The Effects of Diabetes During Pregnancy and Breastfeeding

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Conflicts of Interest
• No COI/Financial Relationship to disclose

Learning Objectives
1. Define teratogen, teratology, and teratogenicity
2. List birth defects, pregnancy complications, and breastfeeding issues related to uncontrolled diabetes
3. Describe the benefits and risks of diabetic medications during pregnancy and breastfeeding

Presentation Outline
• Introduction to Teratology
  – Pregnancy Facts, Causes of Birth Defects, and Basic Embryology
• Diabetes and Pregnancy
  – Birth Defects and Pregnancy Complications
  – Medications
• Diabetes and Breastfeeding
  – Short term and long term effects on the child and milk production
  – Medications
• MotherToBaby-TexasTIPS
Pregnancy Facts & Background

Pregnancy Facts

- 6 million pregnancies in the US per year
  - 50% pregnancies are unplanned
- 1/33 babies are born with a birth defect
  - Accounts for 20% (1/5) infant deaths

https://www.cdc.gov/pregnancy/index.html

Pregnancy Facts - Diabetes

- 3 million American women have diabetes
- 60 million women of reproductive age (18 – 44 years old) have diabetes
  - At least 40% of pregnancies of diabetic women are unplanned
  - Prevalence of birth defects among women with diabetes is estimated to be between 2.7%-18.6%
  - General population risk: 3-5%

Causes of Birth Defects

- Genetic: 20 - 25%
- Drugs/Chemicals: 4.5%
- Radiation: 4 - 5%
- Maternal infections: 2 - 3%
- Maternal metabolic factors: 1 - 2%
- Multifactorial/Unknown: 30%

Adapted from Teratology Primer from The Teratology Society

Background Risk

- Every pregnancy has a 3-5% risk for a birth defect
  - This is known as the background risk.
- 7 - 10% of birth defects are caused by prenatal exposures

What is a Teratogen?

- **Teratogen**
  - Any exposure during pregnancy that has a harmful effect on the developing embryo

- **Teratology**
  - The study of birth defects caused by exposures during pregnancy
### Examples of Teratogens

- **Medications**: ACE Inhibitors, Isotretinoin
- **Maternal Conditions**: Diabetes, Obesity
- **Maternal Infections**: Rubella, Syphilis, CMV
- **Other**: Alcohol, Cigarettes, Radiation
- **Illicit Substances**: Cocaine, Heroin

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### Potential Teratogenic Effects

- Pregnancy loss (miscarriage, stillbirth)
- Growth restriction
- Microcephaly (small head size)
- Patterns of major and minor birth defects
- Developmental delay
- Cognitive dysfunction or intellectual disability

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### Critical Periods of Development

![Diagram showing critical periods of development](#)
Diabetes and Pregnancy

Diabetes During Pregnancy

About 1-2% women who are pregnant have type 1 or type 2 diabetes and ~7-9% of all pregnancies are complicated by gestational diabetes.

Diabetes

- Uncontrolled diabetes in pregnancy is associated with an increased risk of fetal, neonatal, and long-term complications in the offspring.
- Risk for birth defects is significantly impacted by the women’s diabetic control

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal mortality</td>
<td>0.6-4.8</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>12-45</td>
</tr>
<tr>
<td>Prematurity</td>
<td>24-36</td>
</tr>
<tr>
<td>Congenital birth defects</td>
<td>9-27</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>9-47</td>
</tr>
</tbody>
</table>

Table adapted from https://www.uptodate.com/contents/infants-of-women-with-diabetes
Birth defects in infants of diabetic mothers

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Anencephaly, arhinencephaly, microcephaly, holoprosencephaly, neural tube defects</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Transposition of the great vessels, ventricular septal defect, coarctation of the aorta, atrial septal defect, single ventricle, hypoplastic left ventricle, pulmonic stenosis, pulmonary valve atresia, double outlet right ventricle truncus arteriosus</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Duodenal atresia, imperforate anus, anorectal atresia, small left colon syndrome, situs inversus</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Ureteral duplication, renal agenesis, hydronephrosis</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Caudal regression syndrome (sacral agenesis), hemivertebrae</td>
</tr>
</tbody>
</table>

Table adapted from: https://www.uptodate.com/contents/infants-of-women-with-diabetes

Insulin - Pregnancy

- Human insulin does not cross the placenta because of its high molecular weight.
- There are no associated pregnancy complications and/or birth defects with insulin use during pregnancy.
- Risks of uncontrolled diabetes during pregnancy are much higher than any known risks of insulin use.

- ACOG Recommendation - Insulin is the medication of choice for diabetes during pregnancy.
Metformin - Pregnancy

- Oral medication used to treat type 2 diabetes.
- Crosses the placenta and is present at levels similar to mother’s.
- Has not been shown to increase the risk for birth defects, miscarriages, or pregnancy complications.
- No data on long-term effects of drug use.
- ACOG – In instances when insulin is declined, can not be safely administered or is unaffordable → metformin is a reasonable choice.

