Prescribing in pregnancy

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Abstract

There are many challenges to prescribing in pregnancy and a structured approach to guide and organize clinical decision making can be very useful. Our framework considers: a detailed approach to clarifying the risk–benefit relationship; general and safe principles of prescribing medications where uncertainty often exists; and the importance of communicating clearly with patients and engaging them in decision making and treatment. We review teratogenic medications to be avoided in reproductive age women and review medication safety in common medical conditions in pregnancy. Finally, we briefly review the safety of medications used in complex medical conditions including epilepsy, bacterial infections, anticoagulation and autoimmune disorders.

Keywords drug safety; pharmacokinetics; pregnancy; prescribing; teratogen

Introduction

Prescribing in pregnancy considers three domains: the medications considered and their known and unknown risks and benefits; the disease being treated and its anticipated course and consequences in pregnancy; and patient specific factors, such as the severity of their disease and their disposition to treatment in pregnancy. Figure 1a shows these three overlapping domains and the cycle of decision making which includes analyzing the risk/benefit relationship, following a set of safe and pragmatic principles for prescribing in pregnancy and communicating clearly with the patient. Figure 1b includes a partial list of teratogenic medications to be avoided or used cautiously in women of reproductive age. This details the FDA classification, teratogenic mechanism and malformations associated with known teratogens.

The art of prescribing in pregnancy lies in negotiating the uncertainty in the risk–benefit relationship, the skill involves collecting and interpreting information and the task is to compile patient, disease and drug information and make the best therapeutic choice. In Section 1 we first elaborate our framework for prescribing in pregnancy. Section 2 reviews prescribing for common medical conditions in pregnancy and Section 3 briefly reviews medical treatment of complex conditions in pregnancy.

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Section 1: A framework for prescribing in pregnancy

1.1: Organizing and understanding the risk of medications

As medications are used increasingly in pregnancy, both purposefully and inadvertently, information on their fetal risk develops. This information is collected through case reports, drug registries, prospective and retrospective studies. Figure 2 demonstrates the many levels of collecting, organizing and interpreting information that informs a therapeutic decision. Often using summarized data and therapeutic recommendations from the top of the pyramid is sufficient. However, in complex cases where guidelines do not exist or where recommendations from different sources conflict, information from every level must be considered.

In complex cases the quality of the evidence on risk and the clinical importance of the fetal effect must be critically evaluated as reviewed in Figure 2.

1.2: The benefit of treatment

The risk–benefit decision must consider: the anticipated course of disease with and without treatment, alternative treatment options, the effect of the disease on pregnancy and pregnancy on the disease. For example, biologics may be indicated for Crohns disease with fistulae but not for psoriatic arthropathy.

1.3: Principles of prescribing in pregnancy

With the uncertain risk associated with many medications, a broad set of principles should be followed as shown in Figure 1.

1.3.1: Plan ahead: pre-pregnancy, antepartum and postpartum:

Pre-pregnancy – physicians need to anticipate the unplanned pregnancies of their patients. Women of childbearing age should not be on teratogenic medications without a strong indication, a lack of alternative drugs and a contraception plan. Figure 1b lists some of the major medications that are teratogens and that should be avoided. Counselling is essential for women with complex conditions such as renal disease, lupus, and cardiac disease. Planning ahead can improve patient compliance, achieve disease control prior to pregnancy and avoid unnecessary first trimester drug exposures.

Antepartum – management includes: adjusting drug doses, educating patients about essential medications i.e. asthma treatment and thyroid replacement; monitoring fetal development and organizing multidisciplinary care.

1.3.2: Apply physiology: maternal, placental, and fetal:

The physiological changes of pregnancy include an increased glomerular filtration rate, decreased protein binding of drugs, increased volume of drug distribution and alteration of hepatic enzyme activity. These changes may alter the effective dose of the drug and can be anticipated for specific medications. For

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6. Timing is Critical ORGAN	Critical Weeks*
CNS	3-16
Cardiac	3-6
Upper Limbs	4-5
Lower Limbs	4-5
Teeth	6.5-8
Palate	6.5-8.5
External Genitalia	7-9
Ear	4-9

*Critical period when teratogens may induce major abnormality

1: Plan ahead
2: Apply Physiology
3: Consider alternatives
4: Put Risk in context
5: Monitor & Re-assess
6: Timing is critical
7: Collaborate

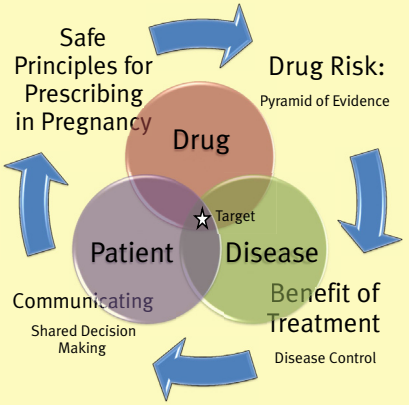
1: Prepregnancy counselling: review necessary medications and compliance. Avoid teratogens in reproductive age women.

