Toward Improved Pregnancy Labelling

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ABSTRACT

Information about the use of a medication in pregnancy is part of overall drug labelling as prepared by the pharmaceutical company and approved by the regulators. It is aimed at assisting clinicians in prescribing, however, very few drugs are labelled for specific indications in pregnancy, since there is rarely information about the use of a drug in this condition. Recently the FDA has drafted new guidelines for the labeling of drugs in pregnancy and breastfeeding, to replace the A,B,C,D,X system that was used for more than 30 years. Here we document the use of the new system through 3 different medications; each representing a different clinical situation in pregnancy- acute infection, chronic pain, and drug use during labor. Advantages and challenges in the new system are being highlighted.

Introduction

This presentation focuses on the information that should be available to physicians to present to women, either pregnant or planning to become so, for decision-making regarding medication use. It will address the question: Does the pregnancy labelling of a medication include sufficient information for the prescriber to provide guidance to their pregnant patient on its safe use? The new guidelines for pregnancy labelling from the U.S. Food and Drug Administration (FDA) are illustrated with sample monographs for 3 medicinal products.

Information about use of a medication in pregnancy is part of overall drug labelling as prepared by the pharmaceutical company and approved by the regulators. It is aimed at assisting clinicians in prescribing, but very few drugs are labelled for specific indications in pregnancy, since there is rarely information about the use of a drug in this condition. Moreover, the manufacturer is rarely interested in the use of their drug in pregnancy, in an attempt to avoid legal risks. They usually note in the labelling that the drug is not known to be safe in pregnancy and therefore recommend against taking it. In pregnancy, there is also a second patient involved: the fetus. In the current hostile medico-legal environment, drug companies do not want to take the risk for either mother or fetus, simply avoiding the issue and potential litigation. Therefore, when women are in the vulnerable pregnant state, they often feel left on their own as regards medication-use guidance.

Some of the general issues to keep in mind about drugs in pregnancy include:

- Only half of all pregnancies are planned.
- Many women need medications for pregnancy-induced conditions (e.g., morning sickness), chronic conditions (e.g., epilepsy), intercurrent conditions (e.g., allergies).
- Some pregnant women work with chemicals, are exposed to radiation, and use illicit drugs.
- During embryogenesis drugs and chemicals may adversely affect fetal development.

Anxiety about birth defects leads women to not take medications during pregnancy and lactation, and leads pharmaceutical companies to not develop drugs for pregnant and lactating women. Everyone's key concern is the potential for malformations to be induced during embryogenesis. Women are often not medicated appropriately even after the first trimester—the most vulnerable period of embryo development—or for life-threatening conditions. The landmark example of a drug causing anxiety about drug treatment in pregnancy is the case of thalidomide.

Thalidomide was used in the late 1950s for morning sickness. At that time, the medical community believed that drugs do not cross the placenta. After birth defects and fallout from thalidomide, the medical and lay reaction then turned to the extreme belief that every drug is potentially dangerous during pregnancy. Furthermore, most drugs will probably have "crosses the placenta" included in their monographs; however, that statement in itself does not provide prescribers with substantive information about the safety of the drug during pregnancy. Theoretically, a drug that does not cross the placenta could be dangerous, possibly damaging the placenta itself; thus the statement about a drug crossing the placenta is not of itself informative.

Depression in Pregnancy as a Powerful Example
Depression in pregnancy is a common condition, affecting up to 20% of pregnant women. Where there may be concerns regarding the use of antidepressants in pregnancy, not treating depression can have its own problems.

Selective serotonin reuptake inhibitors (SSRIs) are believed to be safe, both as regards dysmorphology and neurobehavioural aspects.[1,2] Women taking antidepressants commonly discontinue therapy during pregnancy, resulting in high morbidity,[3] suicide ideation, hospitalization and postpartum depression. Furthermore, those women who are treated are usually on very low average doses. With Prozac as an example, we find in the product monograph—more than 20 years since the drug's release onto the market—the following: "Safe use in pregnancy has not been established. Therefore, it should not be administered to women of childbearing age unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the child or fetus." Such a statement causes concern for the practitioner. However, the scientific reality is that more than 6 morphology studies, 3 neurodevelopmental studies and one meta-analysis have been published showing apparent fetal safety.

