Pregnancy and Commonly Used Drugs in Hematology Practice

Gideon Koren¹ and Michael Lishner²

¹Motherisk Program, University of Toronto, Toronto, Ontario, Canada and ²Meir Hospital, Tel Aviv University, Tel Aviv, Israel

When a woman suffering from a hematological condition is contemplating pregnancy, she may need to continue the use of medications that do not have sufficient evidence of fetal safety. We discuss the evidence existing for some therapies of major hematological conditions in the context of major principles in clinical teratology. It is critical to always balance the potential fetal risks of the drug in question against the maternal and fetal risks of the untreated hematological condition.

Introduction

When a pregnant patient, or a woman who plans pregnancy, is treated with medications that may adversely affect the fetus, the practicing hematologist quite often needs to make difficult decisions. This paper opens with general principles that must be considered regarding drug use in pregnancy, followed by a discussion of major drugs used in hematology, where reproductive concerns have been raised. Due to the short spaced allowed, full details may not be possible; however, key references have been added to address this gap.

The Scope of the Issue

Only a limited number of drugs have been proven to be human teratogens, including thalidomide, isotretinoin, coumarin derivates, valproic acid, and folate antagonists. In some cases, the combination of two drugs may increase the teratogenic risk. The risk of birth defects may also vary with the time at which the drug is administered during pregnancy and with the dose. There are some examples of drugs in which the dose has proven to be a major determinant of teratogenicity in humans. There is more safety information for older than for newer drugs. Proactive teratogen risk counseling should include a critical appraisal of all available data, including the consequences of the untreated maternal condition.

With approximately 50% of pregnancies unplanned,¹² women may be exposed to hematological drugs not necessarily intended to be used during pregnancy. In addition, a large number of pregnant women need continuous therapy such as anticoagulants for chronic conditions. This reality is complicated by the fact that medicines are almost never tested in pregnant women at the time they are introduced into the clinical setting. In addition, maternal conditions and environmental factors may both adversely affect the natural development of the fetus and increase maternal morbidity and mortality rates. For example, the rates of perinatal mortality (25 of 1000) and congenital malformations (99 of 1000) among suboptimally treated type-2 diabetic women are significantly higher than among healthy pregnant women.³ Cigarette smoking during pregnancy has been associated with an increased risk for low birth weight, prematurity, spontaneous abortion, and perinatal mortality,⁴ and alcohol is the most widely used teratogen agent.⁵ On the other hand, pregnancy may alter the pharmacokinetics of a number of drugs,⁶ and dosage adjustment may be required to ensure their efficacy.

With a 20% to 30% risk of major malformations caused between days 34 and 50 of gestation, even more than 40 years ago after the disaster thalidomide is still considered to be the prototype teratogen. Thalidomide has been reintroduced into the clinical setting for treatment of cutaneous forms of leprosy,⁸ and is being tested as a therapeutic option for cancer.⁸ It is also currently being used for myeloma, and thalidomide-like agents have become standard of care for multiple myeloma treatment. However, the suffering it caused has prompted the common belief that every drug has the potential to be a new thalidomide,⁹ and patients commonly discontinue treatment and often unnecessarily consider an abortion of a wanted pregnancy.¹⁰

There are only a limited number of drugs proven to be human teratogens, including thalidomide, isotretinoin, coumarin derivates, valproic acid, and folate antagonists. In some cases, the combination of two drugs may increase the teratogen risk. For example, the addition of a folate antagonist to chemotherapy or antiretroviral treatment may result in a risk of major malformations of 25% and 6%, respectively.¹¹ However, if folate antagonists are not included, the teratogenicity of single-agent chemotherapy decreases to around 6%, whereas that for antiretroviral treatment does not seem to increase above the baseline risk. The risk of birth defects may also vary with the time at which the drug is administered during pregnancy and with the dose. Therefore, even if the mother was exposed to a known teratogenic agent, her risk has to be evaluated in its own context and generalizations may be tenuous.

