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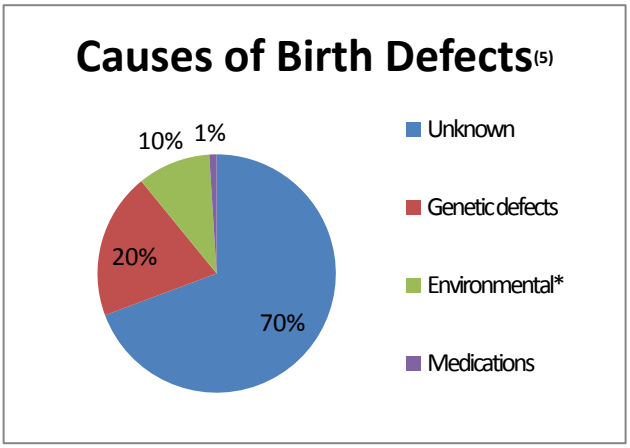
An Approach to Medication Management of Chronic Disease during Pregnancy

There are three simple questions to ask those planning pregnancy or already pregnant who approach you about medication management of chronic disease during pregnancy:

1. Will the pregnancy affect the disease state?
2. Could the condition affect the outcome of the pregnancy?
3. What risk does the drug confer to the pregnancy outcome?

Approximately 90% of women will take some form of drug while pregnant.[1] Pharmacists, as experts on medications, are often asked for advice on the use of medication during pregnancy.[2] It is essential that health care professionals, those planning to have children, and pregnant women are informed about the benefits and risks of drug/chemical exposure during pregnancy.[3] Multiple resources, provided below, are available for healthcare professionals and parents to access up-to-date, accurate information about specific medical conditions and medications in order to make informed decisions about medication use during pregnancy.

Taking certain medications during pregnancy can cause serious birth defects (ex. thalidomide and isotretinoin) but other medication can prevent serious birth defects (ex. folic acid). Many women worry if they take a medication before knowing they are pregnant what the effects of the medication will be on their unborn baby.[4] Because of this, it is important that women talk with their health care professional before starting and stopping medications when planning to become pregnant. As health care professionals, it is important to counsel patients appropriately based on whether the pregnancy is being planned or if the woman is already pregnant.



It is important to communicate baseline risk of birth defects. The baseline risk of congenital malformations is approximately 3 to 6%, with approximately 3% considered severe.[5]
The concepts that not all birth defects are caused by drugs, that not all drugs cause birth defects, and that some untreated maternal conditions can cause birth defects are important pieces of information to relay. Additionally, some birth defects can't be prevented whether because the source is DNA or the fact at this point many causes are simply unidentified.

Figure 1: Causes of Birth Defects
*: includes conditions and infection

Will the pregnancy affect the disease state?[6]

Pregnancy can alter the control of medical conditions – either positively or negatively. The dose used to control a medical condition may require adjustment when the woman becomes pregnant and/or throughout the course of her pregnancy. A dose may need to be increased because of changes in pharmacokinetics (eg. levothyroxine) or reduction in disease control (eg. epilepsy). Conversely, symptoms of some conditions such as myasthenia gravis and rheumatoid arthritis may improve during pregnancy allowing dose reduction, or even discontinuation

of medications. There are also medical conditions that may develop as a result of the pregnancy and subside after delivery including gestational diabetes and gestational hypertension.

Could the condition affect the outcome of the pregnancy?

Maternal diseases can be serious conditions.[2] Fear of using medications during pregnancy can lead to under treatment of these medical conditions. It is necessary to comply with treatment of an underlying condition to ensure the health of the pregnant woman, as well as, the health of her unborn baby.[1,4] The simple equation to be applied is to weigh the therapeutic benefits of the drug to the mother and fetus against its risk potential to the developing fetus.[7]

