DRUGS IN PREGNANCY AND LACTATION

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MEDICATION USE DURING PREGNANCY

TERATOGENICITY

- ***Is it safe to use hair dye when I'm pregnant?***

- **Is it safe to continue breast-feeding if I'm pregnant with another child?**


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- A ***great challenge*** to clinicians

Reasons?


The potential adverse effect on the embryo, fetus, and newborn

Unplanned pregnancy

- Pregnancy is **NOT** a **symptom-producing** condition. As a result, **many drugs regularly are consumed during gestation**, including some that are **potential teratogens**

Limited data

- The ***limited availability*** of **scientific data** from **randomized trials**  **complicates** the **decision** to prescribe and recommend medications for pregnant women, **even when they are medically necessary**

Current methods to assess teratogenicity

- **Pregnancy registries**
- **Case– control** *surveillance studies*
- **Epidemiologic studies**
- **Anecdotal experiences** *in humans*
- **Animal studies**

- **These practices have proven insufficient to determine drug safety accurately**

RCT in pregnancy

- **Randomized, controlled trials** to assess the risk of fetal exposure to drugs → **difficult** and **unethical**

A few of the thousands

- Currently, only a few therapeutic agents of the thousands of drug therapies are **adequately studied** and considered relatively low risk on the development of the embryo and fetus.

only a few therapeutic agents

Risk benefit ratio

- The **potential benefits** of medication therapy must be ***weighted*** against the **possible risks** to the fetus.

Risk benefit ratio

- Although drug-induced teratogenicity is a serious concern during pregnancy, **most drugs** required by pregnant women **can be used safely**

Risk benefit ratio

Informed selection of drug therapy is essential

Reliable resources?

- **Healthcare practitioners** must know **where to find** and **how to evaluate evidence** related to the safety of drugs used during pregnancy and lactation

TERMINOLOGY

- **Teratogenicity**
- **Birth defects**
- **Congential anomalies**
- **Congential malformations**

Teratogenicity definition

- Agent that produce **abnormal development** in the ***fetus*** under certain exposure conditions

TERATOGEN

TERATOGEN

- ***A teratogen is defined as any environmental factor that can produce a:***
- ***permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus***

Birth defects

- **National Institute of Child Health and Human Development:**
- **Birth defects are structural or functional abnormalities present at birth that can cause physical disability, intellectual and developmental disability (IDD), and other health problems. Some may be fatal, especially if not detected and treated early**

- The broader term ***congential anomalies*** include the ***four major*** manifestations of ***abnormal*** fetal **development** which include:

- **GROWTH ALTERATIONS**
- **FUNCTIONAL DEFICITS**
- **STRUCTURAL MALFORMATIONS**
- **AND FETAL DEATH**

- **Teratogenicity = Birth defects = Congential anomalies**

congential malformations

- ***Defined as***:
- ***Structural abnormalities*** of ***prenatal origin*** that are present at ***birth*** and that **seriously interfere** with *viability* or ***physical well-being***."

DEFINITION

- The ***largest concern*** → risk of ***congential malformations***

functional abnormalities

- Some drug-induced defects relate to changes in ***functions*** or ***conditions*** that are **not structural** abnormalities,e.g:

- ***Mental retardation***
- ***CNS depression***
- ***Deafness***
- ***Tumors***
- ***Biochemical changes***

Extent of affect on development

- ***Depends on the***:
- **physical** and **chemical** properties of the drug
- ***Dose***
- ***Duration***
- ***Route***
- ***Timing*** **of exposure**
- ***Genetic composition*** and ***biological susceptibility*** of the ***mother*** and ***fetus***

BACKGROUND RISK

BASIC PRINCIPLES OF TERATOGENICTY

BACKGROUND RISK

- A thorough ***assessment***, including knowledge of the **teratogenic potential** of the drug, the **critical period** of exposure, and **magnitude of risk** must be compared with the ***background risk***

The **background incidence** of birth defects

3%

(4 to 6 percent) in the **general population**

- This number has been derived from large **epidemiologic studies** completed over the past several decades

MEDICATIONS

- **Medication exposure** is estimated to account for ***LESS THAN 1%*** of all birth defects

LESS THAN 1%

OTHER CAUSES

- **Genetic causes** → **15% to 25%**
- **Other environmental issues** (e.g., **maternal conditions** and **infections**) → **10%**
- **unknown causes** → **65% to 75%**

- Ascertain if a particular drug **increases** the risk of developmental toxicity in the fetus **beyond** the **background rate**

Beyond the background rate

The basic principles of TERATOGENICTY

- The **basic principles** of **TERATOGENICTY** can ***help*** to ***assess*** the **risk of exposure** and **interpretation of limited studies** during pregnancy.