Time-Dependent Fetal Effects

The first 3 months of pregnancy are known as the embryonic phase,when all organs of the fetal body form. This has major implications for fetal drug safety, because a drug taken in the second trimester cannot cause a malformation in an organ that is already completely formed.

The second phase of pregnancy, the fetal phase, is characterized by growth and development of all organs. The exception is the brain, where cell division and migration continue. Therefore, fetal toxins such as alcohol and mercury can cause brain damage to the fetus even beyond the first trimester.

Lack of menstruation is the most common way for women and health professionals to become aware of pregnancy. This period
may be associated with inadvertent exposures to therapeutic drugs, more specifically within the first 6 weeks. Although implantation may occur as early as 6 to 8 d after fertilization, in 84% of cases it occurs on d 8 to 10.12 The time from conception until implantation is considered the all or none period, because insults to the embryo will result in either death of the conceptus and miscarriage (or resorption) or in intact survival. At this stage, the embryo is undifferentiated, and repair and recovery are possible through multiplication of the still multipotential cells to replace those that might have been lost. It is biologically plausible that exposure of embryos to teratogens during the implantation stage does not cause congenital malformations unless the agent persists in the body beyond this period. During the embryonic period, from implantation to 54 to 60 d after conception, the basic phases of organogenesis take place. This is the period of maximum sensitivity to teratogenicity, because not only are tissues differentiating rapidly, but damage to them becomes irreparable. Exposure to teratogenic agents during this period has the greatest likelihood of causing a structural anomaly. Finally, the fetal phase, from the end of the embryonic stage to term, is the period when growth and functional maturation of organs and systems already formed occurs. Teratogenic exposure in this period may affect fetal growth, the size of specific organs, or the function of organs, rather than gross structural anomalies.

For most drugs, the major concern is following exposure in the first trimester of pregnancy. The risk of teratogenicity for coumarin derivatives and chemotherapy is high when administered in the first trimester of pregnancy.13 In contrast, the risks significantly decrease when these drugs are administered in the second or third trimester.

Dose Response
Paracelsus (1493–1541) postulated that the dose was the determinant separating a poison from a non-poison. However, there are only a few examples of drugs in which the dose has been proven to be a major determinant of their teratogenicity in humans. In the case of valproic acid, the risk of major congenital malformations seems to increase significantly at 600 mg/d, and the largest attributable risk was observed at doses exceeding 1000 mg/d.14 Similarly, the rate of major congenital malformations of lamotrigine seems to increase from 1.3% to 1.9% at doses of less than 200 mg/d to 5.4% at doses above 200 mg/d.20 The dose of methotrexate, a folic acid antagonist, seems to be critical for determining its teratogenic effects. One study has identified the dose of 10 mg/week of methotrexate as the possible threshold for major congenital malformations.16 However, a recent study documented similar relatively safe results at a dose level of 50 mg/week or less when exposure occurred before 8 weeks of pregnancy.17 In both studies, however, the rate of spontaneous abortions among exposed women remained high.

The basic principle of dose-related teratogenicity of therapeutic drugs seems to be more complex, as illustrated by the axiom that “a teratogenic response depends upon the administration of a specific treatment of a particular dose to a genetically susceptible species when the embryos are in a susceptible stage of development.”18

Old versus New Drugs
Although there are examples of old drugs with only limited published information on their use in pregnancy, most of them have been evaluated at least in post-marketing surveillance studies. It is therefore conceivable that there is more safety information for older than for newer drugs. However, this difference does not imply that the former are safer than the latter. For example, although valproic acid is a relatively old antiepileptic agent associated with a well-recognized increased risk of neural tube defects, it was only recently that the drug was proven to increase the risk of other major congenital malformations, including limb and cardiac anomalies. Even more recently, a meta-analysis examining the overall risk of major congenital malformations with valproic acid has found a cumulative relative risk (RR) of 2.59 compared with other antiepileptic drugs, and of 3.77 when compared with the risk in the general population.14

The selection of drugs for pregnant women or women planning pregnancy has to be supported by the available relevant information about their safety in this population. If the dilemma is between two or more drugs of the same group, the one with better evidence of safety should be selected. For example, among the proton pump inhibitors clinically available, omeprazole has been documented in over 1000 pregnant women with no increased risk of major malformations.19 In contrast, the information for other proton pump inhibitors is still scarce, and therefore omeprazole should be considered the drug of choice for now. In general, the rule of thumb during pregnancy remains to choose an older agent for which there are more fetal safety data.