Table 1: Common Conditions That May Affect Pregnancy Outcome

Condition	Risks of Under Treatment	Management Options	Important Information
Asthma[3,8]	- Low birth weight, small for gestational age, preterm delivery and preeclampsia -congenital malformation including malformation of the nervous, respiratory, and digestive systems	- optimal asthma treatment according to the guidelines and close monitoring - DOC: inhaled short-acting β2-adrenergic agonists and inhaled corticosteroids	- Up to 8% of all pregnant women and women of childbearing age are affected by asthma.
Depression[9-11]	- Adverse fetal outcomes and higher risk of maternal morbidity including suicidal ideation and attempts - Cognitive distortions may prevent mother from seeking prenatal care. - Postpartum depression	- Commonly used antidepressants are low risk during pregnancy (SSRIs) - Gradually taper off a current medication if the decision to stop is made to avoid discontinuation syndrome - The risk of not treating major depression adequately into pregnancy outweighs the risk of harm to the infant	- Depression is most prevalent among people between 25-44 years old - SSRIs have been associated with neonatal withdrawal symptoms when taken close to term
Diabetes[3,9,12,13]	- Pre-existing diabetes (type 1 or 2) increases the risk for miscarriage, perinatal mortality, fetal macrosomia (>8lbs 13oz) and congenital malformations	- Switch to an insulin regimen from oral hypoglycemic agents and aim to achieve an A1C level of <7% (or <6% if safely achievable) - Frequent self-monitoring of blood glucose is recommended	- Undergo an eye exam as pregnancy can accelerate retinopathy - Undergo screening for cardiovascular disease and chronic kidney disease - Discontinue ACEIs, ARBs and statins
Epilepsy[3,9]	- Reports of maternal seizures are associated with increased risk of miscarriage, preterm labour, intracranial hemorrhage, and fetal hypoxia with bradycardia - A woman with epilepsy must be informed that the risk of a congenital malformation for her child is increased 2-3fold even though 90% of women treated with AEDs deliver a healthy baby	- Many of the risks of congenital malformations are associated with AEDs -Available evidence does not allow selection of one or more AEDs that are "best" -Switching AEDs during pregnancy should be avoided; therefore avoid valproic acid in women of childbearing years if possible -Polypharmacy likely increases the risk of congenital malformations	- There is an increased risk of oral contraceptive failure in women taking enzyme-inducing AEDs - 90% of women with epilepsy who are seizure-free for at least 9 months prior to pregnancy will remain seizure-free during pregnancy - Women taking AED treatment during child- bearing years should receive continuous folic acid
Nausea and Vomiting[14]	- Dehydration and malnutrition	-Eat small amounts of bland food every 1-2 hours - Diclectin (doxylamine/pyridoxine) is HC-approved for nausea and vomiting of pregnancy; dimenhydrinate, diphenhydramine are other options (not approved for this indication)	- Affects up to 85% of pregnant women -Nausea and vomiting of pregnancy is not a sign of psychological problems
AED =antiepileptic drug; DOC= Drug of Choice; HC=Health Canada			

What risk does the drug confer to the pregnancy outcome?

The risk that a drug can impose on the pregnancy outcome can be estimated by:

1. Stage of pregnancy
2. Dose and frequency of exposure
3. Safety and efficacy information available on the medication

Stage of Pregnancy:

The timing of exposure can determine the affect a medication can have on the developing fetus.

Table 2: Stages of Pregnancy and Potential Impact of Medications[3,6]

Stage of Pregnancy	Day of Gestation	Fetal Development	Potential Impact of Medications
First	0-18	Fertilization to embryonic differentiation	Unsuccessful implantation or absolutely no harm to the fetus Very little risk unless drug persists
Second	18-60	Organ Development	Highest risk period; malformation, miscarriage
Third	≥61	Growth and functional maturation; development of central nervous system	Growth delays; cognitive/behavioural issues
Term	Full term: >39 weeks		Preterm labour Neonatal withdrawal

Intensity of Exposure

In line with the general principle that any drug can cause adverse effects given a sufficient dose and every drug has a threshold under which no adverse effects occur, the same can be said of teratogenicity.[15] Unfortunately, the threshold exposure to cause teratogenicity is unknown for most, if not all, drugs. As such, the tenet of using the lowest effective dose prevails – keeping in mind, the lowest effective dose may be higher in pregnancy than in the non-pregnancy state.

Safety and efficacy information available on the medication

It is difficult to obtain safety information regarding medication use during pregnancy. While information based on the structure and characteristics of the drug itself may be evaluated to help determine risk of fetal exposure, human experience is preferred. For many drugs, documentation of human exposure is scarce and animal experiments provide the only basis for risk assessment.[3] In terms of human, data, we rely on case-reports and epidemiological investigations to obtain a large portion of our reproductive data since it is unethical to enroll pregnant women in studies.[3] These data sources have inherent limitations such as reporting bias (it is more likely a woman whose baby was born with a defect will report her experience than the ones who used the medication uneventfully during pregnancy), recall bias (retrospective studies rely on the subject's memory, which is prone to inaccuracy), confounding factors (other factors that may affect results such as maternal age, other conditions and severity, obstetrical history), and sample size (as defects are rare a large sample is required to identify patterns). Some pregnancy registries have been established, both by manufacturers and teratology agencies. Since we can always use more information regarding use of medications in pregnancy, recommending patients join existing registries is useful. The manufacturer can be contacted regarding the existence of a registry or teratology centres such as Motherisk or MotherToBaby.

Summary

Many women will use medication during pregnancy. Each woman needs to be evaluated individually regarding the benefit versus risks of each medication considered for use. Using a systematic approach, as described above, ensures that the medical conditions that change during pregnancy are assessed, conditions that show evidence for negative pregnancy outcomes are controlled and the medications used during pregnancy are the safest options with the most available evidence.

Resources:

Textbooks:

- Briggs GG, Freeman RK, Yaffe SJ, editors. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011
- Koren G, editor. Maternal-fetal toxicology: A clinician's guide. 3rd ed. New York: Marcel Dekker, Inc.; 2001
- Schaefer C, Peters P, Miller R. Drugs During Pregnancy and Lactation Treatment Options and Risk Assessment. 2nd ed. San Francisco: Elsevier; 2007

Web Resources:

www.motherrisk.org | www.mothertobaby.org | www.infantrisk.com

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14. Koren G, Maltepe C. How to Survive Morning Sickness Successfully. Available at: http://www.motherisk.org/documents/BSRC_morning_sickness_EN.pdf. Accessed 2014 Jan 29.
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