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Toxicology in Pregnancy

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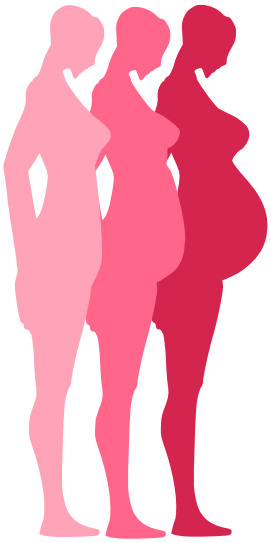

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Introduction

According to studies on medication use during pregnancy, approximately 90% of women take at least one medication during pregnancy. Usually the medication is available over the counter, but 50-70% of women throughout the United States use at least one prescription medicine during pregnancy.[1] As health care practitioners, it is important to understand the role medications play in pregnant patients so we may assist and treat them appropriately.

Medication Exposures in Pregnancy

Poison exposures reported to US poison centers are aggregated by the American Association of Poison Control Centers (AAPCC) annually. In 2015 there were 2,168,371 total human exposures reported to US poison centers, of which 6,932 (0.32%) occurred in pregnant women. Most exposures in pregnancy were unintentional, approximately 5,115 (73.8%).[2] However, approximately 1,379 (19.9%) of exposures in pregnant women involved a self-harm attempt.[2]

Pharmacokinetics during Pregnancy

Data regarding pharmacokinetics of drugs in pregnancy are limited. As a result, predictions regarding drug pharmacokinetics must be made using available data about physiologic changes in the pregnant mother and developing fetus.

Maternal Factors

Physiologic changes may alter how medications behave in the pregnant body compared to women who are not pregnant. The most important factors to consider involve those that alter drug absorption, distribution, metabolism, and/or elimination.

Absorption

During pregnancy, a decrease in gut motility,[3-5] an increase in gastric pH,[4,5] and a delay in gastric emptying occurs.[4] These alterations can affect how oral drugs are absorbed and the timing of their effects, with lower peak concentrations and delayed absorption. In addition, increased tidal volume and pulmonary blood flow in pregnant women allow for greater alveolar uptake of inhaled drugs and may result in decreased amounts needed to reach similar clinical effects.[4]

Distribution

A 30-50% increase in cardiac output as well as a 40% increase in maternal blood volume occurs during pregnancy.[6] Blood flow to certain areas of the body is also altered. The kidneys, mammary glands, and uterus have increased blood flow, while the skeletal muscles have decreased blood flow.[7] Serum albumin concentrations decrease, which affects free plasma concentrations of drugs that are highly protein bound, such as phenytoin.[8] The volume of distribution (Vd) can also be affected due to the increased blood flow. Medications with a low Vd are more concentrated in the blood, and will reach lower plasma concentrations during pregnancy due to a dilutional effect.[4] If there are no other changes in the pharmacokinetics of a medication, this would mean higher doses would be necessary to obtain a therapeutic effect.

Metabolism

Many medications are metabolized by cytochrome P450s, located primarily in the liver. During pregnancy, several of the key enzymes responsible for drug metabolism have altered activity.[8] Table 1 introduces the topic of enzymes utilized during drug metabolism and should help a clinician think about how drug metabolism may be altered during pregnancy, leading to possible dose adjustments or medication changes during pregnancy. Many more medications experience altered metabolism during pregnancy; this list only represents some of the more common drugs encountered in practice.

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The Dangers of Buprenorphine Poisoning

By Taylor Rhien, PharmD, CSPI

Buprenorphine is a synthetic opioid with FDA indications for pain management and opioid dependence. It is formulated alone and in combination with naloxone when used for treatment of opioid addiction.[1] Since its introduction in 2002, buprenorphine products have seen a steady increase in use.[2] This rise in prescriptions has been mirrored by increasing numbers of buprenorphine poisonings.[3]

Buprenorphine's use in opioid dependence is due to its unique activity at opioid receptors. It acts as a partial agonist at mu receptors, and also has weak antagonist activity at kappa receptors.[1] Unlike a full agonist, drugs with partial agonist activity have a plateaued effect at increasing doses. For buprenorphine, this means a lower risk of respiratory depression and euphoria at high doses. While this ceiling effect is true for patients who are tolerant to high doses of opioids, children and opioid naïve patients are at risk of serious toxicity below these larger doses.[4]

Other unique characteristics of buprenorphine include its long half-life, high receptor affinity, and high potency. Although these are good attributes for its use in dependency, they often complicate overdoses. The mean elimination half-life ranges from 24-48 hours, with an active metabolite.[1] The high affinity for mu-opioid receptors means that higher doses of naloxone are often required to reverse overdoses.[1] Because of its high potency, even a single tablet of buprenorphine can be dangerous in pediatric and opioid naïve patients.[5]