Classification of Drugs Based on Fetal Safety
In the late 1970s, the Food and Drug Administration (FDA) introduced a classification system for fetal drug safety that was aimed at guiding clinicians. Alphabetically, this system is as follows:

A: Drugs for which controlled human studies have failed to show teratogenicity.

B: Animal studies but no human studies have failed to show teratogenicity, or animal studies have shown adverse effects that were not confirmed in human trials.

C: Studies in animals have shown adverse effects and no human studies are available, or studies are unavailable for both humans and animals.

D: Positive evidence of human fetal risk, but the benefits of the drug to pregnant women may be acceptable.

X: Animal or human studies have shown clear evidence of fetal damage, and there is no advantage to using the drug in pregnant women.

This system has drawn major criticism for its ambiguity and lack of clarity. For example, three fourth of drugs are in category C. The oral contraceptive pill was designated X for many years, despite large number of studies and two meta-analyses failing to show fetal risks.

Two years ago, after a decade of deliberations, the FDA approved a new system in which the categorical statements will be replaced by narratives describing accurately what is known, similar to any other descriptions of drug safety. This system is expected to be used in drug labeling starting in the next few years.

Specific Drugs Used in Hematology Practice

Warfarin
Warfarin (brand name, Coumadin®) is an oral anticoagulant that inhibits the synthesis of vitamin K-dependent clotting factors,
including factors II, VII, IX, and X, and the anticoagulant proteins C and S. Rats given very high doses (100 mg/kg) of warfarin have had offspring with marked maxillonasal hypoplasia and skeletal abnormalities, including abnormal calcium bridges in the epiphyseal cartilages of the vertebræ and long bones.\textsuperscript{28} Several case series and case reports of human use of warfarin during pregnancy have been published. These reports (which range in size from 1 to 418 subjects) show a clear association between warfarin therapy and embryopathy, on the one hand, and brain damage, probably due to central nervous system bleeding, on the other hand. The exact risk of fetal damage from warfarin therapy during pregnancy is difficult to determine, because most of the available studies are small and anecdotal. However, it is clear that therapy with warfarin should be discontinued before 6 weeks of gestation to prevent the teratogenic risk.

Several reports have indicated that using warfarin between 6 and 12 weeks of gestation is associated with “fetal warfarin syndrome,” which is most commonly manifested by nasal hypoplasia, stippled epiphyses, limb deformities, and respiratory distress. Furthermore, the use of warfarin during the second and third trimesters has been associated sporadically with central nervous system abnormalities, including mental retardation, microcephaly, optic atrophy, and blindness.\textsuperscript{21,22}

Other fetal abnormalities reported with maternal warfarin use including absent or non-functioning kidneys, anal dysplasia, deafness, seizures, Dandy-Walker syndrome, and focal cerebellar atrophy. The use of warfarin throughout pregnancy has been associated with hemorrhagic complications, premature births, spontaneous abortions, stillbirths, and death.\textsuperscript{21} One study\textsuperscript{22} reported on 418 cases of warfarin exposure from conception to 38 weeks after birth. About 16% of all pregnancies ended in spontaneous abortions or stillbirths, and another 15% resulted in babies with abnormalities at birth. These abnormalities included skeletal malformations (e.g., stippling of cervical vertebrae, sacrum, and femurs; kyphoscoliosis; and nasal hypoplasia) and bilateral optic atrophy leading to blindness, deafness, focal cerebral atrophy, respiratory distress, and seizures. Doses of warfarin in that study ranged from 2.5 to 12.5 mg/d.

