MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Medication Teratogenesis and Pregnancy Complications

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose

Learning Objectives

1) Identify the timing and impact of medication exposures on fetal development

2) Describe the knowledge gaps in our understanding of medication safety

3) Demonstrate a general understanding of common obstetrical complications

Describing the Conundrum

- Most pregnancies are unplanned
- Many exposures occur prior to knowledge of pregnancy
- There are many conditions once thought to be incompatible with pregnancy that now have better outcomes but require medications
- Most medications have not been well studied in pregnant women

Adapted from Wood A. NEJM 1998

The Real Risk [1]

2-4% of newborns will have a malformation

- 9% due to maternal medical conditions
- 20-25% due to a genetic etiology
- 65% of unknown origin
- **Fewer than 1% due to drug exposures**

The Perceived Risk [2]

- Pregnant women given a medication *not* considered to be teratogenic **believed their risks of malformations was 24%**

1. Webster et al., Reproductive Toxicology 2001
2. 2. Koren G et al. AJOG 1989

Historical Perspective-Thalidomide

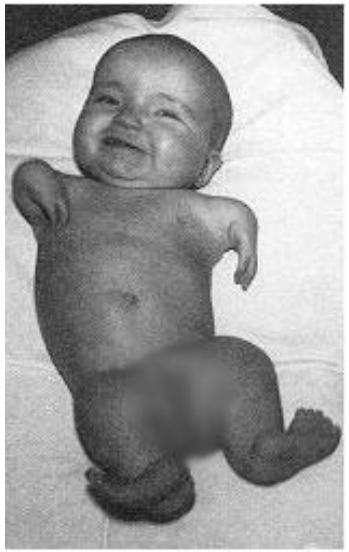
- The Thalidomide disaster of the 1960s shaped the way we think about medications in pregnancy

<u>Prior Beliefs:</u>

  - Placenta as a barrier
  - Animal Studies are always reliable

<u>The Scandal:</u>

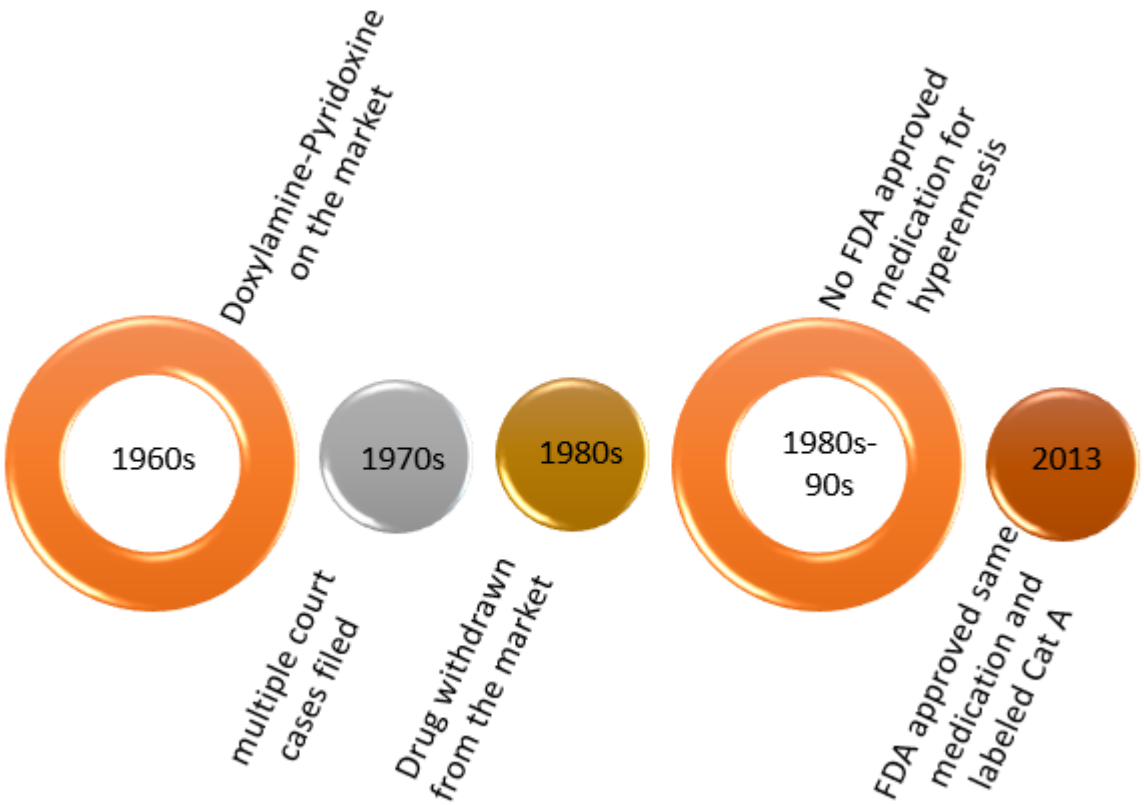
- Malformation rates of 20-30% with a characteristic pattern
- The public left uninformed for 4 years