Basic principles of teratogenicity should be applied when assessing the potential for teratogenicity

- CRITICAL STAGE OF EXPOSURE
- DOSE-RESPONSE CURVE
- EXTRAPOLATION FROM ANIMAL STUDIES
- GENETIC VARIABILITY
- PLACENTAL TRANSFER OF DRUGS

- **After fertilization, THREE main stages:**
  - *Pre-embryonic period*
  - *Embryonic period*
  - *Fetal period*

CRITICAL STAGE OF EXPOSURE

"ALL OR NONE" EFFECT

- **First 2 weeks** after fertilization → **"all or none"** effect

PRE-EMBRYONIC PERIOD

Organogenesis

- **14–56 days** after fertilization:
- The embryo is ***most susceptible*** to the effects of **teratogens**
- **Many women** → are **not yet aware** of the **pregnancy**

EMBRYONIC PERIOD

FETAL PERIOD

- ***57 days to term***:

- **FUNCTIONAL MATURATION** (Mental development and reproduction)

- **MINOR STRUCTURAL CHANGES** are still possible

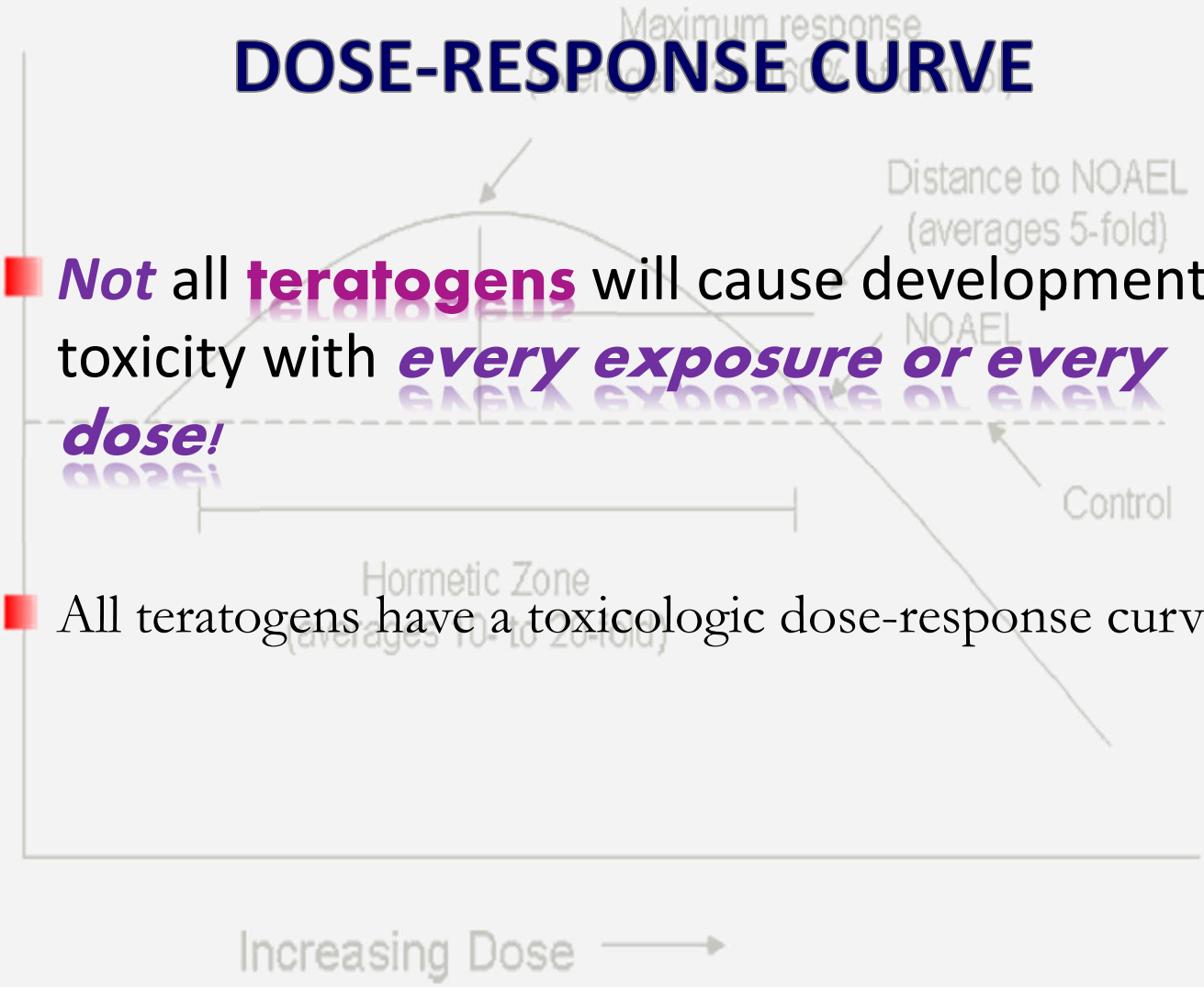
- **knowledge of these stages** is essential for the **interpretation** of the **relationship** between **congenital malformations** and **drugs**.

Drug exposure after the time of organ development

structural defect?!

