

DRUGS IN THE PREGNANT BITCH: ASSESSING AND MANAGING RISKS

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Avoid drugs in pregnancy! This mantra is seen in practically every article on this subject, but what if you can't or really shouldn't? What's safe (and what does that mean?), what's not and how do we know? The greatest problem on this issue is that almost no data specific to dogs is published (known?). So once again, like so much in veterinary pharmacology and therapeutics, we extrapolate from lab animal data and from human exposure experience. However, we do know enough to help us make decisions with owners that, while not guaranteeing risk-free treatment, can reduce those risks and, with informed consent, be in the best interest of our patients and our malpractice insurance rates.

Changes in Drug Pharmacology in Pregnant Dogs

When most individuals think about drugs in pregnancy they automatically think: teratogenicity. But since we are contemplating treating the bitch, we first must consider physiologic changes in her and how these can affect the pharmacology (usually the pharmacokinetics) of the drug(s) we propose to administer. Since we have decided not to “avoid use in of drugs in pregnancy”, we want to be reasonably sure that what we are giving will be safe and effective for our primary patient, the bitch. Once again, there is very little information published on physiologic changes in pregnancy impacting pharmacology in either dogs or cats and we must extrapolate information from other species. In pregnant women, cardiac output is increased, particularly in the last trimester of pregnancy. This increase can be as much as 50% over baseline. Secondarily renal blood flow and glomerular filtration rate (GFR) are increased and drugs that are primarily renally excreted have higher clearance rates. Penicillins, cephalosporins and aminoglycosides may all be removed from the circulation significantly faster than in the non-gravid state. Drugs that are cleared hepatically may also be impacted, probably through induction of microsomal enzymes. It is postulated that increased progesterone levels may be responsible for this effect. Some pregnant women have had reduced blood levels of anticonvulsant medications secondary to increased hepatic clearance. Decreased plasma protein binding may also occur in the pregnant mammal. Increased blood volume, decreased albumin levels and decreased affinity of drugs to the plasma proteins can all result in an increased volume of distribution for a given drug. This can cause lower drug concentrations in plasma and potentially sub-therapeutic levels. Consider more intensive monitoring for therapeutic effect and when available, monitor therapeutic blood levels particularly for drugs where a minimum plasma concentration may be required for efficacy and/or the drug has a narrow therapeutic index.

Drug Effects on Fetal Development

Approximately 3-5% of children born in the USA have some sort of developmental defect. These can range from very mild (depressed nasal bridge) to severe. Approximately 65% of these cases have unknown etiology, 20-25% genetic factors or chromosomal defects, 2-3% caused by maternal viral infections and 2-3% teratogen-induced birth defects.

Teratogenic comes from the Greek meaning “producing a monster” or more sensitively, a malformed fetus. Embryocidal and fetocidal effects, while technically not “teratogenic”, are often lumped together under this and related terms. While often associated with drugs, teratogenicity can be caused by a multitude of insults including inadequate nutrition, ionizing radiation or exposure to environmental (including plant) toxins.

There are four so-called general laws of teratogenicity: 1) Initial event is the cessation of development of the embryo/fetus at the site of the injury, 2) Any type of malformation could be produced, 3) Teratogens act on undifferentiated primordium between the period of determination and that of differentiation, 4) sensitivity of various tissues varies according to the teratogen.

Embryotoxicity

If we define the LH peak as day 0 of pregnancy and implantation and placental development at day 20, then the period when the ovum is bathed in uterine fluid (say, days 6 to 20) is the critical period for continued fetal viability. Drug levels in uterine fluid often mimic those found in the plasma and while malformation usually does not result from a serious chemical insult at this stage, spontaneous abortion or resorption (all or none) is often the result. It is highly recommended that the clinician weigh carefully any drug therapy during this stage of pregnancy and if necessary, use the “safest” drug that is required.