Every drug could be "the new thalidomide"

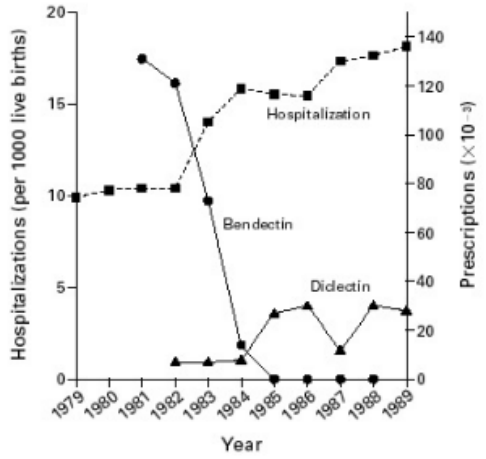
Wood, NEJM 1998

Bendectin
The new Thalidomide?



Adapted from Koren et al, NEJM 1998

Figure 1.



Rates of Hospitalization among Pregnant Women with Severe Nausea and Vomiting and Numbers of Prescriptions for Bendectin and Diclectin in North America, 1979 through 1989.

Human Teratogenesis

Definition: Any agent that acts to irreversibly alter growth, structure, or function of a developing fetus

Types:

- Viruses
- Environmental Factors
- Chemicals
- Therapeutic Drugs

Teratos: derived from Greek, meaning monster

Manifestations:

- Fetal growth restriction
- Pregnancy Loss
- Carcinogenesis
- Malformations in organ structure or function

