Management of Teratogenic Medications

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- This presentation may use the terms 'woman/women' and 'female(s)' to refer to people capable of becoming pregnant
- These terms refer to people who were assigned a biologic sex of female; information in this presentation applies to all people of childbearing potential regardless of gender identity

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Objectives

- **The pharmacist participant will be able to:**
  - Discuss the history of FDA pregnancy category letters
  - Describe the FDA Pregnancy and Lactation Labeling Rule
  - Identify common teratogenic medications taken by women of childbearing age
  - Given a patient on a teratogenic medication, discuss best practices for managing their medication therapy, including contraceptive options and possible drug interactions
- **The pharmacy technician participant will be able to:**
  - Discuss the history of FDA pregnancy category letters
  - Describe the FDA Pregnancy and Lactation Labeling Rule
  - Identify common teratogenic medications taken by women of childbearing age
  - Given a patient on a teratogenic medication, discuss best practices for managing their medication therapy, including contraceptive options and possible drug interactions

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How comfortable are you discussing teratogenic medications with patients?

A. Extremely comfortable
B. Somewhat comfortable
C. Neutral
D. Somewhat uncomfortable
E. Extremely uncomfortable

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Why does it matter?

- **Pregnancy & medication use**
  - In the United States, 9 out of 10 pregnant people take at least one medication during pregnancy
  - Pregnant people take an average of 2.6 medications at any time during pregnancy

Sources: CDC.gov: Treating for Two: https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html
Mitchell AA, Gilboa SM, Werler MM, et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

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Placental Drug Transfer

- Almost all drugs will cross the placenta to reach the fetus
- The greatest risk of adverse drug effects on the fetus is probably during organogenesis during the first trimester
  - Some exceptions, though
- Trasnplacental can be beneficial to treat specific fetal conditions
  - Steroids administered to mom to promote fetal lung maturation

Source: Griffiths SK, Campbell JP. Placental structure, function and drug transfer. Continuing Education in Anaesthesia Critical Care & Pain. 2015;15(2):84-89.

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Teratogen

- Any agent that can disturb the development of an embryo or fetus
- May cause a birth defect in the child
- May cause termination of pregnancy
- Classes of teratogens include radiation, maternal infections, chemicals, and drugs

Source: Griffiths SK, Campbell JP. Placental structure, function and drug transfer. Continuing Education in Anaesthesia Critical Care & Pain. 2015;15(2):84-89.

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Why does it matter?

- ~6% of females become pregnant while taking a potentially teratogenic medication
- **Retrospective database review (2004)**
  - 4.6% (n=6976) received a category X drug within 270 days of delivery

Sources: https://doi.org/10.1016/j.amjmed.2010.05.009; https://pubmed.ncbi.nlm.nih.gov/15343213/ https://pubmed.ncbi.nlm.nih.gov/31300567/

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Why does it matter?

- **Prescription claims data (2010)**
  - 18% of females receiving category X medications also received oral contraceptives
  - Refill patterns suggested non-adherence to oral contraceptives (similar to general pop. 18-44 years old)
- **Retrospective chart review (2019)**
  - 10% of females prescribed a teratogenic medication
  - 62% of these were not using birth control

Sources: https://doi.org/10.1016/j.amjmed.2010.05.009; https://pubmed.ncbi.nlm.nih.gov/15343213/ https://pubmed.ncbi.nlm.nih.gov/31300567/

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Why does it matter?

- **Retrospective review for reproductive life plans (2016)**
  - Medication list included in only 75% of plans
  - 8% of females reported use of at least one potentially teratogenic medication
  - 29% of these reported using contraception
- **Retrospective chart review (2017)**
  - Females taking warfarin (category X)
  - Contraceptive method documented in only 19% of PCP visits after initiation of warfarin
  - Gynecologic consultation associated with greater use of more effective contraception

Sources: https://onlinelibrary.wiley.com/doi/full/10.1111/bcpt.12918 https://journals.lww.com/greenjournal/Abstract/2017/05001/Contraception_Use_in_Reproductive_Age_Women_Taking.472.aspx

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Why does it matter?