2. Maternal: Pharmacokinetics
Placental Transfer & Metabolism
Fetal Organ Development

2. Use minimum effective dose and adjust for:
• increased renal clearance, volume of distribution, altered hepatic metabolism and protein binding

4. Absolute and relative risk.
Positive and negative framing
Clinical oucomes that matter.

5. Response to treatment, Disease activity, Fetal Development



b

δ : Teratogen mechanisms include: (ref 5 - van Gelder, 2010)
Folate Antagonism (FA) | **Oxidative Stress (OxS)** | **Multiple mechanisms (+++)**
Neural Crest Cell Disruption (NCD) | **Vascular Disruption (VaD)** | **Direct DNA Effect (DIR) - this final category added for this table (not from reference)**
Endocrine Disrupting Chemicles (EDC) | **Receptor and Enzyme Medicated Teratogenesis (RET)**

TERATOGEN	Ω	Therapeutic action.	δ	USE	Fetal consequences and comments
Methotrexate	X	Inh. DNA Synthesis	FA	RA/ONC	Abortifacient. T1 - Craniofacial, Limb and CNS Abnormalities. D/C 3 months before conception.
Leflunomide	X	Inh. Pyrimidine Synthesis	DIR	RA.	Low dose toxicity in rats – anopthalmia. D/C 2 years before conception. Cholestyramine may shorten half life
MMF	D	Inh.Purines,B&T cytostatic	DIR	Transp	T1 spontaneous abortions, abnormal phenotype: external ear, cleft lip, facial limb, esophageal and renal
Cyclophosphamide	D	Alkylating agent	DIR	ONC/SLE	T1: ocular, limb, palate,and skeletal abnormalies. In critical illness (cancer) avoid treatment in T1 and late T3
Thalidomide	X	Anti-Angiogenic	OxS	ONC	Limb cardiovascular and bowel anomalies. Specific risk period – day 34 to 50. Used in Multiple Myeloma
Tamoxifen	D	SERM	EDC	ONC	Toxic changes in reproductive tract of animals. Potential DES like syndrome, long term follow up for exposed
Valproate	D	Alters neurotransmission	+++	AED	Highest risk of all AEDS. FA/OxS/RET. Neural-tube defects, clefts, skeletal abnormalities, cognitive delay.
Phenytoin	D	Stabilizes neurons	+++	AED	T1: Fetal Hydantoin Syndrome (FHS): craniofacial anomalies, fingernail and distal digit hypoplasia, growth deficiency, developmental delay, cardiac defects, clefts
Carbamazepine	D	Neural and TCA effect	FA	AED	T1: FHS, spina bifida, cardiovascular and urinary tract defects.
Phenobarbital	D	Barbituate neuro suppress	FA	AED	T1: Clefts, cardiac anomalies, urinary tract abnormalities.
Ergots	X	Constricts cranial vessels	VaD	Migraine	May cause maternal/fetal vascular disruption and reduced placental blood flow
ACEi/ARB/DRI	D	Renin-Angiotensin Block	RET	HTN	T2 and T3 use causes renal dysgenesis and failure, oliguria and secondary pulmonary hypoplasia.
Warfarin	X	Vitamin K. Antagonist.	RET	DVT/PE	Coumadin embryopathy, weeks 6 -12, nasal hypoplasia, stippled epiphyses, limb hypoplasia, CNS effect.
Amiodarone	D	Class 3 anti-arrythmic	EDC		Fetal thyroid abnormalities may develop due to iodine disruption. Other anti-arrythmics preferred.
Bosentan	X	Endothelial rec. antagonist	NCD	P.HTN	Limited human data. Animal malformations and biologically plausible mechanism of teratogenicity
Radioactive Iodine	X	Focal radiation-ablation	DIR	Thyroid	Avidly concentrated in fetal thyroid and destroys fetal thyroid tissue - contraindicated in pregnancy and BF
Hormones	/	Hormonal treatments	EDC	Endo	Testosterone, Anabolic steroids, Androgenic progestins, Danazol. ♀virulization :♂lack of masculization
Lithium carbonate	D	Alters nerve ion transport	RET	Bipolar	T1: Small risk of Ebstein' s anomaly and cardiac defects. Transient newborn effects: hypotonia, cyanosis, DI
VIT. A Analogues.	X	Cellular differentiation	NCD	DERM	Isotretinoin (acne). CNS, craniofacial, cardiac, thymic. Acitretin (psoriasis). D/C 3 years before conception.

ABBREVIATIONS: Column 1. MMF: Mycophenolate. ACEi- Angiotensin converting enzyme inhibitor eg. Ramipril. ARB-Angiotensin Receptor Blocker eg. Losartan. DRI: Direct Renin Inhibitor eg. Aliskerin. Column 2. Ω: FDA Classification#: A: Controlled human studies show no risk, B: No evidence of risk in studies. C: Risk Cannot be ruled out. D: Positive evidence of risk. X: Contraindicated in pregnancy #. Column 3. B&T-B and T Cells. SERM-Selective Estrogen Receptor Modulator. TCA-tricyclic acid. Column 4. see header. Column 5. RA-Rheumatoid Arthritis. SLE-Lupus. ONC-Oncology. Transp-Post organ transplantation. HTN. Hypertension. Bipolar- Mood disorder. DERM-dermatolog. DVT: Deep venous thrombus. PE: Pulmonary Embolism. P. HTN: Pulmonary Hypertension. Column 6: T1/T2/T3-first/second/third trimester. D/C-discontinue. DI-diabetes insipidus

Figure 1 (**a**) The approach and principles for prescribing in Pregnancy. (**b**) Table X: The drug teratogens (A Partial List Only).