Severity: varies greatly

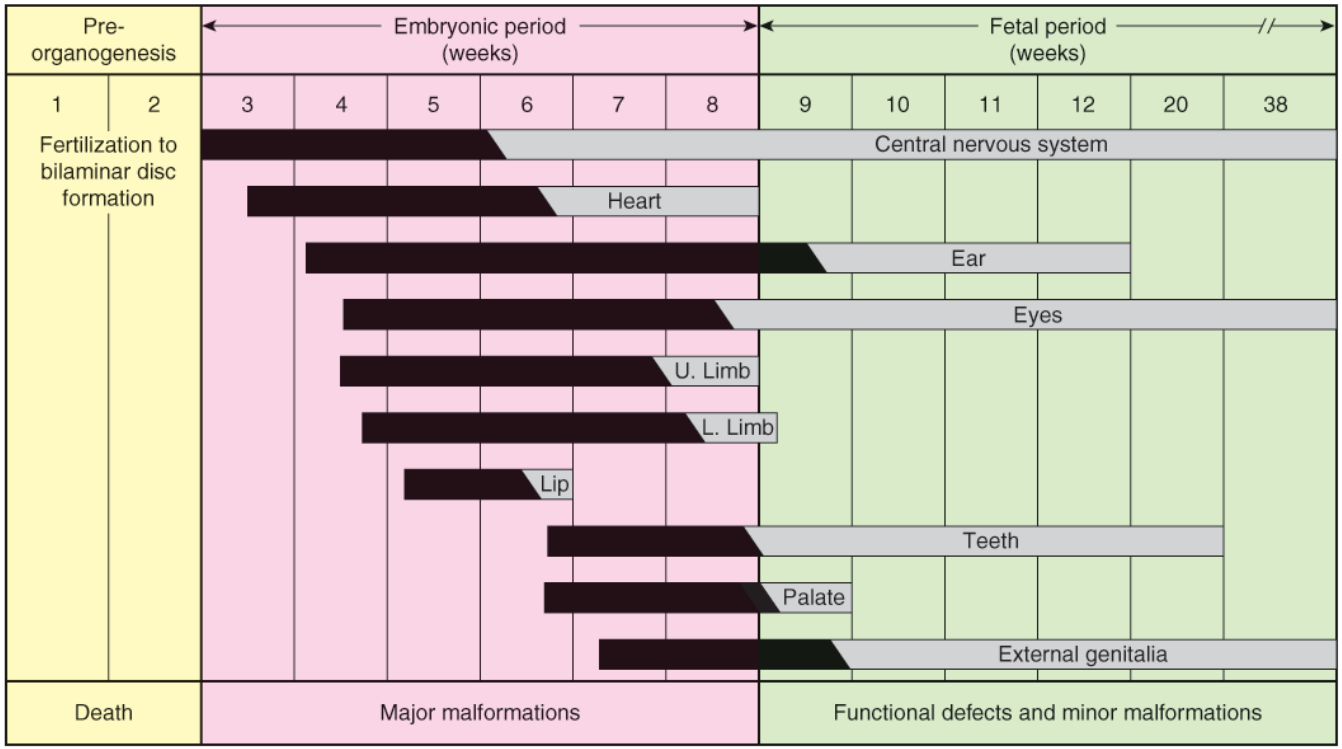
Buhinschi and Weiner Obset and Gynec 2009

Wilson's Principles of Teratogenesis

1) Susceptibility depends on the **genotype** of the conceptus
2) Susceptibility depends on the **timing** of exposure
3) Teratogenic agents act in specific ways initiating abnormal embryogenesis
4) Possible **manifestations** are: death, malformation, growth restriction and/or functional disorder
5) Access of adverse environmental influences depends on the **nature** of the agent
6) Abnormal manifestations can increase as **dosage** increases

Wilson JG: Current status of teratology—general principles and mechanisms derived from animal studies. 1977

Timing of Organogenesis During the Embryonic Period



Cunningham G, et al Williams Obsetrics 25th Edition

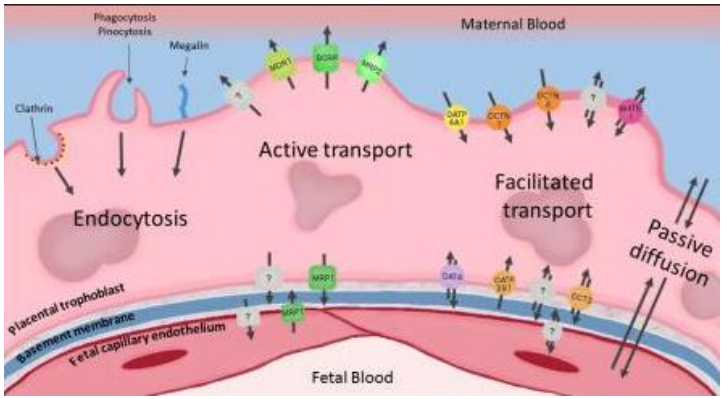
Factors That Impact Exposure

- Gestational Age
- Route of Exposure
- Absorption of the Drug
- Dose of the Drug
- Maternal Serum Levels
- Maternal and Placental Clearance system

Buhimschi and Weinerb Obstet and Gynecol Jan 2009

Placental Transfer of Medications

If a medication doesn't cross the placental barrier it is not a teratogen!