- **These stages** of development differ significantly from other species

DOSE-RESPONSE CURVE



- ***Not*** all **teratogens** will cause development toxicity with ***every exposure or every dose!***
- All teratogens have a toxicologic dose-response curve

Threshold Dose

- **All teratogens** → *threshold dose* below which adverse effects will not occur.

DOSE-RESPONSE CURVE

Thalidomide

- **Developmental toxicity under specific conditions:**

1-mg dose of thalidomide → at **anytime** during pregnancy

.

↓

No observable effects on the fetus

Thalidomide

- **Developmental toxicity under specific conditions:**

- **A single 50-mg dose:**

- **26th day** after conception → **major structural malformation**

Thalidomide

- **A single 50-mg dose:**

- **Minimal risk** → if taken in the **10th week** after conception.

- **Increasingly higher dosages incidence** of malformations. → increase in the **severity** and

valproic acid dosages **>1,000 mg/day during the first trimester**

↓

↑ ***NTD*** **and** ***minor anomalies*****, are increased**

ALWAYS ADMINISTER MINIMUM EFFECTIVE DOSE

Extrapolation From Animal Studies

- **Animal studies** → data must be carefully interpreted → birth defects are **species specific** and influenced by many factors

- **Newly marketed drugs** → estimation of teratogenic risk based on **animal studies** until → **human data become available**.

- **The drug** appears to have a **low risk for teratogenicity If** :
  - The **toxic dose in animals** is greater than **ten times** the anticipated **human dose**

- **Risk assessment** using animal data is **more complicated** than **just considering the dosage** alone.
- ***Other major factors, including***:
  - **The effects of metabolism**
  - **Active metabolites**
  - **Species differentiation**
  - **Route of administration, and type of defects**

- **Must be considered**

GENETIC VARIABILITY

- The **teratogenic potential** of **some drugs** is influenced by the **GENOTYPE** of both the **MOTHER** and **FETUS**

GENETIC VARIABILITY

- **DIFFERENCES IN:**
  - **Cell sensitivities**
  - **Placental transport**
  - **Drug metabolism**
  - **Enzyme composition**
  - And **receptor binding**

PHENYTOIN

- **Poor metabolizer** → ***Higher risk for fetal hydantoin syndrome***

- **Increased susceptibility to the teratogenic effect** caused by ***elevated levels of oxidative metabolites (epoxides)***

FOOD AND DRUG ADMINISTRATION RISK FACTORS

- **1979** → the **FDA system** of rating pregnancy
  - This system categorizes all drugs approved **after 1983** into one of **five pregnancy risk categories**

The *OLD* FDA pregnancy classification

- ***A***, ***B***, ***C***, ***D***, and ***X***

- May mislead healthcare providers?

The *OLD* FDA pregnancy classification

RISK OR RISK BENEFIT?

- A drug in categories C or D may pose risks similar to a drug in category x

The *OLD* FDA pregnancy classification

- The risk factors may be:
- Ambiguous, outdated, and do not provide information regarding the full range of potential developmental toxicity (i.e., **structural defects**, **growth restriction**, **functional deficits**, and **fetal death**)

The *OLD* FDA pregnancy classification

- In addition, the categories do not always **distinguish** between:
- ***RISKS*** based on ***human versus animal data*** findings
- or
- Differences in **frequency**, **severity**, and **type** of fetal developmental toxicities

The *OLD* FDA pregnancy classification

- The proposed rule **would remove the categories** from the labeling of all drug products

The *NEW* FDA pregnancy system

- The FDA revising the pregnancy labeling and category system to include ➡ **narrative text** to provide more clinical management advice that includes consideration of both animal and human data

- **A** → **GENERAL INFORMATION** DESCRIBING **OVERALL RISK AND BENEFIT**
- **B** → SPECIFIC **FETAL RISK SUMMARY**
- **C** → **CLINICAL CONSIDERATIONS**
- **D** → PREGNANCY **DATA** IN **HUMANS** AND **ANIMALS**
- **E** → **REFERENCES**

structured narratives

8.1 Pregnancy

Risk Summary

Neonates born to mothers using zolpidem late in the third trimester of pregnancy have been reported to experience symptoms of respiratory depression and sedation *[see Clinical Considerations and Data]*. Published data on the use of zolpidem during pregnancy have not reported a clear association with zolpidem and major birth defects *[see Data]*. Oral administration of zolpidem to pregnant rats and rabbits did not indicate a risk for adverse effects on fetal development at clinically relevant doses *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Zolpidem crosses the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to AMBIEN during pregnancy and labor for signs of excess sedation, hypotonia, and respiratory depression and manage accordingly.

Data

Human data

Published data from observational studies, birth registries, and case reports on the use of zolpidem during pregnancy do not report a clear association with zolpidem and major birth defects.

There are limited postmarketing reports of severe to moderate cases of respiratory depression that occurred after birth in neonates whose mothers had taken zolpidem during pregnancy. These cases required artificial ventilation or intratracheal intubation. The majority of neonates recovered within hours to a few weeks after birth once treated.

