported smoking cigarettes during the 3 months prior to pregnancy
- 29.1% reported taking folic acid within 1 month prior to pregnancy
- 66.3% of women reported having a routine check-up within the year prior to pregnancy
- 54.2% reported drinking alcohol during the 3 months prior to pregnancy
- 45% of pregnancies are unintended

Preconception Counseling

What could we avoid EACH YEAR by providing preconception care for women with diabetes?

- 8397 preterm births
- 3725 birth defects
- 1872 perinatal deaths

National Initiative on Preconception Health and Health Care (PCHHC)
Clinical Toolkit

- National Preconception/Interconception Clinical Toolkit
  - "One Key Question:" Would you like to become pregnant in the next year?
    - Women who desire pregnancy in the next year
    - Women who are ambivalent about pregnancy in the next year
    - Women who do not desire pregnancy in the next year

Nutrition Status

Diane has been trying to improve her dietary choices and sees a possible pregnancy as an additional incentive. She does not take any nutritional supplements and is lactose intolerant.

Case Study

Diane is a 32 year old woman with type 2 diabetes diagnosed at age 30. She has determined that she is interested in conceiving within the next 1-2 years. She would like to stop using contraception (she has had a levonorgestrel IUD placed for 4 years).

Weight Management

Diane's BMI is now 29 kg/m². This is improved from 33 kg/m² 2 years ago. She finds it hard to exercise routinely due to her busy schedule.

Substance Use/Exposures

Diane does not smoke but she does drink 2-3 alcoholic beverages 3-4 times per week. She denies illicit drug use. She works as a human resources manager for a retail clothing chain.

Nutrition Status

- 600 IU daily Vitamin D
- 1000 mg daily Calcium
- 15 mg daily Iron
- 8-12 ounces of EFA containing seafood weekly
- Avoid high mercury content Fatty Acids
- 150 ug daily Iodine
- 400 mcg daily Folic Acid

Substance Use/Exposures

- Discuss risks of alcohol, tobacco, and illicit drug use prior to pregnancy
  - No safe level of alcohol use during pregnancy (associated risk for fetal alcohol syndrome)
  - Pharmacologic tobacco cessation methods generally not recommended for use during pregnancy
  - Many illicit drugs associated with pregnancy risk and long-term child developmental dysfunction
- Assess for environmental and occupational exposures

Weight Management

- Underweight
  - Assess risk for eating disorders
  - Review impact on preterm birth, low birth weight

- Normal BMI
  - Encourage weight maintenance and physical activity

- Overweight BMI
  - Counsel on long-term health risks
  - Encourage weight loss
  - Consider pregnancy risk with medications for weight loss

- Obese BMI
  - Same as overweight BMI
  - Consider lower efficacy of certain contraceptives
Immunizations and Pregnancy

Avoid During Pregnancy
- MMR (avoid pregnancy for 1 month after vaccine)
- Varicella/Zoster (avoid pregnancy for 1 month after vaccine)
- Influenza LAIV
- HPV

Give Only If Indicated
- Hepatitis A, Hepatitis B*
- Meningococcal conjugate/polysaccharide
- Pneumococcal polysaccharide*
- Polio

Give During Pregnancy
- Influenza (IIV)*
- Tdap

Avoid During Pregnancy
- Diane received all childhood vaccines and her last Td booster was 7 years ago. She has never received hepatitis A or B vaccines. She has never had chicken pox and doesn’t remember receiving the vaccine or pneumococcal vaccines. She does not usually get a flu shot.

Chronic Disease Management

Recommended preconception diabetes assessments
- Glucose control (A1C <6.5% recommended prior to pregnancy due to associated reduction in risk for congenital anomalies)
- Renal function assessment (urinary albumin-to-creatinine ratio/serum creatinine)
- Comprehensive eye exam
- Assessment of thyroid function
- HIV testing
- Up-to-date Pap test


Chronic Disease Management

Diane has a physical exam and laboratory assessments:
- Quarterly A1C for past year: 6.9%, 7.8%, 7.2%, 7.4% (most recent)
- Blood pressure: 128/82 mmHg (prior to medication 150/98)
- Renal function
  - Serum creatinine 1.1 mg/dL
  - Urinary albumin-to-creatinine ratio 14 mg/g
- FSH (To 156 mg/dL, 404, 44 mg/dL, UI, 15 mg/dL)
- Comprehensive eye exam WNL
- TSH 2.95 (0.5-4.7 mIU/L)
- HIV negative
- Most recent Pap test negative 1 year ago

Medication Safety

• General approach
  - Review medications for pregnancy risk
  - Identify potentially safer alternatives, if possible
  - Recommend effective contraception methods if high risk medications used
  - If pregnancy desired, plan transition period for medications and optimize other factors associated with disease control

Medication Safety

• Interpretation of pregnancy risk is complicated by available information
  - Limited clinical trial data
  - Oversimplification of risk with prior use of pregnancy letter categories
• Communication of risk prior to conception is also poor1,2
  - Studies indicate little attention given to contraception counseling for potentially teratogenic medications
  - ~50% of women receiving a prescription for a category D or X medication received contraceptive counseling

Medication Safety

• Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling
  - Newly approved prescription drug products as of June 30, 2015 must comply with this rule
  - Previously approved products (since 2001) will be phased in over time
  - Letter categories will be removed from all products over time

http://federalregister.gov/a/2014-28241

http://www.cdc.gov/vaccines/pubs/preg-guide.htm


2 Med Care 2010;48:834-842
Medication Labeling

Subsections of 8.1 and 8.2 include "risk summary," "data," and "clinical considerations.