Teratogenicity During the Placental Stage

After placental formation, drugs given to the mother that reach her systemic circulation cross into the fetus via the placenta. For years, it was thought that the placenta limited certain drugs from entering fetal circulation, but the concept of a “placental barrier” is more myth than reality in studied mammalian species. While practically all drugs enter fetal circulation, there are certain factors that can either limit or enhance the amounts of a given drug into the fetus. Species, drug dose, duration of exposure, drug size and lipid solubility, placental blood supply, gestational age, maternal/fetal differences in pH and protein binding, as well as the placenta’s ability to metabolize drugs can all contribute to the amount of exposure of the fetus to a given drug. One potentially important difference between humans and dogs is that human fetal livers can metabolize drugs while it is believed that in dogs this does not occur.

In humans, the first “trimester” and in particular the first 2/3 of the first trimester is the most critical period. Major organogenesis, limb, ear and palate formation occur during this period. In dogs, if we are using the LH peak as day 0 and the average whelping is day 65, while the first “trimester” is critical, major organ and limb development extend well past this time. It is probably best to assume that the critical period for exposure to teratogens in dogs extends to perhaps day 40.

Although avoiding drugs during pregnancy may be recommended, many mothers (human and canine) do take some drugs during pregnancy without a detectable problem in the offspring. While most drugs are probably safe to use in a cautious manner, there are some drugs where their risks for causing teratogenic effects MAY outweigh the benefits to the mother.

The FDA uses a five-letter system (**A, B, C, D, X**) of assigning potential teratogenicity risk for a given drug during human pregnancy: **A** = Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters. **B** = Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters. **C** = Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there

are no animal reproduction studies and no adequate studies in humans. **D** = There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. **X** = Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit. Dr Mark Papich uses a slightly different system in a table originally published in CVT X (see references) to evaluate safety of drugs in canine and feline pregnancy: **A** = Probably safe. Although specific studies may not have proved the safety of all drugs in dogs and cats, there are no reports of adverse effects in laboratory animals or women. **B** = Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term. **C** = These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks. **D** = Contraindicated. These drugs have been shown to cause congenital malformations or embryotoxicity.

While it is best to avoid drugs in pregnancy, the risks associated with most drugs, while real, are slight. However, there are specific drugs and classes of drugs that the data either suggests or confirms greater risk to offspring.

Antibiotics/Antifungals

Of the antibiotics/antifungals, **aminoglycosides, fluoroquinolones, tetracyclines** and **griseofulvin** are usually better avoided. However, at least in humans, ciprofloxacin appears to be relatively safe to give to women during pregnancy. No cartilage abnormalities or arthropathy has been noted in human offspring with ciprofloxacin. Birth defects seem to mirror background rates (Report, Pregnancy Team, US FDA Center for Drug Evaluation and Research October 2001).

When Gram-negative bacterial infections are either suspected or confirmed, **aminoglycosides** or **fluoroquinolones** are often drugs of first choice in dogs. This situation can present a therapeutic challenge to the clinician dealing with a pregnant animal, particularly in the interim period between when the infection is suspected/confirmed and when a pathogen can be determined with resultant antibiotic susceptibility. While there are several clinical variables that must be taken into account (site, severity, progression, pregnancy stage, other clinical signs, etc) that should influence antibiotic choice, I would assign relative safety of drugs that may be effective in unknown Gram negative infections in first or second trimester pregnant dogs as: 3rd generation cephalosporins > fluoroquinolones > aminoglycosides. However, most of the reports of birth defects associated with aminoglycosides were associated with kanamycin and streptomycin. It must be remembered that a dead mother ensures 100% fetal death and an aminoglycoside such as amikacin may be the difference.

Antibiotics that might be assumed to be unsafe, such as metronidazole and trimethoprim/sulfa apparently are relatively safe to use in dogs.

Antifungals

Griseofulvin is particularly teratogenic in cats (skeletal and brain malformations), but should not be used in any species during pregnancy. **Fluconazole** has been associated with craniofacial ossification defects in lab animals and birth defects in humans have been most commonly associated with high-dose parenteral therapy. **Ketoconazole** has reportedly caused increased stillbirths in dogs.