Zolpidem has been shown to cross the placenta.

Animal data

Oral administration of zolpidem to pregnant rats during the period of organogenesis at 4, 20, and 100 mg base/kg/day, which are approximately 5, 25, and 120 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) based on mg/m^2 body surface area, caused delayed fetal development (incomplete fetal skeletal ossification) at maternally toxic (ataxia) doses 25 and 120 times the MRHD based on mg/m^2 body surface area.

Oral administration of zolpidem to pregnant rabbits during the period of organogenesis at 1, 4, and 16 mg base/kg/day, which are approximately 2.5, 10, and 40 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m^2 body surface area caused embryo-fetal death and delayed fetal development (incomplete fetal skeletal ossification) at a maternally toxic (decreased body weight gain) dose 40 times the MRHD based on mg/m^2 body surface area.

Oral administration of zolpidem to pregnant rats from day 15 of gestation through lactation at 4, 20, and 100 mg base/kg/day, which are approximately 5, 25, and 120 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m^2 body surface area, delayed offspring growth and decreased survival at doses 25 and 120 times, respectively, the MRHD based on mg/m^2 body surface area.

Azithromycin

8.1 Pregnancy

Risk Summary

Available data from published literature and postmarketing experience over several decades with azithromycin use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. Developmental toxicity studies with azithromycin in rats, mice, and rabbits showed no drug-induced fetal malformations at doses up to 4, 2, and 2 times, respectively, an adult human daily dose of 500 mg based on body surface area. Decreased viability and delayed development were observed in the offspring of pregnant rats administered azithromycin from day 6 of pregnancy through weaning at a dose equivalent to 4 times an adult human daily dose of 500 mg based on body surface area *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes with azithromycin use in pregnant women. Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

Animal Data

Azithromycin administered during the period of organogenesis did not cause fetal malformations in rats and mice at oral doses up to 200 mg/kg/day (moderately maternally toxic). Based on body surface area, this dose is approximately 4 (rats) and 2 (mice) times an adult human daily dose of 500 mg. In rabbits administered azithromycin at oral doses of 10, 20, and 40 mg/kg/day during organogenesis, reduced maternal body weight and food consumption were observed in all groups; no evidence of fetotoxicity or teratogenicity was observed at these doses, the highest of which is estimated to be 2 times an adult human daily dose of 500 mg based on body surface area.

In a pre- and postnatal development study, azithromycin was administered orally to pregnant rats from day 6 of pregnancy until weaning at doses of 50 or 200 mg/kg/day. Maternal toxicity (reduced food consumption and body weight gain; increased stress at parturition) was observed at the higher dose. Effects in the offspring were noted at 200 mg/kg/day during the postnatal development period (decreased viability, delayed developmental landmarks). These effects were not observed in a pre- and postnatal rat study when up to 200 mg/kg/day of azithromycin was given orally beginning on day 15 of pregnancy until weaning.

The *NEW* FDA pregnancy system

GEMIFLOXACIN

Anti-infective (Fluoroquinolone)

PREGNANCY RECOMMENDATION: Contraindicated (Use only if no other alternatives)

BREASTFEEDING RECOMMENDATION: No Human Data—Probably Compatible

PREGNANCY SUMMARY

No reports describing the use of gemifloxacin during human pregnancy have been located. The animal toxicity (fetal growth restriction) observed at exposures close to those obtained in humans should be considered before this agent is used in pregnant women. Moreover, some reviewers have concluded that all quinolones should be considered contraindicated in pregnancy (e.g., see Ciprofloxacin and Norfloxacin) because safer alternatives are usually available.

Additionally, the FDA has added warnings to all fluoroquinolones for the risk of disabling and potentially permanent effects involving the tendons, muscles, joints, nerves, and central nervous system. Fluoroquinolones should be reserved for those who do not have alternative treatment options (1).

Fetal risk summary

- The fetal risk summary would begin with a **ONE SENTENCE RISK CONCLUSION** that characterizes **the likelihood that** the drug increases the **risk** of **four types** of **developmental abnormalities**:
- **structural anomalies**, **fetal and infant mortality**, **impaired physiologic function**, **alterations to growth**

Azithromycin

8.1 Pregnancy

Risk Summary

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The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

- The risk conclusion would state whether it was based on **animal** or **human** data.
- **More than one risk conclusion** may be **needed** to characterize the likelihood of risk for **different developmental abnormalities** ➡ **doses**, **durations of exposure**, or **gestational ages at exposure**.

Azithromycin

8.1 Pregnancy

Risk Summary

Available data from published literature and postmarketing experience over several decades with azithromycin use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. Developmental toxicity studies with azithromycin in rats, mice, and rabbits showed no drug-induced fetal malformations at doses up to 4, 2, and 2 times, respectively, an adult human daily dose of 500 mg based on body surface area. Decreased viability and delayed development were observed in the offspring of pregnant rats administered azithromycin from day 6 of pregnancy through weaning at a dose equivalent to 4 times an adult human daily dose of 500 mg based on body surface area *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

- **If** there are **only animal data**  the **fetal risk summary** would contain **only the risk conclusion**.