More and more cases of pediatric bupropion poisonings are being published. These cases demonstrate the potential for serious toxicity, including death, following exploratory ingestions.[5] A recent single-center, retrospective cohort study found that pediatric patients exposed to buprenorphine experience high rates of clinical effects. Of the 88 children admitted for observation, the most common symptoms were respiratory depression (83%), decreased mental status (80%), miosis (77%), and emesis (45%). Also notable is the onset of respiratory depression was regularly delayed (median 263 minutes).[4]

With the increasing focus on opioid addiction and treatment, buprenorphine exposures are becoming more common. All pediatric buprenorphine exposure should be recognized as potentially serious. Since delayed respiratory depression is possible, children should be admitted for longer observation and never discharged during the night.

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TABLE 1: Changes in Cytochrome P450 Enzyme Activity during Pregnancy[8]

CYP Changes	Examples of Drugs Affected
↓ 1A2 Activity	Caffeine, duloxetine, cyclobenzaprine
↓ 2C19 Activity	Omeprazole, lansoprazole, pantoprazole
↑ 2A6 Activity	Nicotine
↑ 2C9 Activity	Phenytoin, ibuprofen, glipizide
↑ 2D6 Activity	Dextromethorphan, metoprolol, tramadol, paroxetine
↑ 3A4 Activity	Nifedipine, dilitiazem, alprazolam

Evidence suggests that alterations in hormones such as progesterone and estrogen during pregnancy lead to the up- or down-regulation of different enzymes used during drug metabolism.[8] Drug doses may need to be increased or decreased in pregnant women based on these metabolic changes.

Elimination

Most medications are eliminated unchanged or as metabolites in the urine. During pregnancy, glomerular filtration rate is increased.[9] Medications that are primarily renally excreted may require increased dose adjustments to account for increased clearance during pregnancy. Depending on the medication, dose increases anywhere from 20-65% are recommended to maintain pre-pregnancy therapeutic concentrations.[8]

Fetal Factors

There are many aspects of fetal development to consider during a drug exposure. The most important of these is the timing of the exposure in terms of the gestational age. The gestational age should be determined using either time since conception or time since last menstrual period. Common practice is to use time since last menstrual period until ultrasound confirmation. In the first 2 weeks following conception, a medication could result in a spontaneous abortion due to failure of development of the maternal-placental-fetal unit.[10] This is due to the rapidly dividing cells during this time frame and any insult or injury that may occur typically results in a catastrophic effect leading to serious damage that prevents implantation.[10]

Organogenesis occurs in the first 8 weeks of pregnancy and drug exposure during this time frame may result in teratogenesis. (A detailed description of teratogenesis is beyond the scope of this article.) Ideally, no medications should be used during this critical developmental period. Medication exposures later in pregnancy, during the second and third trimesters, are more likely to cause harm related to growth and development.[10]

The Placenta

The placenta acts as a barrier between the mother and fetus. To have effects on the fetus, drugs must cross the placenta and enter fetal circulation. The primary ways drugs are transferred across the placenta include passive diffusion, facilitated diffusion, and active transport.[11]

Passive Diffusion

Passive diffusion is the most common form of exchange in the placenta.[11] For drugs to cross the placenta by passive diffusion, there must be a higher concentration of drug in the mother and lower *(cont. on pg. 3)*

(cont. from pg. 2)

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concentration in the fetus resulting in a concentration gradient and the medication must have certain chemical properties. Drugs that are most likely to undergo passive diffusion have low molecular weight, are highly lipid soluble, are mostly unionized in the body, and are not highly protein bound.[12]

Facilitated Diffusion

Facilitated diffusion requires a carrier protein in the cell membrane to assist diffusion of the drug.[11] Similar to passive diffusion, facilitated diffusion also requires a concentration gradient. Only a few drugs have been found to move across the placenta this way, including ganciclovir, glucocorticoids, and some cephalosporin antibiotics.[11]

Active Transport

Active transport requires energy in the form of adenosine triphosphate (ATP) or electrochemical gradients (such as those provided by Na+, Cl-, or H+) to power a protein that pumps drugs across either the maternal or fetal membrane bordering the area where maternal blood pools.[11] It differs from the other transport methods because it requires energy and can move drugs against a concentration gradient. The drugs that are transported via active transport often resemble endogenous substances in the body such as dexamethasone.[11]

In addition to acting as a physical barrier to drug transport, the placenta also may act as a metabolic barrier. The placenta contains different forms of CYP isoenzymes, but to date, these enzymes have not been found to be clinically significant.[11]