- **Retrospective observational study (2015)**
  - 26% of females prescribed potentially teratogenic antiepileptic drugs (AEDs) reported using contraception
  - 89% of females using AEDs and oral contraceptives had potential drug-drug interactions
  - Less than 7% had received contraceptive counseling

Sources: https://doi.org/10.1016/j.yebeh.2015.08.004 https://onlinelibrary.wiley.com/doi/full/10.1002/bdra.20618 · https://pubmed.ncbi.nlm.nih.gov/20087677/

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Why does it matter?

- **Physician survey (2010)**
  - 62.3% had cared for people of childbearing potential taking cat D or X medications in the past year
  - 58.1% felt residency did not adequately prepare them to counsel about contraceptives
- **Focus group (2009)**
  - Most common source of "counseling" was a pamphlet

Sources: https://doi.org/10.1016/j.yebeh.2015.08.004 https://onlinelibrary.wiley.com/doi/full/10.1002/bdra.20618 · https://pubmed.ncbi.nlm.nih.gov/20087677/

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Patient perspectives

- "They never asked me if I planned on becoming pregnant soon, unless it was for, like, a research study. No, they never really have, and I just wonder how much it has to do with me being single."
- "I could see him [my doctor] asking the question, "Are you planning a family?" or something like that. But everybody… don't want children! Everybody's not in the planning your family stage."

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2808515/

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Patient perspectives

- "The two things they pushed were the pill and abstinence… they briefly discussed the other options, but it was not really a choice, it was like, this is what you should do."
- "No one ever explained anything to me, ever. They just said you are going to have to be on hormonal birth control."
- "Looking back, I wish it [contraceptive counseling] had been longer because now that I know more about various types of birth control and the various side effects… I wish they would have told me some of those things."

Source: https://jamanetwork.com/journals/jamadermatology/fullarticle/2783063

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Patient perspectives

- In these qualitative studies, participants expressed a preference for their provider to **not make assumptions about their reproductive life plans**, and to **provide comprehensive contraceptive counseling**
- Patients taking potentially teratogenic medications should be counseled on options, including **safe & effective contraception to prevent pregnancy** and **switching medications if/when a pregnancy is desired**

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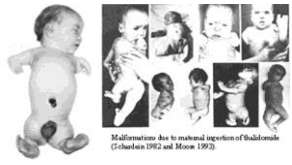
- 1957: Thalidomide entered the market advertised as "completely safe" for everyone
- 1962: FDA inspector Frances Kelsey prevented thalidomide from approval in the US
- 1962: Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act
- 1979: FDA introduces Pregnancy Category Letters



Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

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FDA Pregnancy Categories

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

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FDA Pregnancy Categories

Category	Translation (from Drugs in Pregnancy & Lactation)
A	The possibility of fetal harm appears remote.
B	If there is a clinical need for a drug in this category they are considered safe to use.
C	These drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.
X	The risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are, or may become pregnant.

Source: Drugs in Pregnancy and Lactation. Briggs GG, Freeman RK, Yaffe SJ Editors. Wolters Kluwer Health

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FDA Pregnancy Categories

Category	Examples
A	Multivitamins, levothyroxine
B	Diphenhydramine, penicillin, ondansetron
C	Aspirin (1st & 2nd trimester), guaifenesin, fluconazole,
D	ACE inhibitors (2nd & 3rd trimester), gentamicin, valproate for seizures, ibuprofen (3rd trimester)
X	Isotretinoin, statins, valproate for migraine, oral contraceptives, warfarin

Source: Drugs in Pregnancy and Lactation. Briggs GG, Freeman RK, Yaffe SJ Editors. Wolters Kluwer Health

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So what's the problem?

- Pregnancy letter category system was criticized as overly simplistic, confusing, and inaccurate
- Little to no guidance about possible fetal injuries and their severity
- Misinterpreted as a grading system
- Outdated content
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information

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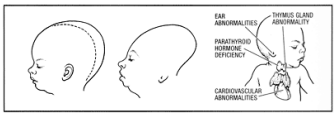
So what's the problem?