- However, when there are ***human data***, the risk conclusion would be followed by ***approximately a paragraph*** describing the ***most important data*** about the ***effects*** of the drug **on the *fetus***

- **To the extent possible, this narrative would include the:**

- ***Specific developmental abnormality*** (e.g., **Neural tube defects**)

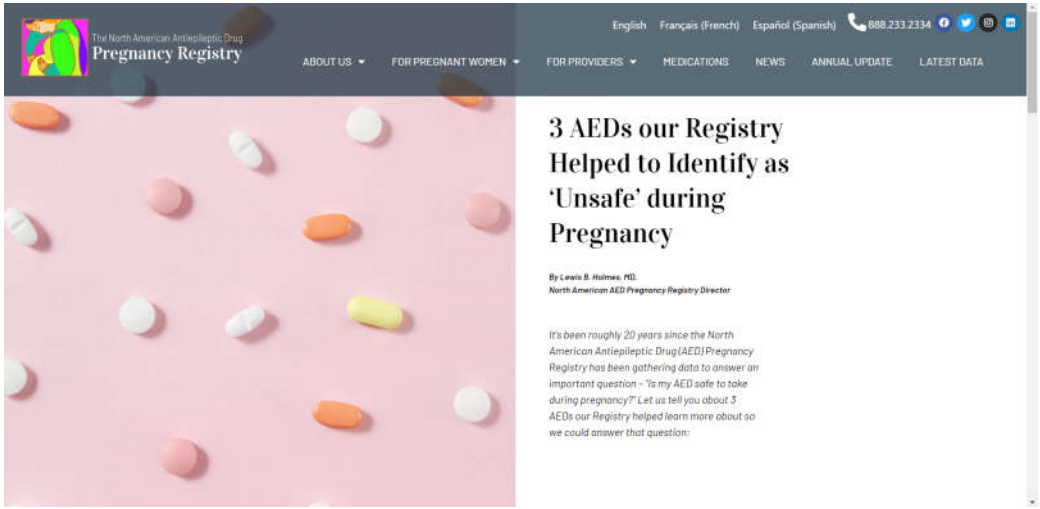
- **The *incidence*, *seriousness*, *reversibility*,** and ***correctability*** of the abnormality

- **The effect of dose, duration of exposure,** and **gestational timing of exposure on the risk of the abnormality**

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), including Valproate sodium, during pregnancy. Encourage women who are taking Valproate sodium during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling toll-free 1-888-233-2334 or visiting the website, http://www.aedpregnancyregistry.org/. This must be done by the patient herself.



Risk Summary

For use in prophylaxis of migraine headaches, valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception *[see Contraindications (4)]*.

For use in epilepsy or bipolar disorder, valproate should not be used to treat women who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable *[see Boxed Warning and Warnings and Precautions (5.2, 5.3)]*. Women with epilepsy who become

pregnant while taking valproate should not discontinue valproate abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life.

Maternal valproate use during pregnancy for any indication increases the risk of congenital malformations, particularly neural tube defects including spina bifida, but also malformations involving other body systems (e.g., craniofacial defects including oral clefts, cardiovascular malformations, hypospadias, limb malformations). This risk is dose-dependent; however, a threshold dose below which no risk exists cannot be established. *In utero* exposure to valproate may also result in hearing impairment or hearing loss. Valproate polytherapy with other AEDs has been associated with an increased frequency of congenital malformations compared with AED monotherapy. The risk of major structural abnormalities is greatest during the first trimester; however, other serious developmental effects can occur with valproate use throughout pregnancy. The rate of congenital malformations among babies born to epileptic mothers who used valproate during pregnancy has been shown to be about four times higher than the rate among babies born to epileptic mothers who used other antiseizure monotherapies *[see Warnings and Precautions (5.2) and Data (Human)]*.

Epidemiological studies have indicated that children exposed to valproate *in utero* have lower IQ scores and a higher risk of neurodevelopmental disorders compared to children exposed to either another AED *in utero* or to no AEDs *in utero [see Warnings and Precautions (5.3) and Data (Human)]*.

An observational study has suggested that exposure to valproate products during pregnancy increases the risk of autism spectrum disorders *[see Data (Human)]*.

In animal studies, valproate administration during pregnancy resulted in fetal structural malformations similar to those seen in humans and neurobehavioral deficits in the offspring at clinically relevant doses *[see Data (Animal)]*.

There have been reports of hypoglycemia in neonates and fatal cases of hepatic failure in infants following maternal use of valproate during pregnancy.

Pregnant women taking valproate may develop hepatic failure or clotting abnormalities including thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors, which may result in hemorrhagic complications in the neonate including death *[see Warnings and Precautions (5.1, 5.8)]*.

Available prenatal diagnostic testing to detect neural tube and other defects should be offered to pregnant women using valproate.