Glyburide - Pregnancy

- Second-generation oral sulfonylurea
- From 2000-2011 the use of glyburide increased from <10% to >60% among women with gestational diabetes
- Crosses the placenta but has not been associated with increased risk of birth defects or pregnancy complications.
- A recent meta-analysis demonstrated higher rates of hypoglycemia in infants when compared to insulin
- ACOG: Should not be used as first choice because of transfer to placenta and theoretical long-term effects on offspring.

Dipeptidyl peptidase-4 inhibitors (Gliptins) - Pregnancy

- Januvia (Sitagliptin) - Oral medication used to treat type 2 diabetes.
- Based on experimental animal studies, sitagliptin is not expected to increase the risk of congenital anomalies.
- No large humans studies.
- A registry is following exposed human pregnancies:
  - Women can report pregnancy exposures to this agent to the Merck Pregnancy Registry for JANUVIA, 1-800-986-8999 or http://www.merckpregnancyregistries.com/januvia.html
Diabetes and Breastfeeding

Teratogen Basics - Breastfeeding

- There is a higher rate of transfer in colostrum (72 hours postpartum)
  - Absolute dose transferred is low due to low volume
- Once ingested by an infant, the medication must go through GI tract
  - Many break down in stomach or liver; never become systemic in infant
  - Bioavailability of medication is important

Summary
- Short half-life (1 – 3 hours)
- < 1 M/P ratio
- Low Vd (< 1)
- > 90% PB
- Short Tmax and avoid Tmax
- Low oral bioavailability
- High molecular weight (> 500 or 200 – 500)
- < 7.2 Pka
Diabetes and Breastfeeding

• Effect on infant from high maternal glucose levels
• Effect on milk production
• Long term effects on child development

Recommended
• More benefits than risks for mom and baby
• Can help moms control glucose levels
• Breastfeeding reduces risk of diabetes in breastfed infants

Diabetes and Breastfeeding - Complications

• Not well-controlled diabetes
  • High maternal glucose levels → high glucose levels in breastmilk
  • Hyperinsulinemia in infants → Hypoglycemia, food-seeking behaviors

• Delayed lactation in women with diabetes
  • Pregnancy complications, prematurity, birth defects, separation after delivery, etc.
Insulin - Breastfeeding

• Necessary for milk production
• Natural component of breast milk
• Necessary for the infant’s intestinal maturation
• May decrease the risk of Type 1 diabetes in breastfed infants (Shehadeh et al, 2001)

Mothers may require less insulin during breastfeeding
• Exogenous insulin does enter breast milk
• Peak levels about 30 – 50 minutes after IV injection
• Benefits of breastfeeding > Insulin-exposure

Ringholme et al, 2012; Roeder et al, 2016; Stanley et al, 1998

Insulin - Breastfeeding

• Small study measuring breastmilk insulin in non-diabetic mothers, mothers with T1DM, and mothers with T2DM
  – No differences in the amount of insulin among the three groups
    • T1DM group had entirely artificial insulin found in milk
  – Exogenous insulin enters breast milk similarly to endogenous insulin

Whitmore et al, 2012
**Metformin - Breastfeeding**

- Metformin does enter breastmilk in very low amounts
  - Infants receive < 0.5% of their mother’s dosage
- Milk metformin levels are relatively constant during maternal use
  - Therefore, timing breastfeeding around administration times is of little use
- No adverse effects in breastfed infants
  - Use with caution in infants with compromised kidney function (e.g. premature, polycystic kidneys, etc.)

**Glyburide - Breastfeeding**

- Glyburide does enter breastmilk in low amounts
  - Infants receive < 1.5% of their mother’s dosage
  - Case report of mother receiving 85mg, then 90mg in pregnancy
    - Milk levels postpartum were 7.3 mcg/L and 3.1 mcg/L at 3 and 6 days, respectively
      - Infant to receive no more than 0.01 mg/day
- No adverse effects reported in breastfed infants

**Sitagliptin - Breastfeeding**

- No data available
- Shorter half-life than most other dipeptidyl-peptidase IV inhibitors
  - May be preferred over others in this class
- Consider alternate medication in preterm infants and newborns
MotherToBaby–TexasTIPS

- For healthcare professionals and general public
- Inquiries addressed within 24 hours or next business day
- Call, text, email, online form
- Free information and counseling by teratogen information specialists (English and Spanish)
- 1-855-884-7248 (Toll Free)
- 7AM – 4PM, Monday – Friday

Resources

- MotherToBaby Fact Sheets (https://mothertobaby.org/)
- Reprotox (https://reprotox.org/)
- Call or text a Teratogen Information Service (TIS)!
References

• Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018


• https://reprotox.org
• https://mothertobaby.org/fact-sheets-parent/


• Hale, T., Medications and Mothers' Milk, 2012, 15th ed.

• https://www.cdc.gov/pregnancy/index.html