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Conflicts of Interest

- No COI/Financial Relationship to disclose

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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

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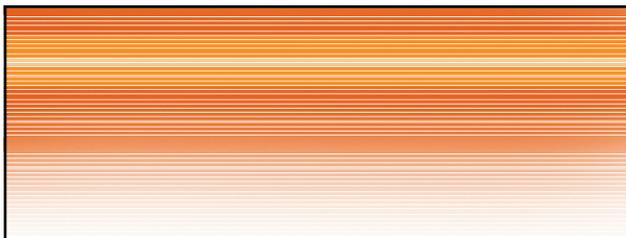
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Presentation Outline

- 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

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Pregnancy Facts & Background

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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



Spina Bifida Gastroschisis Cleft Palate Clubfoot

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

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Pregnancy Facts - Diabetes

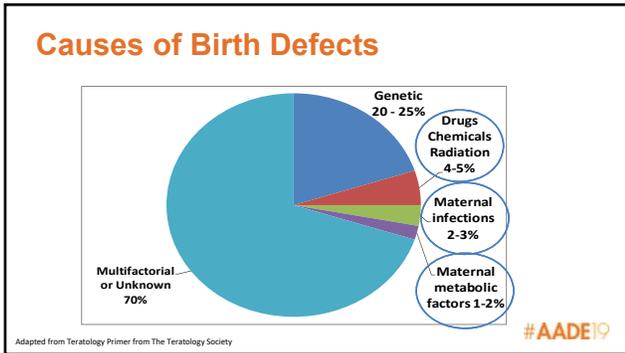


- 3 million American women have diabetes
- 60 million women of reproductive age (18 – 44 years old) have diabetes
 - At least 40% of pregnancies of diabetic women are unplanned
 - Prevalence of birth defects among women with diabetes is estimated to be between 2.7%-18.6%
 - General population risk: 3-5%

Gabbay-Benziv, R., Reeco, E. A., Wang, F., & Yang, P. (2015). Birth defects in pregestational diabetes: Defect range, glycemic threshold and pathogenesis. *World journal of diabetes*, 6(3), 481.

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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
 - TERATOGENS

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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

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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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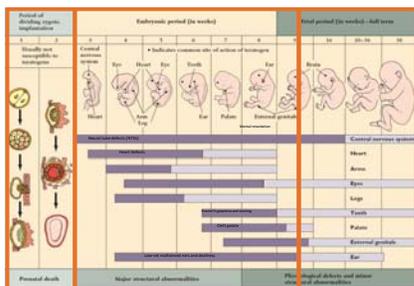
Potential Teratogenic Effects

- 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



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Diabetes and Pregnancy

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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.

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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

Condition	Rate (%)
Perinatal mortality	0.6-4.8
Cesarean delivery	32-45
Prematurity	24-36
Congenital birth defects	9-27
Macrosomia	9-47

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

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Pregestational Diabetes (Type I or Type II)	Pregestational and Gestational Diabetes
<ul style="list-style-type: none"> • <u>Congenital birth defects</u> • Cardiovascular • Neurologic • Gastrointestinal • Skeletal anomalies • Genitourinary • <u>Pregnancy complications</u> • Spontaneous abortions, stillbirth 	<ul style="list-style-type: none"> • <u>Pregnancy complications</u> • Preterm birth, C-section • Macrosomia → birth injury • Perinatal asphyxia • Respiratory distress • Hypoglycemia and hypocalcemia • Preeclampsia • Cardiomyopathy • <u>Long-term complications</u> • Obesity and T2D

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Birth defects in infants of diabetic mothers

System	Manifestations
Neurologic	Anencephaly, arrhinencephaly, microcephaly, holoprosencephaly, neural tube defects
Cardiovascular	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
Gastrointestinal	Duodenal atresia, imperforate anus, anorectal atresia, small left colon syndrome, situs inversus
Genitourinary	Ureteral duplication, renal agenesis, hydronephrosis
Skeletal	Caudal regression syndrome (sacral agenesis), hemivertebrae

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

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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.

Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018 Feb;131(2):e49-e54.

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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.

Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018 Feb;131(2):e49-e64.



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Glyburide - Pregnancy

- Second-generation oral sulfonylurea
- From 2000-2011 the use of glyburide increased from <10% to >60% among women with gestational diabetes¹
- 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 insulin²
- **ACOG**: Should not be used as first choice because of transfer to placenta and theoretical long-term effects on offspring.

1. Camello-Castro W, Roggeis K, Stummer T, Brodthurn MA et al, Benjamin DK Jr, Johnson 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):1173-84.

2. Song R, Chen L, Chen Y, et al. Comparisons of glyburide and insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2017;12:e0182468



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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>



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Diabetes and Breastfeeding

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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

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Teratogen Basics - Breastfeeding

Pregnancy Risk B		Lactation Risk L1	
$T_{1/2}$	= 2 hours	M/P	= 0.91–1.42
Vd	= 0.8–1.0 l/kg	PB	= 10–25%
T_{max}	= 10–60 minutes	Oral	= >85%
MW	= 151	pKa	= 9.5

Summary

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

Hale, T., *Medications and Mothers' Milk*, 2012, 15th ed. #AADE19

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Diabetes and Breastfeeding

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

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Diabetes and Breastfeeding

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

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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.

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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)

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Insulin - Breastfeeding

- 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

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

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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

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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.)

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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

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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

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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

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Resources

- Lactmed (<https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>)
- MotherToBaby Fact Sheets (<https://mothertobaby.org/>)
- Reprotox (<https://reprotox.org/>)
- Call or text a Teratogen Information Service (TIS)!

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MotherToBaby
 Fact Sheet
 by the Organization of Teratology Information Specialists (OTIS)
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Diabetes and Gestational Diabetes

In every pregnancy, a woman starts out with a 3-7% chance of having a baby with birth defects. This is called her background risk. This sheet talks about whether you may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your health care provider.

What is diabetes?
 Diabetes is a medical condition in which the body either does not make enough insulin or cannot use insulin correctly. Insulin is a hormone in the blood that is necessary for providing our cells with energy to function. Insulin helps sugar (glucose) move from the bloodstream into the cells. When glucose cannot enter our cells, it builds up in the blood (hyperglycemia). These high sugar levels can lead to damage of organs like the eyes and kidneys, and damage blood vessels and nerves.

There are different classes of diabetes. Some people have Type 2 diabetes (once called adult-onset diabetes). This means that the body does not produce enough insulin or the insulin it does make does not work well. In contrast, people with Type 1 diabetes (once called juvenile-onset diabetes or insulin-dependent diabetes) have a condition where the body does not produce any insulin at all. People with Type 1 diabetes need insulin injections and close monitoring to control their blood sugar levels.

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QUESTIONS?
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