Evidence suggests that folic acid supplementation prior to conception and during the first trimester of pregnancy decreases the risk for congenital neural tube defects in the general population. It is not known whether the risk of neural tube defects or decreased IQ in the offspring of women receiving valproate is reduced by folic acid supplementation. Dietary folic acid supplementation both prior to conception and during pregnancy should be routinely recommended for patients using valproate *[see Warnings and Precautions (5.2, 5.4)].*

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

CLINICAL CONSIDERATIONS

- The Clinical considerations component would address **three main topics** important when **counseling with**, and **prescribing** for, women who are:
- **Pregnant**, **lactating**, or of **childbearing age**

Clinical considerations in pregnancy

- **Inadvertent exposure**
- **Prescribing decisions for pregnant women**
- **Drug effects during labor or delivery**

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

To prevent major seizures, women with epilepsy should not discontinue valproate abruptly, as this can precipitate status epilepticus with resulting maternal and fetal hypoxia and threat to life. Even minor seizures may pose some hazard to the developing embryo or fetus *[see Warnings and Precautions (5.4)]*. However, discontinuation of the drug may be considered prior to and during pregnancy in individual cases if the seizure disorder severity and frequency do not pose a serious threat to the patient.

Maternal adverse reactions

Pregnant women taking valproate may develop clotting abnormalities including thrombocytopenia, hypofibrinogenemia, and/or decrease in other coagulation factors, which may result in hemorrhagic complications in the neonate including death *[see Warnings and Precautions (5.7)]*. If valproate is used in pregnancy, the clotting parameters should be monitored carefully in the mother. If abnormal in the mother, then these parameters should also be monitored in the neonate.

Patients taking valproate may develop hepatic failure *[see Boxed Warning and Warnings and Precautions (5.1)]*. Fatal cases of hepatic failure in infants exposed to valproate *in utero* have also been reported following maternal use of valproate during pregnancy.

Hypoglycemia has been reported in neonates whose mothers have taken valproate during pregnancy.

during pregnancy).

Data

Human

Neural tube defects and other structural abnormalities

There is an extensive body of evidence demonstrating that exposure to valproate *in utero* increases the risk of neural tube defects and other structural abnormalities. Based on published data from the CDC's National Birth Defects Prevention Network, the risk of spina bifida in the general population is about 0.06 to 0.07% (6 to 7 in 10,000 births) compared to the risk following *in utero* valproate exposure estimated to be approximately 1 to 2% (100 to 200 in 10,000 births).

The NAAED Pregnancy Registry has reported a major malformation rate of 9-11% in the offspring of women exposed to an average of 1,000 mg/day of valproate monotherapy during pregnancy. These data show an up to a five-fold increased risk for any major malformation following valproate exposure *in utero* compared to the risk following exposure *in utero* to other AEDs taken as monotherapy. The major congenital malformations included cases of neural tube defects, cardiovascular malformations, craniofacial defects (e.g., oral clefts, craniosynostosis), hypospadias, limb malformations (e.g., clubfoot, polydactyly), and other malformations of varying severity involving other body systems *[see Warnings and Precautions (5.2)]*.

Animal

In developmental toxicity studies conducted in mice, rats, rabbits, and monkeys, increased rates of fetal structural abnormalities, intrauterine growth retardation, and embryo-fetal death occurred following administration of valproate to pregnant animals during organogenesis at clinically relevant doses (calculated on a body surface area [mg/m^2] basis). Valproate induced malformations of multiple organ systems, including skeletal, cardiac, and urogenital defects. In mice, in addition to other malformations, fetal neural tube defects have been reported following valproate administration during critical periods of organogenesis, and the teratogenic response correlated with peak maternal drug levels. Behavioral abnormalities (including cognitive, locomotor, and social interaction deficits) and brain histopathological changes have also been reported in mice and rat offspring exposed prenatally to clinically relevant doses of valproate.

INADVERTENT EXPOSURE

- This section would describe **known or predicted risks** to the fetus from exposure to the drug **early in pregnancy before a woman knows she is pregnant**, including **data** on **dose**, **timing**, and **duration** of exposure.

Risk Summary

Leflunomide is contraindicated for use in pregnant women because of the potential for fetal harm. In animal reproduction studies, oral administration of leflunomide during organogenesis at a dose of 1/10 of and equivalent to the maximum recommended human dose (MRHD) based on AUC, respectively in rats and rabbits, caused teratogenicity (rats and rabbits) and embryo-lethality (rats) *[see Data]*. Pregnancy exposure registry data are not available at this time to inform the presence or absence of drug-associated risk with the use of leflunomide during pregnancy. The background risk of major birth defects and miscarriage for the indicated populations is unknown. The background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, stop treatment with leflunomide, apprise the patient of the potential hazard to a fetus, and perform the accelerated drug elimination procedure to achieve teriflunomide concentrations of less than 0.02 mg/L (0.02 mcg/mL) *[see Warnings and Precautions (5.3)]*.