Practical Applications

FDA Classifications of Medications for Use in Pregnancy

In 1979, the FDA began classifying medications according to their safety in pregnancy. There were five letter categories created, ranging from safe in pregnancy (A) to contraindicated in pregnancy (X). However, over the past decade, these categories have been revised multiple times. The Pregnancy and Lactation Labeling (Drugs) Final Rule (PLLR) was released in December 2014 and replaces the previously used pregnancy categories.[13]

PLLR is required for all newly marketed drugs but has not replaced the previously noted FDA Pregnancy categories on drugs that were available prior to the PLLR release. Specifically, all drugs approved after June 30, 2015 require this new labeling, while drugs approved after June 30, 2001 are being transitioned to the new labeling gradually. By June 29, 2018, the previous pregnancy letter category must be removed from all labels, even drugs approved prior to June 29, 2001 that are not subject to the PLLR.[13] Thus it is important for clinicians to understand both methods of labeling at this time.

TABLE 2: 1979 FDA Pregnancy Categories for Drug Labeling[13]

FDA Pregnancy Category	Description
A	Studies in pregnant women have been performed and have documented no risk to the fetus.
B	Studies in pregnant women have not been performed in humans, but animal studies have not shown harm to the fetus.
C	Studies in pregnant women have not been performed in humans, but animal studies have shown adverse effects in the fetus.
D	Studies in pregnant women have been performed and shown potential for harm to the fetus. This may be outweighed by benefits of the drug to the mother.
X	Studies in pregnant women have been performed and have shown evidence of fetal abnormalities. Use is contraindicated.

TABLE 3: Sampling of Medications for FDA Pregnancy Letter Category[14]

FDA Pregnancy Category	Medications
A	Thyroid preparations, folic acid, pyridoxine, vaginal nystatin, magnesium sulfate
B	Famotidine, metformin, amoxicillin
C	Ibuprofen, acetaminophen, albuterol, sertraline, fluoxetine
D	Paroxetine, lithium, phenytoin
X	Isotretinon

FDA Pregnancy and Lactation Labeling Final Rule

The new PLLR labeling requirements consist of three main sections: Pregnancy, Lactation, and Females and Males of Reproductive Potential. Each section may be further broken down into subsections. The final rule also requires the subheading of "Risk Summary" in each section and then other subsections are included if pertinent information is available.[13]

The PLLR also includes information for Pregnancy Exposure Registries if one is available for each drug, which will allow for further data to be obtained on risks of medication use during pregnancy.[13]

These new labeling requirements should provide a more accurate picture of risk associated with use of medications without leading to a false sense of security due to lack of understanding associated with previous labeling methods.

A more in-depth discussion of the PLLR is beyond the scope of this article but should be recognized as pertinent when considering drug prescribing practices in pregnancy.

FDA Pregnancy Categories

Many practitioners know what pregnancy category a medication falls under and base clinical decisions on this information. Due to this fact, it is important to understand these categories and their limitations. Table 2 describes the different FDA Pregnancy Letter Categories and what level of evidence is needed to achieve a certain letter labeling.

Assignments to the FDA Pregnancy Categories are based on the level of evidence available. Clinicians should not assume that the level of risk of harm to the fetus increases from Category A to B to C to D to X. This may be true in some *(cont. on pg. 4)*

(cont. from pg. 3)

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but not most cases; note in Table 2 that in Categories C, D, and X, the FDA assesses risk to fetus versus benefit to mother.

Few drugs fit into Category A, but many drugs are Category B and C and their use in clinical practice is not as clear. Several agents and their pregnancy categories are listed in Table 3.

Approach to the Pregnant Patient in a Suspected Poisoning

The same general principles used to approach any patient in the emergency department can be applied to pregnant patients. They should initially be stabilized, and then provided with supportive care.

Resuscitation

Taking care of the mother is the best way to ensure good outcomes for both mother and baby. Current Advanced Cardiac Life Support (ACLS) guidelines should be followed during resuscitation of a pregnant patient. In addition, emergency caesarian section should be considered in the first 5 minutes of cardiac arrest in the mother.[6] This decision depends on the gestational age of the fetus, and is generally considered at ages greater than 24 weeks.[6,15]

Toxicology

Decontamination measures can be considered in pregnant patients. Activated charcoal is safe to administer and whole bowel irrigation can also be considered. These methods may also be effective outside of the initial 1-hour window considered in the case of the non-pregnant patient due to delayed gastric emptying.[10] In severe cases of toxicity, dialysis can also be utilized in pregnant patients for substances amenable to dialysis or for severe acid/base and/or electrolyte abnormalities.[10] Commonly used antidote agents such as sodium bicarbonate, naloxone, N-acetyl cysteine, and deferoxamine are all safe in the pregnant patient.