Factors that Effect Placental Transfer:

- Maternal Metabolism
- Gestational Age
- Protein Binding and Storage Capacity
- Charge (↑ionization=↑ passage)
- Liposolubility of the Drug (↑fat =↑passage)
- Molecule size
  - Substances < 500 Da diffuse rapidly
  - Substances > 500 Da more varied migration rates

Shepard's Criteria to Prove Teratogenicity

1) Proven exposure during critical times of human development
2) Consistent dysmorphic findings recognized in well-conducted epidemiologic studies
3) Specific defects or syndromes associated consistently with specific teratogens
4) Rare anatomic defects associated with environmental exposure
5) Proven teratogenicity in experimental animal models

Shepard TH Catalog of Teratogenic Agents 2007

Criteria for Evaluating Epidemiologic Studies About Medications

At Least **two** Epidemiologic Studies With:

(a)Exclusion of bias

(b)Adjustment for confounding variables

(c)Adequate sample size (power)

(d)Prospective Ascertainment if possible

(e)Relative risk (RR) of 3.0 or greater, some recommend RR of 6.0 0r greater

Or

For a **rare** exposure with a **rare** defect, **at least 3 reported cases**

Data from Shepard 1994, 2002a

Using Animal Data to Assess Human Risks

Method: Animals receive a wide range of doses during the period of organogenesis vs. untreated control animals

How Accurately Do Animal Studies Assess Human Risk?

- Fairly accurately!
- Thalidomide story led to the false belief that animal studies could not predict teratogenic effects in humans
- It is important to consider the dose given to animals

Koren G, et al. NEJM 1998

Pregnancy Risk Assessment

1979-2014

FDA Pregnancy Risk Categories

CATEGORY A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
CATEGORY B	Animal studies have revealed no evidence of harm to the fetus: however, there are no adequate and well-controlled studies in pregnant women. **OR** Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
CATEGORY C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. **OR** No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
CATEGORY D	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
CATEGORY X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.
CATEGORY NA	A US Food and Drug Administration pregnancy rating is not available.

2015-present

"Pregnancy and Lactation Labeling Rule"

- Replaced categories with narrative
- Drugs marketed after 2001 do not have categories

The Words We Use Matter

2% Risk of a Malformed Newborn

98% chance of an unaffected infant

Tripling or a 200% increase in Risk

1 per 1000 to 3 per 1000 increase risk or 99.7 percent likelihood of no affect

.. Williams Obstetrics Cunningham et al 2018 2. Jasper, Lancet 2001 3. Conover EA Am Journal of Genet C Semin Med Genet 2011

Presenting Risk Information[1]

- Review risks and benefits of untreated disease vs. medication exposure
- Chose words carefully
  - Frame in a positive rather than negative way
  - Site the **absolute risk** rather than the **odds ratio** [3]
- Remember most drugs are low risk teratogens that produce defects in 10 per 1000 maternal exposures [4]
- All women have a 3% risk of having a newborn with a birth defect
- The magnitude of risk may only be elevated 1 or 2 % from baseline with a drug exposure

1.. Williams Obstetrics Cunningham et al 2018 2. Jasper, Lancet 2001 3. Conover EA Am Journal of Genet C Semin Med Genet 2011 , Shepard Teratology 2002

Pregnancy Medication Safety Resources

BOX 7.3

Teratogen Information Databases

- IBM Micromedex: 6200 South Syracuse Way, Suite 300, Greenwood Village, CO 80111-4740; 800-525-9083 (in US and Canada); http://www.micromedex.com.ezp-prod1.hul.harvard.edu
- REPROTOX (Reproductive Toxicology Center): 7831 Woodmont Avenue, Suite 375, Bethesda, MD 20814; 301-514-3081; http://www.reprotox.org
- Mother to Baby: 200 W. Arbor Drive, #8446, San Diego, CA 92103-9981; 886-626-6847; http://mothertobaby.org

Pregnancy Complications

Miscarriage

- Rates are 11-22% of pregnancies 5-20 weeks end in miscarriage [1,2]
- 2/3 are clinically silent → **Consider an US at 6-8 weeks gestation**