PRESCRIBING DECISIONS FOR PREGNANT WOMEN

- **Risk to** the **pregnant woman** and the **fetus** from the **disease** the drug is indicated to treat
- **Dosing adjustments** during **pregnancy**
- **Adverse reactions** unique to **pregnancy** associated with use of the drug.

- Any **interventions** that may be **needed** (e.g., **monitoring blood glucose** for a **drug** that **causes hyperglycemia in pregnancy**)

- Any **complications** in the **neonate** associated with drug use, including **severity** and **reversibility**, and interventions needed

Drug effects during labor or delivery

- Drug with a **recognized use during labor** or **delivery** (**whether or not** the drug is **indicated for that use**), include information about the:

- **Effect** of the drug on the **mother**; the **fetus/neonate**
- **Duration** of **labor** and **delivery**
- **Possibility** of **complications**, including **needed interventions**; and the **later growth**, **development**, and **functional maturation** of the child.

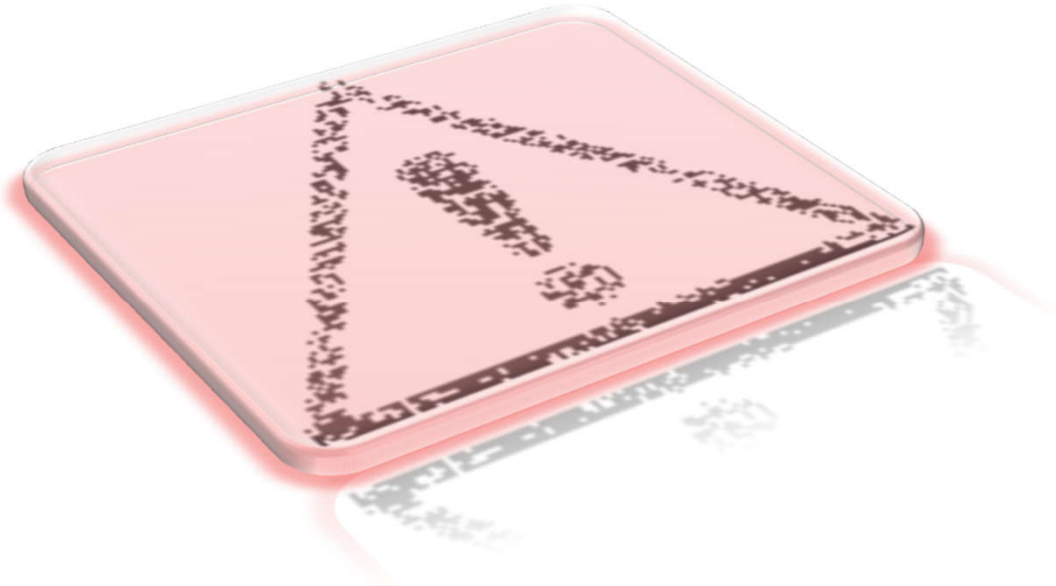
DATA

- The data section would have a **more detailed discussion** of available data.
- **Human data** would **appear before animal data**.

DATA

- The section would include:
- A description of the **types** of **studies**
- **Animal species** used
- **Dose exposure information** (**animal doses** described in terms of **human dose equivalents**)
- **Nature** of any **identified fetal developmental anomalies** and **other adverse events**
- For **animal data**, an **explanation** of what is known about the **relationship** between **drug exposure** and **mechanism of action** in **animals** versus **humans**.

- Because the **potential for fetal risks** cannot be entirely **disregarded for many drugs**, the need to medicate during pregnancy should be **evaluated carefully**



BREAST-FEEDING

Why BREAST-FEEDING?

- Breast milk is recognized as the **optimal source of nutrition** for infants, with documented benefits not only to infants but also to **mothers**, **families**, and **societies**.

- **Incidence** or **severity** of many infectious in infants e.g.:
  - **Otitis media**
  - **Respiratory infections**
  - **Urinary tract infections**

BREAST-FEEDING BENEFITS

- In **children** and **adults** who **were breast-fed**:
- **Obesity**
- **Inflammatory bowel disease**
- **Celiac disease**
- **Childhood leukemia**

→ **Were reduced**

BREAST-FEEDING BENEFITS

- Lactation may also positively influence **cognitive and intellectual development** in children and young adults.

BENEFITS TO THE MOTHER

- Decreased **postpartum blood loss**
- More rapid **uterine involution**
- Earlier return to **prepregnancy weight**
- Decreased risks of **breast cancer**, **ovarian cancer**, and **osteoporosis**.