- **Risk categories ≠ grades**
- Two drugs within same category can have variable fetal risks
  - e.g., isotretinoin vs. oral contraceptives



Source: https://accpjournals.onlinelibrary.wiley.com/doi/full/10.1002/phar.1385; https://onlinelibrary.wiley.com/doi/full/10.1111/acem.12691

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Pregnancy & Lactation Labeling Rule (PLLR)

- 1997: Public Affairs Committee of the Teratology Society
- 2008: Proposal of PLLR
- 2015: Effective as of June 2015
- 2020: Pregnancy categories to be removed by June 2020

Intended to provide prescriber with the information needed to better evaluate risks vs. benefits

Source: https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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Pregnancy & Lactation Labeling Rule (PLLR)

- Eliminated the standard pregnancy category letters for prescription medications
- Provide the prescriber with relevant information needed to better evaluate the risks and benefits of pharmacologic treatment for patients that are pregnancy or lactating
- Explicitly states when no data are available

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Pregnancy & Lactation Labeling Rule (PLLR)

- Effective date June 30, 2015
- All prescription drugs to remove pregnancy letter categories by June 2020 as a gradual process
- Reorganizes information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs

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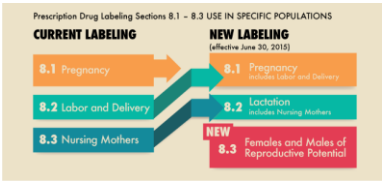
Changes in labeling



Source: https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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Pregnancy & Lactation Labeling Rule (PLLR)

- **Pregnancy (8.1)**
  - Information from pregnancy exposure registry when available
  - Risk summary, clinical considerations, data
- **Lactation (8.2)**
  - Amount of drug in breast milk
  - Potential effects on infant
- **Females & Males of Reproductive Potential (8.3)**
  - Need for pregnancy testing
  - Contraception recommendations
  - Infertility

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A patient comes to the pharmacy counter and asks you: "Is it safe to take voclosporin if I'm planning to get pregnant?"

A. Yes
B. No
C. Depends on risk/benefit for your personal medical conditions
D. I don't know

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Avoid use of LUPKYNIS in pregnant women due to the alcohol content of the drug formulation. The available data on the use of LUPKYNIS in pregnant patients are insufficient to determine whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE) *(see CLINICAL CONSIDERATIONS)*.

LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes MMF. MMF used in pregnant women and men whose female partners are pregnant can cause fetal harm (major birth defects and miscarriage). Refer to the MMF prescribing information for more information on its use during pregnancy.

In animal reproductive studies, oral administration of either voclosporin or a 50:50 mixture of voclosporin and its cis-isomer was embryocidal and fetocidal in rats and rabbits at doses 15- and 1-times, respectively, the maximum recommended human dose (MRHD) of 23.7 mg twice a day, based on drug exposure AUC. There were no treatment-related fetal malformations or variations. Additional findings of reduced placental and fetal body weights occurred in rabbits at 0.1 to 0.5-times the MRHD and in rats at higher drug exposures. Voclosporin was transferred across the placenta in pregnant rats. For rats, but not all doses in rabbits, these effects were associated with maternal toxicity consisting of reductions in body weight gain. Dystocia was evident in a pre- and postnatal study in rats, but there were no effects of voclosporin on postnatal growth and development *(see DATA)*.

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

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Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal LN increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Fetal/Neonatal adverse reactions

The formulation of LUPKYNIS contains alcohol (21.6 mg of dehydrated ethanol per capsule for a total daily dose of 129.4 mg/day). Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders and impaired intellectual development. There is no safe level of alcohol exposure in pregnancy; therefore, avoid use of LUPKYNIS in pregnant women.

Data

Animal Data

Voclosporin (90 to 95% trans-isomer) is the active ingredient in LUPKYNIS. Animal reproductive studies were primarily conducted with an approximate 50:50 mixture of voclosporin and its cis-isomer. Similarity of the toxicity effects of the 50:50 mixture and voclosporin was demonstrated in comparative toxicity studies with adult rats. Interconversion between cis and trans isomers was not detected with in vitro or in vivo studies.