Conclusions

Many factors influence fetal drug exposure during pregnancy. Limited data are available regarding drug pharmacokinetics during pregnancy. Clinical decisions should take into account the balance between risks and benefits to the mother as well as the fetus for appropriate prescribing practices. Because it is crucial to the survival of the fetus in a poisoned pregnant patient, preserving the health of the mother should always be the top priority. The Utah Poison Control Center is available for consultation 24 hours a day, 7 days a week at 1-800-222-1222.

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OUTREACH EDUCATION

Helping You Help Your Patients

By Sherrie Pace, MS, MCHES

Utah Poison Control Center (UPCC) plays an important role in the health care system of the state. Not only do our specialists consult with the general public when they call for poison-related help, they also assist physicians and other health care providers in the management of patients with poison exposures. In 2016, 22% of human exposure calls to the UPCC originated from health care facilities.

The UPCC offers physicians, pre-hospital providers, nurses, EMS, and physician assistants access to a board-certified medical toxicologist available through our specialists 24 hours a day, 7 days a week, 365 days a year for consultation and backup. Specialists can also arrange for a direct physician-to-physician consultation on difficult and unusual cases. This is particularly helpful for emergency health care providers who frequently consult with UPCC specialists on poison exposure cases.

The UPCC follows patients through their hospital stay and provides ongoing consultation with the treating health care provider. This means that our specialists and trained pharmacy students place calls to hospitals inquiring about the status of those patients. The cooperation of health care professionals is greatly appreciated and helps us ensure that our treatment recommendations stay current and gather important information to best monitor outcomes. Rest assured that sharing information with the poison center is fully compliant with HIPAA regulations. The HIPAA privacy rule permits a covered entity to disclose protected health information to health care providers for treatment purposes. The preamble to the HIPAA rule states that poison control centers are health care providers.

The UPCC welcomes your call anytime, day or night, and wants to support you in your lifesaving work. Working in tandem with health care providers, we will provide the best possible care and outcome for patients.

TOXINS IN THE NEWS

Sodium Acetate

By B. Zane Horowitz, MD, FACMT

Every hospital in the country is struggling with a nation-wide shortage of sodium bicarbonate.

We have been here before, when this occurred in 2012. The poison center has several overdoses, including aspirin and tricyclic antidepressants (TCAs) where sodium bicarbonate plays a crucial role. *(cont. on pg. 5)*

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Sodium Acetate

The "fix" to this problem when alkalization is required for tricyclic antidepressants or salicylate toxicity is the substitution of sodium acetate 1 meq equal to each 1 meq of sodium bicarbonate. To make a typical drip, add 150 meq of sodium acetate to 1 liter of D5W and run it at twice the maintenance rate, or about 200 to 250 cc/hr. The goal is to get the serum pH between 7.50 and 7.55 based on a venous blood gas.

However, sodium acetate cannot be pushed rapidly as a bolus. Some clinicians supported the use of a "test bolus sodium bicarbonate to see if the QRS interval will shorten." However, this is not reinforced by the literature. While years of clinical experience suggests that for TCAs the test bolus does shorten the QRS interval, it has never been reported for any other agent with sodium channel blocking potential such as antihistamines. Given we now have a scarce resource in sodium bicarbonate we should not use the test bolus to see if the QRS narrows.

Sodium bicarbonate should be reserved for the following situations where bolus doses are necessary: a patient with a TCA overdose who is deteriorating despite sodium acetate therapy with wide QRS > 160 msec, hypotension, or seizures. Bolus sodium bicarbonate is also recommended as a pre-intubation medication when intubation is required for a salicylate or TCA overdose.

MEET THE UPCC STAFF

Candice Colby, PharmD, CSPI, is a Utah native and attended pharmacy school at The University of Utah. She discovered her interest in toxicology during a pharmacy school rotation at the UPCC. She finds working at the poison center deeply rewarding because it allows her to continue learning in a fast-paced environment while making a difference in people's lives. When not at the poison center, she enjoys live music, being outdoors, traveling, and caring for her two retired racing greyhounds. Being a lifelong animal lover, she is most interested in animal toxins such as snake envenomations and rabies.

Peter Chad Adamovich, BS, has been working at UPCC since the summer of 2015, shortly after being accepted to The University of Utah College of Pharmacy. He graduated from Brigham Young University with a BS in Biochemistry in April of that year. He is working toward completing both a PharmD and a PhD, with a focus in pharmaceutical chemistry. While he enjoys clinical work, his goal is to help develop novel therapeutics and therapeutic aids for the advancement of medicine. Though his ultimate goal is to work in the industry, he hopes his clinical experience here at the poison center will influence his work in developing the next generation of pharmaceutical therapeutics. He loves fly fishing, rock climbing, reading and writing science fiction, and camping with his family. His most memorable calls are those where a mom goes from crying and afraid, to relieved and confident in trusting her child to our expertise.

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