BREAST-FEEDING BENEFITS

PARAMETERS AFFECT DRUG EXCRETION INTO BREAST MILK

MATERNAL PARAMETERS

DRUG PARAMETERS

INFANT PARAMETERS

- Drug **dosage** and **duration** of therapy
- **Route** and **frequency** of administration
- **Metabolism**
- **Renal clearance**
- **Blood flow** to the breasts
- Milk **pH**
- Milk **composition**

- Oral ***bioavailability*** (to mother and infant)
- ***Molecular weight***
- ***pKa***
- ***Lipid solubility***
- ***Protein binding***

DRUG PARAMETERS

- ***Age*** of the infant
- ***Feeding pattern***
- ***Amount*** of breast milk consumed
- Drug **absorption**, **distribution**, **metabolism**, **elimination**

Reducing Risk of Infant Exposure to Drugs in Breast Milk

- A drug should be used only ***IF MEDICALLY NECESSARY*** and **treatment cannot be delayed until the infant is ready to be weaned**

IF MEDICALLY INDICATED

- Consider whether the drug can be **safely given directly to the infant**.
- Select a drug that passes poorly into breast milk with the **lowest predicted M:P ratio**, and a RID (relative infant dose) <10%.
- Avoid **long-acting formulations** (e.g., **sustained-release**).

Drug Selection

- Consider possible ***ROUTES*** of administration that can **reduce drug excretion into milk**.
- Determine ***LENGTH*** of therapy and if possible **avoid long-term use**.

Drug Selection

FEEDING PATTERN:

- ***Avoid nursing during times of peak drug concentration.***
- ***If possible, plan breast-feeding before administration of the next dose.***

Other Considerations

- Always observe the infant for ***UNUSUAL SIGNS*** (e.g., sedation, irritability, rash, decreased appetite, failure to thrive).

- ***DISCONTINUE*** breast-feeding during the course of therapy if the ***RISKS*** to the fetus ***OUTWEIGH*** the ***BENEFITS*** of nursing.

Other Considerations

- Provide ***ADEQUATE PATIENT EDUCATION*** to increase understanding of risk factors.

FDA Lactation Subsection

Risk summary

- If appropriate, include ***A STATEMENT*** that the use of the ***DRUG IS COMPATIBLE*** with breast-feeding.
- Effects of the drug on ***MILK PRODUCTION***
- Whether the ***DRUG*** is ***PRESENT IN HUMAN MILK*** (and if so, ***HOW MUCH***)
- The ***EFFECT*** of the drug on the ***BREAST-FED CHILD***

Clinical considerations

- Ways to minimize exposure to the breast-fed child, such as ***TIMING*** or ***PUMPING AND DISCARDING MILK***.
- ***POTENTIAL*** drug ***EFFECTS*** in the ***CHILD*** and recommendations for ***MONITORING*** or ***RESPONDING*** to these ***EFFECTS***.
- ***DOSING ADJUSTMENT*** during lactation.

Data

- ***OVERVIEW*** of data on which ***RISK SUMMARY*** and ***CLINICAL CONSIDERATIONS*** are ***BASED***.

REFERENCE LIBRARY

- Because the pharmacologic therapy of pregnant women is undergoing continuous change, no single source, will have all of the published reports or even cover all of the drugs.
- Thus, we recommend a *reference library* that contains several other sources

Books

Briggs GG, Freeman RK, Yaffe SJ. ***Drugs in Pregnancy and Lactation***. *A Reference Guide to Fetal and Neonatal Risk*.

Hale T. ***Medications and Mothers' Milk***

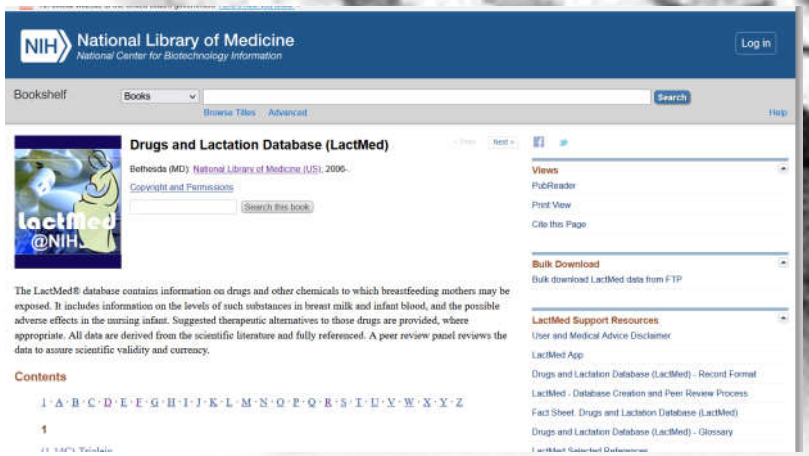
Koren G. ***Medication Safety in Pregnancy and Breastfeeding***. New York: McGraw-Hill

Schaefer C, Peters P, Miller RK. ***Drugs during Pregnancy and Lactation***

Schardein JL. ***Chemically Induced Birth Defects***. 3rd ed. New York: Marcel Dekker

Shepard TH, Lemire RJ. ***Catalog of Teratogenic Agents***

- https://mothertobaby.org/
- https://www.nlm.nih.gov/
- https://www.acog.org/
- Drugs and Lactation Database (LactMed)



THANK YOU