In an embryofetal developmental study, pregnant rats were dosed orally, during the period of organogenesis from gestation days 6-17, with the 50:50 mixture of voclosporin and its cis-isomer; litter size was reduced due to increased fetal resorptions and deaths at drug exposures approximately 15-times the MRHD (on an AUC basis with a maternal oral dose of 25 mg/kg/day). Surviving fetuses had reduced placental weights and slightly reduced fetal weights. There were no treatment-related fetal malformations or variations with doses up to 15-times the MRHD, although reductions in ossification sites were observed in the metatarsal bones. This dose was associated with maternal toxicity based on decreased body weight gain. The no effect dose for both fetal and maternal effects occurred at a drug exposure approximately 7-times the MRHD (on an AUC basis with a maternal oral dose of 10 mg/kg/day).

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8.2 Lactation

Risk Summary

There are no available data on the presence of voclosporin in human milk, the effects on the breastfed infant, or the effects on milk production. Voclosporin is present in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adult patients treated with LUPKYNIS such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 7 days after the last dose of LUPKYNIS (approximately 6 elimination half-lives).

8.3 Females and Males of Reproductive Potential

LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes MMF. If LUPKYNIS is administered with MMF, the information for MMF regarding pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to MMF prescribing information for additional information.

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Overview by Selected Disease States

- **Each patient and their medication list should be evaluated individually**
- The following are **common disease states** among reproductive-age females…
- that are also frequently treated with potentially teratogenic medications (**"red flag" medications**)…
- and/or have **notable drug interactions with contraceptives**…
- and/or have **notable US CDC MEC considerations**.
- **Interprofessional management of the patient is likely needed.**

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US CDC MEC

Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Condition	Sub-Condition	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
		I	C	I	C	I	C	I	C	I	C	I	C
Diabetes	a) History of gestational disease	1		1		1		1		1		1	
	b) Nonvascular disease												
	i) Non-insulin dependent	1		2		2		2		2		2	
	ii) Insulin dependent	1		2		2		2		2		2	
	c) Nephropathy/retinopathy/neuropathy[‡]	1		2		2		3		2		3/4*	
	d) Other vascular disease or diabetes of >20 years' duration[‡]	1		2		2		3		2		3/4*	
Dysmenorrhea	Severe	2		1		1		1		1		1	
Endometrial cancer[‡]		4	2	4	2	1		1		1		1	
Endometrial hyperplasia		1		1		1		1		1		1	
Endometriosis		2		1		1		1		1		1	
Epilepsy[‡]	*(see also Drug Interactions)*	1		1		1*		1*		1*		1*	
Gallbladder disease	a) Symptomatic												
	i) Treated by cholecystectomy	1		2		2		2		2		2	
	ii) Medically treated	1		2		2		2		2		3	
	iii) Current	1		2		2		2		2		3	
	b) Asymptomatic	1		2		2		2		2		2	

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Epilepsy

- carbamazepine; fosphenytoin; phenytoin phenobarbital; primidone; topiramate; valproate
- **Possible drug interactions**
  - Many antiepileptic drugs induce CYP450
  - phenytoin, carbamazepine, barbiturates, primidone, topiramate (especially at >200mg/d), oxcarbazepine
  - *Non-enzyme inducing drugs: valproate, BZDs, gabapentin, levetiracetam*

Sources: https://www.sciencedirect.com/science/article/pii/S152550501500462X?via%3Dihub#t0005
https://www.aafp.org/afp/2008/0901/p634.html - https://journals.viamedica.pl/ginekologia_polska/article/view/GP.2019.0010/47685

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Epilepsy

Anticonvulsant therapy

a. Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)

Method	Category (Init. / Cont.)	Clarification Evidence Comment SPR Info
Cu-IUD	1	>
LNG-IUD	1	>
Implants	2†	>
DMPA	1†	>
POP	3†	>
CHCs	3†	>

Anticonvulsant therapy

b. Lamotrigine

Method	Category (Init. / Cont.)	Clarification Evidence Comment SPR Info
Cu-IUD	1	>
LNG-IUD	1	>
Implants	1	>
DMPA	1	>
POP	1	>
CHCs	3†	>

Source: US CDC MEC

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Anticoagulation

- warfarin (previously D/X)
- DOACs – very limited evidence in pregnancy
- Enoxaparin, heparin recommended in pregnancy

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Anticoagulation

c. DVT/PE and established anticoagulant therapy for at least 3 months

i. Higher risk for recurrent DVT/PE (one or more risk factors)
• Known thrombophilia, including antiphospholipid syndrome
• Active cancer (metastatic, on therapy, or within 6 months of clinical remission), excluding non-melanoma skin cancer
• History of recurrent DVT/PE