GI Drugs

Misoprostel is one GI drug that definitely should be avoided during pregnancy, as it can potentially be an abortifacient. Human babies delivered to term after mothers took misoprostel have a thirty times greater likelihood of exhibiting Möbius syndrome (lifetime facial paralysis). **Colchicine** is sometimes used for hepatic cirrhosis or fibrosis in dogs and has been implicated in birth defects in laboratory animals. It is also can lower sperm counts and cause sperm defects in male animals that can affect the ploidy of sperm with resultant birth defects in offspring.

Anticonvulsants/CNS Drugs

Anticonvulsant medications are another class of agents where there could be potential problems. The two agents most commonly used in dogs, are phenobarbital and bromide salts.

Phenobarbital can cause potential problems such as congenital defects and bleeding in neonates, but these are thought to be very rare. In humans, **bromides** are not recommended in pregnancy as rat pups exposed to bromides *in utero* had lower brain and body weights at birth and demonstrated developmental delay and resultant lower ability levels at maturity. There is controversy as to whether pregnant dogs with seizure disorders should be treated with anticonvulsant therapy during pregnancy, as some believe the risk to fetuses from uncontrolled maternal seizures (fetal anoxia, falls) probably outweighs the risks to the fetuses from the drug(s). However, a study in humans showed a higher incidence of birth defects in offspring whose mothers took medications as opposed to those who did not.

Benzodiazepines

Diazepam and **midazolam** are generally best avoided during pregnancy, particularly in the early stages. Pregnancy safety studies conflict or are complicated by multiple drug use (*e.g.*, alcohol), but enough data is available that causes concern. Of the benzodiazepines, chlordiazepoxide is probably safe and flurazepam, temazepam, triazolam, and probably alprazolam are definitely not.

Pentobarbital has been associated with a high incidence of neonatal mortality (probably respiratory depression) and should be avoided particularly near term.

Analgesic/Antiinflammatory

The newer NSAIDs, carprofen, etodolac, deracoxib, tepoxalin and meloxicam have apparently not been well studied with respect to their safety during pregnancy. **Aspirin**, while used much less today in dogs because of its tendency to cause GI bleeding, and has a relatively controversial track record when used during pregnancy. It may cause excessive bleeding problems or pulmonary hypertension if administered late in pregnancy. **Corticosteroids** used in humans in the first trimester increases the chance of cleft palate, but these drugs are used routinely in women during the 2nd and 3rd trimesters. These agents have been associated with anasarca in brachycephalic breeds.

Cardiac Drugs

ACE inhibitors such as enalapril appear to have teratogenic qualities when used in the second and third trimesters in women. Unlike many teratogens, they are thought to be safe to use in the first trimester. One study demonstrated that regardless of when the drugs were given during pregnancy, approximately 88% of children exposed *in utero* evaluated at 2 years of age were “normal”. The β -blocker **atenolol** appears to cause intrauterine growth restriction (IUGR) in humans, which may be caused by increased vascular resistance in both the mother and fetus. Length and time of exposure (earlier in pregnancy) to atenolol tends to exacerbate this effect.

Sex Hormones/Endocrine

While uncommonly used in dogs, **methimazole** is often used to treat hyperthyroidism in cats. In people, methimazole has been linked to increase in premature births, scalp defects and small-for-gestational-age infants.

Estrogens, such as **DES** and **estradiol cypionate** can cause feminization of male offspring.

Progesterone or androgens such as **testosterone** or **mibolerone** can cause masculinization of females.

Cytotoxic/Antitumor Drugs (including mitotane)

Because many of these agents directly affect actively dividing cells they as a class are definitely problematic in the pregnant patient, although some of these agents appear to be relatively “safe”. The ethical dilemma that faces physicians dealing with pregnant women who require these agents is probably less of a problem in veterinary medicine, but on occasion an owner may accept the risks of therapy to fetuses to get that “one last litter”. Should a veterinarian prescribe these agents knowingly to a pregnant animal, it is recommended to get written and signed acceptance of risk from the animal’s owner before embarking on treatment.