United States Food and Drug Administration - Pregnancy Categories
In 1978, the FDA put into place a letter categorization to denote the risks of drugs in pregnancy (Table 1). Category A is the best, the safest; however, very few drugs are in this category, as almost no one conducts randomized trials in pregnancy. Category B is based on animal studies, often conducted as part of the drug workup and included in drug submissions. These usually use much larger doses in animals, sometimes up to 1000-fold, again identifying that the drug is safe for use in pregnancy. Alternately, Category B can mean that some animal studies showed uninterpretable results when applied to humans, e.g., a drug resulting in rat tail malformations. Category C is the most commonly applied, encompassing about 70% of drugs, but provides neither the practitioner nor the patient with any information or guidance. Category D indicates some potential risk with using the drug in pregnancy, e.g., valproic acid. Category X identifies drugs that should not be used in pregnancy, e.g., isotretinoin. Problems with this system include the fact that over 70% of all drugs fall into one category, "C". Some drugs may be unsafe in the first trimester—during embryogenesis—but may be safe in the third, such as lithium and warfarin. That is, the categorization into "A", "B", "C" may not apply over the course of the entire pregnancy. Furthermore, different drugs within the same class may be assigned to different categories, as occurs with benzodiazepines.

TABLE 1 FDA Pregnancy Categories

Pregnancy Category	Description
A	Appropriate human studies - no risk
B	Insufficient human studies, but animal research suggests safety **or**: Animal studies show issues but human studies show safety
C	Insufficient human studies, but animal studies show problems **or**: No animal studies, and insufficient human studies
D	Human studies, with/without animal research show fetal risks, but the drug is important to some women to treat their conditions
X	Fetal risks are evident; there are no situations where the risk/benefit justifies use

One of the most problematic situations is that of a drug being categorized in a manner that misses the point. For example, oral contraceptives are the most commonly prescribed drugs taken in the first trimester, due to contraceptive failure: women continue to take them not knowing they are pregnant. Case reports of sexual changes associated with oral contraceptives resulted in these drugs being labelled as Category X in the 1970s. Numerous studies and several meta-analyses failed to show teratogenic potential. Furthermore, in some contexts, oral contraceptives have been used to maintain pregnancy, yet the "X" label stayed unchanged until two years ago.

New FDA Approach
In 2000, the FDA was advised by its experts and advisors to change the labelling system from "categories" to "structured narratives" that describe to clinicians all that is known on the specific drug, even if the company does not wish to have a pregnancy indication. This change was approved in 2009 to be enacted in 2010.

The elements of information in the new FDA system include the following:

- General information: overall risk/benefit,
- Specific fetal risk summary,
- Clinical considerations,
- Data: human first, then animal,
- All references.

The proposed method is one that has been used effectively at Motherisk and similar services for decades. It provides the clinician with a narrative regarding what may happen with their patient if they decide to treat or not to treat. Using the new FDA guidelines presented - examples for their application in 3 different clinical situations: acute first trimester drug use, drug use during labour, and chronic drug use.

1.   **OSELTAMIVIR (Tamiflu®)**

General Information
All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure.[4] In a case of influenza virus infection during pregnancy, potential benefits of treating the infection with oseltamivir outweigh the theoretical risks of oseltamivir on pregnancy and fetus, especially if the woman is in the second or the third trimester.

Fetal Risk Summary
Based on available human data, exposure to oseltamivir in early pregnancy is unlikely to be associated with a significant increase in major congenital abnormalities above the background risk.

Clinical Considerations
Pregnant women, especially in the third trimester, are known to be at higher risk for complications from infection with seasonal influenza viruses, and severe disease among pregnant women has been reported during past pandemics. Ward et al., discuss historical data from the influenza pandemics of 1918 and 1957, which illustrated the potential risks of influenza infection in pregnant women and their fetuses. In the 1918-1919 pandemic, mortality associated with infection during pregnancy was reported to be over 50%, with higher rates of mortality reported in the later stages of pregnancy.[5] During the 1957 pandemic, the obstetrical literature reported that 50% of the women of childbearing age who died of influenza infection were pregnant.[6] Literature reports have shown that epidemic influenza illness is common in women in the second and third trimesters of pregnancy during the influenza season. Pregnant women may be at higher risk of developing serious complications of influenza infection than the normal population.[7]

High mortality and severe complications have been reported among pregnant women with the 2009 H1N1 influenza virus infection. It was reported that of patients admitted to the ICU, 66 of 722 patients (9.1%) in Australia and New Zealand and 18 of 272 patients (7%) in the U.S. were pregnant women.[8,9] It is also reported that postpartum women, similar to pregnant women, might be at increased risk for severe complications and death from 2009 H1N1 influenza.