Method	Category (Init. / Cont.)	Clarification Evidence Comment SPR Info
Cu-IUD	2	>
LNG-IUD	2	>
Implants	2	>
DMPA	2	>
POP	2	>
CHCs	4†	>

Deep venous thrombosis/ Pulmonary embolism

b. Acute DVT/PE

Method	Category (Init. / Cont.)	Clarification Evidence Comment SPR Info
Cu-IUD	2	>
LNG-IUD	2	>
Implants	2	>
DMPA	2	>
POP	2	>
CHCs	4	>

Source: US CDC MEC

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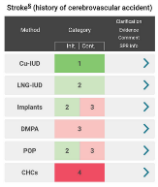
Anticoagulation



Source: US CDC MEC

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Migraine

- valproate; ergot derivatives; topiramate; NSAIDs in 3rd trimester
- **Possible drug interactions**
  - topiramate, nefazodone

Sources: https://www.migrainedisorders.org/pregnancy-and-migraine-medications/

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Migraine

Source: US CDC MEC

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Autoimmune Disorders

- methotrexate; leflunomide; mycophenolate mofetil
- Many biologics relatively safe; previously B/C

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8206731/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6342831/
https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/04/immune-modulating-therapies-in-pregnancy-and-lactation

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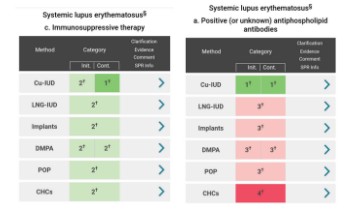
Autoimmune Disorders



Source: US CDC MEC

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Autoimmune Disorders

Source: US CDC MEC

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Autoimmune Disorders

Source: US CDC MEC

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Cardiovascular conditions

- ACE inhibitors; ARBs
- Statins

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Cardiovascular conditions

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Cardiovascular conditions

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Other Considerations

- Diabetes
- HIV
- Depression
- Bipolar disorder
- Organ transplantation
- Other?

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Patient Case

What recommendations are there for management of a pregnant patient who conceived while taking a potentially teratogenic anti-epileptic drug (AED)?

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Patient Case

"You can't get pregnant on this drug"

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Patient Case

HPI: 24-year-old G0P0. Presents to clinic for confirmation of pregnancy after positive home pregnancy test (taken after two missed periods).

PMH: migraine with aura

Vital signs & labs WNL except:
positive urine HCG (115,000 mIU/ml)

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Patient Case

Medication List:
Depakote 250mg, 1 tablet by mouth twice daily for migraine prophylaxis *(taking for four months)*

Nor-QD, 1 tablet by mouth daily
discontinued POPs after being told she "can't" get pregnant when starting Depakote

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Patient Case

Patient counseled on pregnancy options and would like to proceed with pregnancy, but wants to know "Will there be anything wrong with my baby?"

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Patient Case

Valproate associated with increased risk of neural tube defects, craniofacial defects, limb malformations, hearing impairment, neurodevelopmental disorders, lower IQ

Neural tube defects: 1-2 per 100 births

Dose-dependent – but no safe threshold established

Risk highest in first trimester

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=08ad65cf4-7749-4ceb-b895-8f4805e2b01f

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Patient Case

AED Pregnancy Registry:
https://www.aedpregnancyregistry.org/ or 888.233.2334

Recommend folic acid supplementation

D/C Depakote
Discussed beta blockers for prophylaxis; patient declined: "I'll just deal with it."

Encouraged follow-up for routine ultrasounds to detect neural tube defects and organ abnormalities

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=08ad65cf4-7749-4ceb-b895-8f4805e2b01f

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Patient Case

The patient asks what she should do about birth control in the future if she is to resume valproate. What recommendations do you have?

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Conclusions

- Updated FDA labeling requirements (PLLR) provide additional information for evaluating risks & benefits of medication use in pregnancy
- Use of teratogenic medications by people of childbearing potential is common, but these patients often receive inadequate contraceptive counseling
- Many potentially teratogenic medications have drug interactions with hormonal contraceptives
- A team-based approach can help to optimize use of teratogenic medications and contraceptives

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Questions?

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