Medication Safety

Non-insulin antidiabetics with the MOST safety data during pregnancy:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Primarily studied for GDM in comparison with insulin (appeared equal except higher risk for preterm birth)</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Most clinical evidence from use in GDM Glipizide and glimepiride have greater evidence of placental transfer Recent study of glyburide identified hypoglycemia risk (and other adverse pregnancy outcomes) versus insulin</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Limited data available for nateglinide (not recommended)</td>
</tr>
</tbody>
</table>

Diane’s medications include:

- Metformin 1000 mg BID
- Sitagliptin 100 mg once daily
- Lisinopril 5 mg once daily

Medication Safety

Diabetes-related medications

- Glucose control
  - Insulin
  - Non-insulin antidiabetic medications
- Blood pressure management and renal protection
  - Antihypertensives
  - Lipid management
  - Statins
  - Other antihyperlipidemics

Medication Class Considerations

- GLP-1 agonists: Limited human data, malformations in animal studies
- DPP-4 inhibitors: No human data, limited risk shown in animal studies
- SGLT-2 inhibitors: No human data, renal malformations in animal studies
- Thiazolidinediones: Limited human data, adverse pregnancy outcomes in animal studies
- Meglitinides: Limited human data, limited risk in animal studies
- Amylin mimetics: Limited human data, malformations in animal studies

Medication Safety

Insulin considered gold standard for treating DM during pregnancy

- Safety of regular and NPH insulin well established in clinical studies
- Experience with insulin lispro, insulin aspart, and insulin detemir appears positive
- Limited information available in humans on other insulin analogs in pregnancy

Clinical dilemma

- Obstet Gynecol 2013;122:1122-1131
- Diabetes Care 2016;39(Suppl 1):S1-119
Medication Safety

Select Medication Classed Considerations in Pregnancy with DM
ACE inhibitors/ ARBs/direct renin inhibitors CONTRAINDICATED (Category X in prior pregnancy risk format) Evidence of renal malformations, oligohydramnios, fetal growth restriction
Diuretics Thiuram diuretics typically avoided due to risk for reduced placental perfusion Spironolactone CONTRAINDICATED due to antiandrogen effects

Medication Safety

• Antihyperlipidemics
  – Use of statin therapy is first-line agent supported for use in non-pregnant patients with diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years with ASCVD or risk factors</td>
<td>Moderate to high intensity statin (&lt;consider use for ASCVD risk factors/high intensity for ASCVD&gt;)</td>
</tr>
<tr>
<td>40-75 years</td>
<td>Moderate to high intensity statin (high intensity for those with ASCVD/risk factors)</td>
</tr>
</tbody>
</table>

Medication Safety

• Non-statin antihyperlipidemics in pregnancy
  – Limited information on safety of bile acid resins, omega-3 fatty acids, niacin, ezetimibe during pregnancy
  – Limited human safety data for fibrates, but animal data indicate possible risk

• General approach in women of reproductive potential
  – Statins appropriate with the use of effective contraception
  – Colesevelam may be an option for women of childbearing age who require treatment but are not appropriate candidates for a statin (not shown noting to use effective contraception)

Medication Transition Plan

Diane’s medications include:
Metformin 1000 mg BID
Sitagliptin 100 mg once daily
Lisinopril 5 mg once daily

BP management (138/88 on medication)
• Avoid ACE inhibitor
• Consider nifedipine?
• Optimize diet, weight, exercise

Glucose control (A1C is 7.4%)
• Consider transition to insulin
• Optimize diet, weight, exercise

Family Planning

• Discuss development of a “reproductive life plan”
  – Set of personal goals about having or not having children, including a plan on how to achieve those goals based upon personal beliefs (marriage, abstinence, use of pharmacologic contraception, etc…)
Family Planning

Contraception and Diabetes

Medical eligibility criteria for contraceptives in women with diabetes

<table>
<thead>
<tr>
<th>DM Condition</th>
<th>CHC</th>
<th>POP</th>
<th>INJ</th>
<th>MP</th>
<th>LNG-IUD</th>
<th>Cu-IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GDM</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-vascular disease</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nephropathy/neuropathy</td>
<td>2/4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other vascular disease</td>
<td>3/4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus

1 = no restriction
2 = advantages of method generally outweigh risks
3 = risks of method generally outweigh advantages
4 = do not use

Contraception

- Considerations:
  - Hormone-based methods are often the most effective reversible option when high risk medications are used or if glycemic control needs improvement before pregnancy
  - If macrovascular or microvascular disease is present, certain progestin-only methods are preferred (Cu-IUD)
  - Blood pressure considerations are important with estrogen-containing products
  - Weight considerations:
    - Obesity affects the pharmacokinetics of hormonal contraceptives, but efficacy is not clearly impacted with most options (reduced efficacy with the contraceptive patch >90 lb)
    - Weight gain caused by contraceptives is often a concern; injectable medroxyprogesterone acetate and the copper IUD appear to be most associated

Summary

- Preconception care is appropriate to provide at all clinical visits with women of reproductive potential (not only for women planning pregnancy)
- Optimization of lifestyle factors, immunizations, and medication risks prior to pregnancy positively impacts pregnancy outcomes
- Reproductive life plans can enable women with diabetes to time pregnancy once maximal glycemic control and management of macrovascular and microvascular risk has been achieved

Additional Resources

- Before, Between, and Beyond Pregnancy [http://beforeandbeyond.org/]
- CDC [http://www.cdc.gov/preconception/index.html]
- CDC “Show Your Love” Campaign [http://www.cdc.gov/preconception/showyourlove/index.html]