During the 2009 H1N1 influenza pandemic, the U.S. Centers for Disease Control and Prevention (CDC) recommendations for pregnant patients and women who are up to 2 weeks postpartum (including following pregnancy loss) are that antiviral drugs should be started as soon as possible after the onset of influenza symptoms. Recommendations for use of antiviral medications may change as data on antiviral effectiveness, clinical spectrum of illness, adverse events from antiviral use, or resistance among circulating strains become available.

Oseltamivir is a viral neuraminidase inhibitor for the treatment of influenza A and B, reducing both the duration and severity of flu symptoms. The treatment dose is 75 or 150 mg orally twice daily for 5 days. The prophylaxis dose is 75 mg orally once or twice daily for 10 days. It is not known whether the dose of oseltamivir requires adjustment during pregnancy.

Data
Human Data
- A study using an *ex vivo* human placenta model showed that transplacental transfer of oseltamivir and its metabolite were incomplete with minimal accumulation on the fetal side.[6]
- In postmarketing surveillance reported by the manufacturer, 61 pregnant women were exposed to oseltamivir with unknown timing. Among these pregnancies there were 10 abortions, including 6 therapeutic terminations, and 1 case each of trisomy 21 and anencephaly.[10]

- Two Japanese groups prospectively followed 90 pregnant women who took therapeutic doses of oseltamivir (75 mg twice a day for up to 5 days) during the first trimester. In these 90 cases, there was 1 malformation (1.1%), which is within the incidence of major malformations in the general population (1-3%).[11]
- There have been no data available regarding the effect of oseltamivir on other pregnancy outcomes, such as premature delivery, fetal growth, or prenatal complications.

Animal Data
- Data from the manufacturer (*Hoffman–La Roche*) demonstrated that oseltamivir crosses the placenta in rats and rabbits. Preclinical studies did not show adverse fertility effects in male or female rats with oral doses up to 1500 mg/kg/day, or in rabbits given up to 500 mg/kg/day by the oral route. These doses produced blood levels up to 100 times those achieved in humans on therapy. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicity were observed. An increased incidence of abortion was seen in the 500 mg/kg/day group. There was also a dose-dependent increase in minor skeletal abnormalities. However, such minor skeletal variations remained within the standard rates of occurrence in the species studied.

2. MISOPROSTOL (Cytotec®) - for labour induction

General Information
All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. One to three percent of all pregnancies are associated with birth defects.[4] With every drug the potential risk of exposure in pregnancy must be weighed against the benefits of the drug.

Fetal Risk Summary
Human data do not indicate that misoprostol used for labour induction increases the overall risk of maternal or neonatal complications (*see* Data section). Prospective randomized trials comparing misoprostol to other methods of labour induction did not demonstrate a significant difference in the rates of adverse neonatal outcome. These outcomes include low Apgar scores, admission to NICU, neonatal respiratory distress syndrome, and meconium aspiration syndrome. It does not appear that misoprostol carries a higher risk of pregnancy-related adverse events than other methods of labour induction. In patients with a scarred uterus, misoprostol is associated with higher rates of uterine rupture. Uterine rupture may result in high rates of neonatal morbidity and mortality.
There are no animal data regarding the safety of misoprostol for labour induction.

Clinical Considerations
Labour induction at term is applied as required in 15-30% of pregnancies for various fetal or maternal indications in obstetrical practice. Misoprostol (Cytotec®) is a synthetic prostaglandin E1 analogue indicated for the prevention of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs. Although it is not approved by the FDA for any obstetric indication, it has been incorporated into obstetric practice, especially for third trimester labour induction in a patient with unfavourable cervix. Off-label use of misoprostol for cervical ripening is supported by the American College of Obstetricians and Gynecologists in a recent publication (ACOG Practice Bulletin No. 107, August 2009).[12] Potential complications include uterine rupture and uterine hyperstimulation, which may result in adverse maternal and neonatal outcome. Published human data compared misoprostol to other methods of labour induction for efficacy and safety.

Data

Human Data

- Several randomized clinical trial reported intravaginal use of misoprostol for labour induction and compared its efficacy and safety to vaginal dinoprostone (PGE2).[13-20] Misoprostol dosage was 25-100 mcg and dinoprostone dosage was 0.5 mg. The number of subjects included in these trials varied from 61 to 1308 (subjects exposed to misoprostol: 31 to 872). Outcome data included low Apgar scores, cord pH, admission to NICU, neonatal respiratory distress syndrome, neonatal need of resuscitation, and meconium aspiration syndrome. None of these trials showed a significant difference in adverse neonatal outcome. Only one of these studies reported higher rates of neonatal admission to NICU in the misoprostol group (13% in the misoprostol group vs. 3% in the dinoprostone group p value – 0.02).[16]