Fetal Risk Factors

- 50% have a chromosomal abnormality [3]

Maternal Risk Factors

- Infections
- Medical Disorders
- Age

Controversial Risk Factors

- Cancer
- Surgical Procedures
- Nutrition
- Substance Use
- Caffeine Consumption
- Environmental Toxins
- Occupational Exposures

1. Avalos et al. Birth Defects Res A Clin Mol Teratol 2012 2. Wilcox et Al NEJM 1988 3. Jederny J Molec Cytogenetics 2014

OPINION

MEGHAN, THE DUCHESS OF SUSSEX

The Losses We Share

Perhaps the path to healing begins with three simple words: Are you OK?

Recurrent Miscarriage

- Definition: 3 or more consecutive pregnancy losses <20 weeks gestation
- Affects 1% of fertile couples

Widely Accepted Etiologies:

- Parental chromosomal abnormalities (2-4% of cases)
- Antiphospholipid antibody syndrome
- Structural uterine anomalies

40-50% of recurrent pregnancy loss is idiopathic [2]

2. Li et al, Fetil and Steril 2002

Miscarriage Management Options

- Expectant Management
  - Avoided due to high failure rates of up to 50%
- Medical Management
  - First trimester medication can be self administered at home
  - 5-20%→ will still need a procedure for retained products of conception [1]
  - Can be painful and traumatic to miscarry at home
  - Many patients prefer to avoid the operating room
- Surgical Management- D&C
  - Recurrent D&Cs can lead to uterine scarring

ACOG Practice Bulletin: Early Pregnancy Loss 2018

Stillbirth

- Definition: Death of a fetus greater than 20 weeks gestation
- Fetal mortality rate has been stable at 3-4/1000 in the US [1]

Causes of 512 Stillbirths in the Stillbirth Collaborative Research Network Study

Cause	Percent	Examples
Obstetrical complications	29	Abruption, multifetal gestation, ruptured membranes at 20–24 weeks
Placental abnormalities	24	Uteroplacental insufficiency, maternal vascular disorders
Fetal malformations	14	Major structural abnormalities and/or genetic abnormalities
Infection	13	Involving the fetus or placenta
Umbilical cord abnormalities	10	Prolapse, stricture, thrombosis
Hypertensive disorders	9	Preeclampsia, chronic hypertension
Medical complications	8	Diabetes, antiphospholipid antibody syndrome
Undetermined	24	Not applicable

Macdorman et al Obstet and Gynecol 2015

Stillbirth

Risk Factors:

- Advanced maternal age
- African -American race
- Smoking
- Illicit drug use
- Maternal medical diseases-overt diabetes, HTN
- Assisted reproductive technology
- Nulliparity
- Obesity
- Prior adverse pregnancy outcome

Only a small number of stillbirths have risk factors
and
routine surveillance based on risk factors does not effectively prevention occurrence [1]

1.Reddy UM et al , Obstet and Gynecol 2010

Stillbirth Management

Delivery Timing

- If counseled appropriately and medically stable delivery can be delayed
- Spontaneous labor will occur within 1-2 weeks of fetal death but increases the risks of complications.

Route :

Prior to 24 Weeks Gestation

- Dilation and evacuation is less morbid if technical expertise is available [1,2]
- Induction of labor is also an option

After 24 Weeks Gestation

- Vaginal delivery is most desirable because it is generally safer for the mother than cesarean
- Some women prefer cesarean to avoid to experience of labor and vaginal birth of a fetal demise

1. Bryant AG et al Obstet and Gynecol 2011, 2. Edlow AG et al Obstet and Gynecol 2011

Second Trimester Stillbirth Options Counseling

Dilation and Evacuation	Induction of Labor
Surgical environment	Labor and Delivery environment
Unable to see or hold intact fetus	Can hold fetus after delivery
Autopsy less informative	Full autopsy possible
Brief same day procedure	Hospitalization can be prolonged