Salazar et al.\textsuperscript{23} reported on 128 babies exposed to warfarin therapy from 0 to 38 weeks of gestation. About 8% of the 38 live-born infants displayed teratogenic effects of warfarin at birth, including nasal hypoplasia, choanal stenosis, and stippled epiphyses. When compared with 68 pregnancies in which warfarin therapy had been replaced with 1 g of acetylsalicylic acid and 400 mg of dipyridamole daily at the onset of pregnancy, it was clear that the rate of spontaneous abortions was significantly higher in the warfarin group (28% vs. 10%). The rate of neonatal deaths was also higher in the warfarin group (2.3% vs. 0%). The rate of stillbirths was approximately 7% in both groups. Warfarin dose was adjusted for a target therapeutic International Normalized Ratio (INR) of 2 to 3.

In a systematic review of all available data up to 2000, Chan et al. concluded that substituting oral anticoagulants with heparin between 6 and 12 weeks reduces the risk of fetopathy effects, but with an increased risk of thromboembolic complications. The use of low-dose heparin is definitely inadequate; the use of adjusted-dose heparin warrants aggressive monitoring and appropriate dose adjustment.\textsuperscript{24} Large prospective trials to determine the best regimen for these women are needed.

A recent review\textsuperscript{25} recommends that women receiving long-term oral anticoagulation therapy have warfarin replaced with unfractionated or low-molecular-weight heparin when they become pregnant. However, there have been case reports of unfractionated heparin also being associated with adverse pregnancy outcomes such as fetal loss and maternal thrombocytopenia, hemorrhage, and osteoporosis. Needless to say, the women in these studies were often sick, and their complications could have been caused by underlying illness. In a systematic review of 2777 pregnancies in 64 reports, Greer et al. concluded that low-molecular-weight heparin is both safe and effective to prevent or treat venous vein thrombosis in pregnancy.\textsuperscript{26}

Women of childbearing age taking warfarin should be using effective birth control methods. Risks and benefits of treatment should be discussed with each woman who plans to become or is pregnant while taking this drug.

**Acetyl Salicylic Acid**

Aspirin is widely used for a variety of indications, including anticoagulation. In a meta-analysis of all available studies,\textsuperscript{27} we calculated the pooled RR or weighted mean difference with a 95% confidence interval (CI), assuming a random-effect model. Thirty-eight studies met the inclusion criteria. The risk for miscarriage did not differ between women treated with aspirin and those treated with placebo (7 studies; RR, 0.92; 95% CI, 0.71–1.19). Women who took aspirin had a significantly lower risk of preterm delivery than did those treated with placebo (22 studies; RR, 0.92; 95% CI, 0.86–0.98). There was no significant difference in perinatal mortality (20 studies; RR, 0.92; 95% CI, 0.81–1.05) or in the risk of small-for-gestational-age infants (912 studies; RR, 0.96; 95% CI, 0.87–1.07) among offspring of mothers treated with aspirin and those of mothers treated with a placebo. Similarly, there was no increased risk for major malformations in general, although there was a slight increased risk for gastrointestinal.\textsuperscript{28} For women with moderate- and high-risk pregnancies, aspirin treatment seemed to have a small but significant effect on reducing the rate of preterm deliveries, but did not reduce the rate of perinatal death.

Putting these findings in a clinical-hematology context, the benefits of aspirin in reducing, for example, the risk of thrombosis in essential thrombocytopenia, are supported by its overall fetal safety profile.

**Hydroxyurea**

Hydroxyurea is widely used in women of reproductive age with sickle-cell disease. We followed a patient being treated for sickle-cell disease with hydroxyurea (1 g/d) who became pregnant, and in whom drug treatment was discontinued at 9 weeks gestational age. The pregnancy and delivery were complicated by vaso-occlusive crises. A healthy male infant was born at 39 weeks with no evidence of congenital malformations.\textsuperscript{29} A literature review, including this case, suggests that the risk of hydroxyurea exposure during in pregnancy may have been overestimated. In 2009, Ballas et al. reported on pregnancy outcomes in patients with sickle-cell disease receiving hydroxyurea during a controlled trial, which failed to show evidence of increased teratogenic risk.\textsuperscript{30}