Miscellaneous

Vitamin A Analogs

Certain vitamin A analogs (**isotretinoin**, **acetrein**) are occasionally used in small animal dermatology and are confirmed teratogens in humans and presumably in dogs and cats as well. Before prescribing these agents for veterinary use, the veterinarian must both take the time to explain these risks for the veterinary patient, but more importantly have the owner sign that neither they nor anyone in their household is pregnant and that they clearly understand the potential risks to human offspring if administered during pregnancy. Excessive **vitamin A** alone may cause teratogenic effects as well in dogs or cats; cleft palates, kinked tails and in kittens, cardiac defects have been reported.

Vitamin D

Excess vitamin D in pregnancy can cause cardiac defects, tissue calcinosis, and enamel hypoplasia.

Gold Salts

Gold salts such as **auranofin** are sometimes used to treat pemphigus complex or idiopathic polyarthritis in dogs. These drugs have been demonstrated to be teratogenic in laboratory animals and should only be used in pregnant dogs when the owner accepts the risk.

Acetohydroxamic Acid

An inhibitor of urease that may be useful in the adjunctive treatment of persistent struvite uroliths, this drug is considered to be contraindicated in pregnancy. Pregnant beagles given 25 mg/kg/day (approximate usual dose) had offspring that showed several birth defects, including cardiac, coccygeal, and abdominal wall abnormalities.

Ammonium Chloride

Although little used today, this drug has been shown to cause fetal acidosis and is not recommended for use during pregnancy.

DMSO

Some teratogenic effects have been noted in lab animals and the manufacturer recommends to not use during pregnancy.

Penicillamine

The chelating agent, penicillamine, has been demonstrated to be both teratogenic in rats (at high dosages) and in humans. Birth defects noted include connective tissue and skeletal defects, hydrocephalus, cleft palates and fetal resorption.

Warfarin

Although seldom used in small animal medicine, warfarin has been implicated in a wide variety of birth defects in children and is considered contraindicated in pregnancy.

Conclusion

While drugs should be avoided in pregnancy, when they are deemed necessary the clinician should attempt to use the ‘safest’ effective agent at the lowest effective dose for the shortest effective duration of treatment, particularly in the first trimester of pregnancy. Whenever drugs are used in pregnant animals the clinician is obligated to explain the relative benefits and risks of treatment and obtain informed consent (written if possible) from the owner. Owners should understand that even if a drug is “relatively safe”, that does not preclude adverse outcomes. Airline travel is relatively much safer than automobile travel, unless you are on the plane that crashes.

Additional Sources for Guidance on Drug Safety During Pregnancy

Note: Not an exhaustive list, but known to the author

Veterinary

- 1) Dr Mark Papich has a very nice table that gives recommendations for a wide variety of drugs for both dogs and cats during pregnancy. Although becoming somewhat dated, it is still an excellent source of information. It can be found in *Current Veterinary Therapy X* or in the chapter on canine pregnancy in *Small Animal Theriogenology* by Johnston, Root Kustritz and Olson (see reference list).
- 2) Plumb’s Veterinary Drug Handbook has reproductive safety information within its monographs and the author assures that there will be “much more” in the 5th edition.

Human

- 1) www.perinatology.com has links to many other websites and is an excellent web portal to begin a web-based search for information
- 2) Organization of Teratology Information Services <http://www.otispregnancy.org/> has some useful information/links and includes some very well done patient information sheets on the use of certain drugs and herbals during pregnancy
- 3) Micromedex. If you have access to this extensive database through your library, several teratology databases can be queried.
- 4) The reference book: "Drugs for Pregnant and Lactating Women" by Weiner and Buhimschi; Churchill-Livingston 2003. This is a comprehensive reference that reviews over 750 drugs.

Additional References

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