Preterm Birth

Definition: delivery prior to 37 weeks gestation

US Rate: approx. 9.5%

Threshold of viability: 23-24 weeks

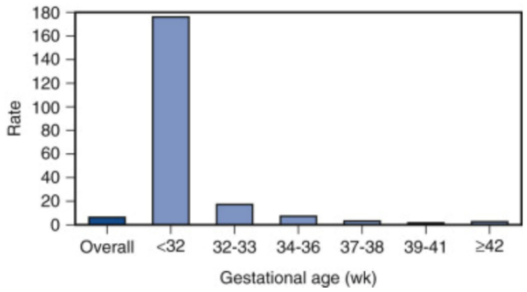


Fig. 36.4

Proportion of All Infant Deaths in the United States in 2008 by Gestational Age at Birth.

(Modified from Centers for Disease Control and Prevention. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2008 period linked birth/death data set. *Natl Vital Stat Rep.* 2012; 60[5]:1–27.)

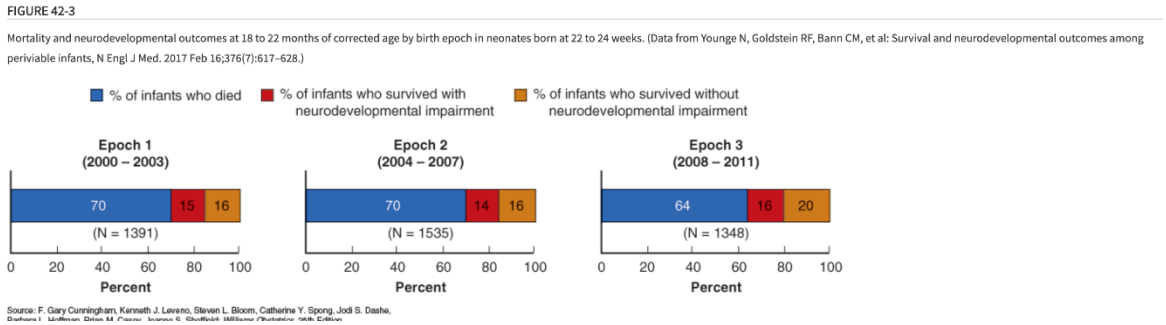


FIGURE 42-3

Mortality and neurodevelopmental outcomes at 18 to 22 months of corrected age by birth epoch in neonates born at 22 to 24 weeks. (Data from Younge N, Goldstein RF, Bann CM, et al: Survival and neurodevelopmental outcomes among periviable infants, N Engl J Med. 2017 Feb 16;376(7):617–628.)

Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Ivanna S. Sheffield: Williams Obstetrics, 25th Edition

Preterm Birth Complications

Major Short- and Long-Term Problems in Very-Low-Birthweight Infants

Organ or System	Short-Term Problems	Long-Term Problems
Pulmonary	Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity	Bronchopulmonary dysplasia, reactive airway disease, asthma
Gastrointestinal or nutritional	Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure	Failure to thrive, short-bowel syndrome, cholestasis
Immunological	Hospital-acquired infection, immune deficiency, perinatal infection	Respiratory syncytial virus infection, bronchiolitis
Central nervous system	Intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus	Cerebral palsy, hydrocephalus, cerebral atrophy, neurodevelopmental delay, hearing loss
Ophthalmological	Retinopathy of prematurity	Blindness, retinal detachment, myopia, strabismus
Cardiovascular	Hypotension, patent ductus arteriosus, pulmonary hypertension	Pulmonary hypertension, hypertension in adulthood
Renal	Water and electrolyte imbalance, acid-base disturbances	Hypertension in adulthood
Hematological	Iatrogenic anemia, need for frequent transfusions, anemia of prematurity	
Endocrinological	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

Data from Eichenwald, 2008.