- Several other reports compared other methods of labour induction to misoprostol, such as oxytocin infusion and artificial rupture of membranes.[20-22] These publications did not demonstrate significant differences in the delivery mode nor in perinatal outcome (cord pH, low Apgar scores, RDS, neurological morbidity, meconium aspiration and NICU admissions). A systematic review and meta-analysis of randomized trials comparing vaginal misoprostol 20-25 mcg to dinoprostone and oxytocin has been published.[23] A total of 2937 patients met the inclusion criteria. Outcome measures included low Apgar scores, meconium stained amniotic fluid, NICU admission, prenatal mortality, and uterine rupture. There was no significant difference among the groups in all of these outcome measures. Misoprostol use in patients with a scarred uterus may increase the risk of uterine rupture.[24,25]

Animal Data

- There are no published studies examining the efficacy and safety of misoprostol for labour induction in animal models.

3. **OXYCODONE**

General Information

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes regardless of drug exposure. One to three percent of all pregnancies are associated with major birth defects.[4] With every drug the potential risk of exposure in pregnancy must be weighed against the benefits of the drug. In breastfeeding women, the potential risk from any drug exposure in the baby needs to be weighed against the benefits to the mother.

Fetal Risk Summary

Based on limited human data from one prospective cohort study and one surveillance study, oxycodone therapy does not appear to be associated with increased risk for congenital malformations (*see* Data section). If used by a pregnant woman at high doses and continuously near term, oxycodone, as other opioids, may cause neonatal abstinence syndrome in the neonate. Available data from animal reproduction studies have not revealed any teratogenic effects.

Clinical Considerations

Based on limited human data, exposure to oxycodone in early pregnancy is unlikely to be associated with major congenital abnormalities. It has been shown that most opioid analgesics can cross the placenta and enter the fetal central nervous system. However, opioids as a class do not seem to be teratogenic. If used continuously near term, the clinician should be aware of the risk of withdrawal syndrome in the neonate and consider alternative treatments for maternal pain, such as non-steroidal anti-inflammatory drugs. In the neonate, withdrawal is characterized by tremor, jitteriness, irritability, sweating, diarrhoea, and poor feeding. In addition, the use of oxycodone in

high doses around the time of delivery may be associated with neonatal respiratory depression. Neonates should be closely observed after birth for signs of possible withdrawal. Concerns arise with illicit use of oxycodone where maternal addiction is present; and the possibility of neonatal withdrawal must be considered. A case report of neonatal withdrawal has been described in an infant whose mother abused oxycodone and other narcotics during pregnancy.[26]

Data

Human Data
- In a surveillance study of 229,101 Michigan Medicaid recipients from 1985 to 1992, 281 newborns were exposed to oxycodone *in utero* during the first trimester.[27] Thirteen (4.6%) of these newborns had major birth defects, including three cases of cardiovascular defects and one case of hypospadia.
- An abstract of a prospective cohort study from a teratogen information service reported 78 women were exposed to oxycodone during the first trimester for postoperative pain, general pain or upper respiratory infection.[28] Six (7.7%) infants of these women had birth defects. However, this was not statistically significant and no pattern of birth defects was observed.

Animal Data
- Dark Agouti pregnant rats were administered either 0.8 mg/kg intravenous oxycodone or 1 mL/kg normal saline solution from gestational day 8 to 21. At birth, there were no differences between the oxycodone and the saline-exposed pups in timing of parturition, litter size, and body weight.[29]
- Studies in rats and rabbits with oral doses of oxycodone equivalent to 3 and 47 times an adult dose of 160 mg/day, respectively, did not reveal evidence of harm to the fetus due to oxycodone.[30]

Is It Going to Work?

Based on our experience in producing the above information by following the new FDA guidelines, we identified that there were some elements missing. For example, where one or more drugs have more published data and experience than others in a given class, it may be wise to refer clinicians to drugs of the same class that have more data on fetal safety, or perhaps rank the drugs according to years of experience and published patient sample sizes.

Lastly, some clinical information regarding the need to treat specific conditions in pregnancy would be useful to the clinician. This could take the form of a statement, such as, "It is important to treat depression in the third trimester of pregnancy due to high risk for postpartum depression associated with untreated depression in late pregnancy …"

Society is now demanding more information than has been provided in the past. Industry will have an overwhelming task of review to synthesize these new narratives, so it will probably be many years before this system will replace the old one. However, once this system is in place, clinicians will have more information with which to make decisions, use their clinical judgment, assess their patients' needs, and provide their patients with data to make better-informed decisions.

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