Corticosteroids to Promote Fetal Lung Maturity

- 2 doses of dexamethasone or betamethasone at 24-34 weeks
- Lower rates of: [1]
  - Perinatal death
  - Neonatal death
  - Respiratory Distress Syndrome
  - Intraventricular hemorrhage
  - Necrotizing enterocolitis
  - Need for mechanical ventilation
  - Systemic infection in the first 48 hours of life

Roberts et al. Cochrane database 2017

Hypertensive Disorders of Pregnancy

Diagnoses: Gestational HTN, Mild Preeclampsia, Severe Preeclampsia, HELLP Syndrome, Eclampsia

Definition: spectrum of disorders with new onset HTN and significant end organ dysfunction

Incidence: 5% of pregnancies worldwide

Risk Factors: [1]

- First Pregnancy
- Prior pregnancy with preeclampsia
- Age>40 or <18
- Chronic Medical Conditions: HTN, renal, vascular, DM, autoimmune
- Multiple gestation
- Obesity
- Black Race
- New Partner

Duckitt et al BMJ 2005

Hypertensive Disorders of Pregnancy

- Pathophysiology: poorly understood-involves maternal and **placental** factors
- Typical Clinical Presentation:
  - Third Trimester
  - New onset Proteinuria
  - Lab abnormalities
  - New onset HTN
  - Headache, vision changes, RUQ pain
  - Fetal Growth Restriction
- Management: Delivery vs. Expectant Management--> depends on disease severity and gestational age
- Prevention: Baby ASA is the only evidence based intervention

Gestational Diabetes

Definition: glucose intolerance diagnosed in pregnancy

Etiology: predisposing risk factors + placental hormones

Incidence: 6% of pregnancies in the US

Screening: Universal

Treatment:

- BG checks 4 times a day
- Diet
- Medications (insulin or Metformin)

Women with GDM have a 50% chance of developing Type 2 Diabetes later in life

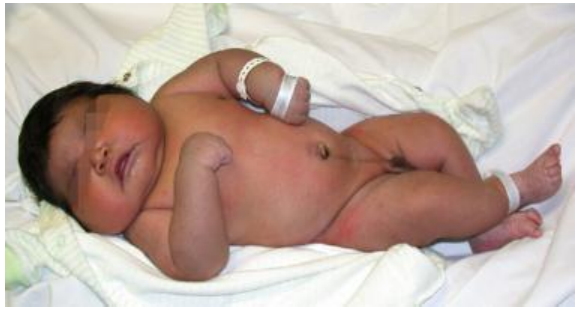
Gestational Diabetes and Adverse Pregnancy Outcomes

Maternal Risks

- Preeclampsia
- Increased cesarean section rates
- Increased risk of Type 2 DM later in life

Fetal Risks

- Macrosomia (BW > 4000 g)
- Shoulder Dystocia
- Neonatal Hypoglycemia
- Birth Injuries
- Possible metabolic effects



Preconception Optimization

Core Interventions:

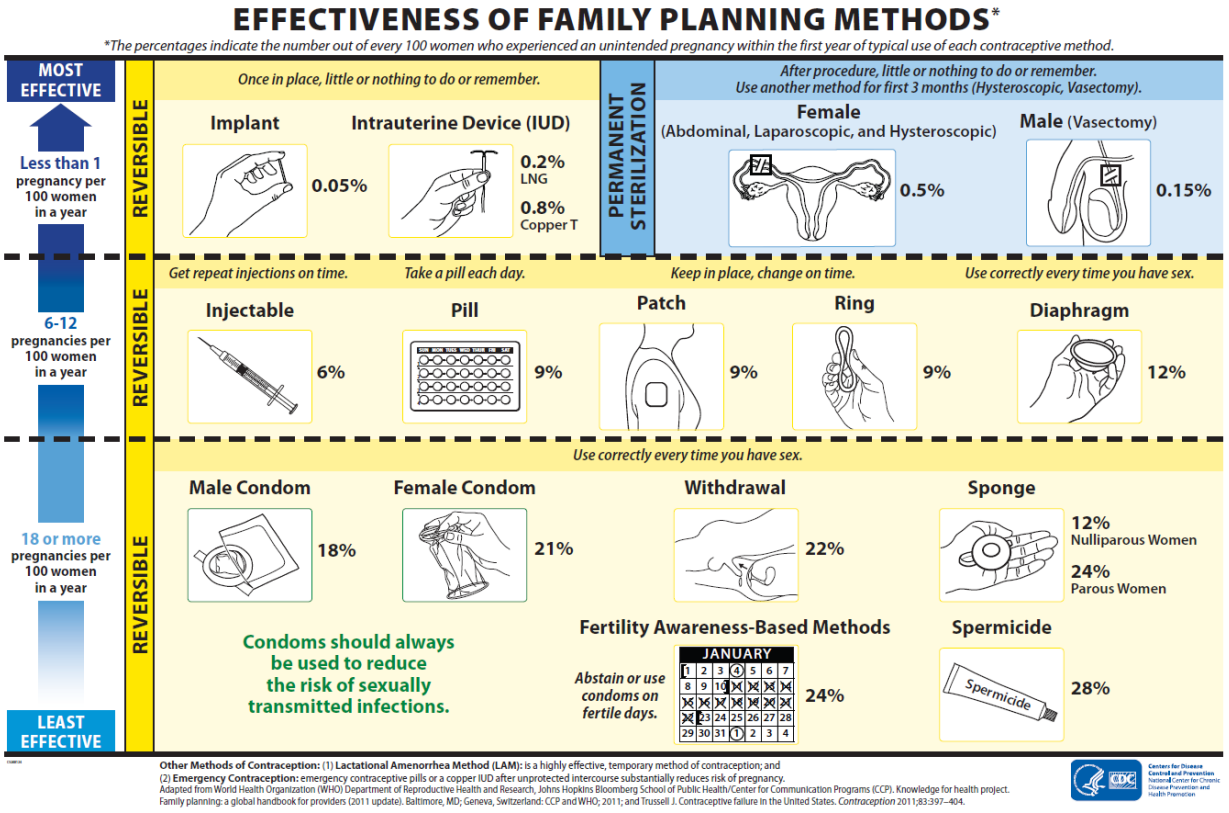
- Folic Acid supplementation
- Abstinence from alcohol and illicit substances
- Nicotine and THC cessation
- Update vaccinations
- Weight gain or reduction to achieve optimal BMI
- Medication changes or discontinuation
- Avoidance of environmental teratogens
- Disease optimization (ex Hgb A1C < 7)

Korenbrot CC et al. Matern Child Health 2002

Consider a Maternal Fetal Medicine Preconception Consultation

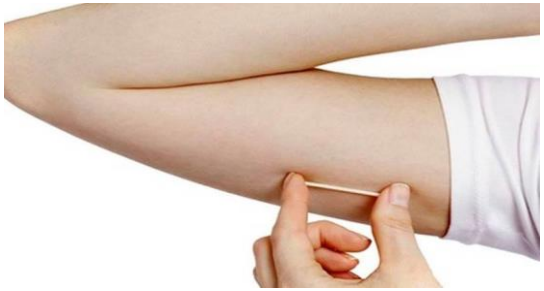
Options for Contraception

- ✓ Effectiveness
- ✓ Reversibility
- ✓ Medical Safety



Long Acting Reversible Contraception (LARC)

- Etonogestral Implant (Nexplanon)
  - Use up to 3 years



- Copper Containing IUD (Paraguard)
  - Use up to 10 years

- Levonorgestral IUD-releasing
  - Mirena (use up to 5 years)
  - Liletta (use up to 4 years)
  - Kyleena (use up to 5 years)
  - Skyla (use up to 3 years)

Enzyme Inducing AEDs and Contraception

Strong Inducers

- Carbamazapine
- Oxcarbamazapine
- Perampanel
- Phenobarbital
- Phenytoin
- Primidone

Weak Inducers:

- Clobazam
- Eslicarbazepine
- Felbamate
- **Lamotrigine**
- Rufinamide
- **Topiramate**

IUD or Intramuscular depot provera are the best options!

Thank you!