**Folic Acid**

The use of folic acid-fortified multivitamin supplements has long been associated with a decrease in the risk of neural tube defects. Several studies have also proposed the effectiveness of these supplements in preventing other birth defects; however, such effects
have never been systemically examined. We conducted a systematic review and meta-analysis to evaluate the protective effect of folic acid-fortified multivitamin supplements on other congenital anomalies.31

From the initial search, 92 studies were identified, and 41 of these met the inclusion criteria. Use of multivitamin supplements provided consistent protection against neural tube defects (random effects odds ratio [OR] 0.67, 95% CI, 0.58–0.77 in case-control studies; OR 0.52, 95% CI 0.39–0.69 in cohort and randomized controlled studies), cardiovascular defects (OR 0.78, 95% CI 0.67–0.92 in case-control studies; OR 0.61, 95% CI 0.40–0.92 in cohort and randomized controlled studies), and limb defects (OR 0.48, 95% CI 0.30–0.76 in case-control studies; OR 0.57, 95% CI 0.38–0.85 in cohort and randomized controlled studies). For cleft palate, case-control studies showed an OR of 0.76 (95% CI 0.62–0.93), and cohort and randomized controlled studies showed an OR of 0.42 (95% CI 0.06–2.84); for oral cleft with or without cleft palate, case-control studies showed an OR of 0.63 (95% CI 0.54–0.73), and cohort and randomized controlled studies showed an OR of 0.58 (95% CI 0.28–1.19); for urinary tract anomalies, case-control studies showed an OR of 0.48 (95% CI 0.30–0.76), and cohort and randomized controlled studies showed an OR of 0.68 (95% CI 0.35–1.31); and for congenital hydrocephalus, case-control studies showed an OR of 0.37 (95% CI 0.24–0.56), and cohort and randomized controlled studies showed an OR of 1.54 (95% CI 0.53–4.50). No effects were shown in preventing Down’s syndrome, pyloric stenosis, undescended testis, or hypospadias.

High red-cell turnover states can lead to folate deficiency, which is very important to avoid in pregnancy, necessitating daily folate doses of 5 mg. Hematological patients, such as women with hemolytic anemia, are an excellent example of patients in whom increased folate intake to 5 mg/d is warranted. Recent systematic reviews by the Motherisk program on the safety of 5 mg/d folate acid, including pharmacokinetics and rates of adverse effects and cancers, have failed to document increased risks.

In conclusion, maternal consumption of folic acid-containing prenatal multivitamins is associated with decreased risk for several congenital anomalies, not just neural tube defects. These data have major public health implications, because until now fortification of only folic acid has been encouraged. This approach should be reconsidered.31

Corticosteroids

Corticosteroids are first-line drugs for the treatment of a variety of conditions in women of childbearing age. However, information regarding human pregnancy outcomes with corticosteroids is limited. We collected data prospectively on and followed up 184 women exposed to prednisone in pregnancy and 188 pregnant women who were counseled by Motherisk for non-teratogenic exposure. The primary outcome was the rate of major birth defects. A meta-analysis of all epidemiological studies was subsequently conducted. In the meta-analysis, the summary OR for major malformations with all cohort studies was 1.45 (95% CI 0.80–2.60) and 3.03 (95% CI, 1.08–8.54) when Heinonen et al. (77) was removed. This suggests a marginally increased risk of major malformations after first-trimester exposure to corticosteroids. In addition, the OR for case-control studies examining oral clefts was significant (3.35; 95% CI, 1.97–5.69). In conclusion, although prednisone does not represent a major teratogenic risk in humans at therapeutic doses, it does increase by an order of 3.4-fold the risk of oral cleft, which is consistent with the existing animal studies.32

Hematologic Malignancies in Pregnancy

The incidence of hematologic malignancies in pregnancy range from 1:1000 to 1:10,000, but these conditions pose major challenges to the practicing hematologist.

Hodgkin’s Disease

Because the peak incidence of Hodgkin’s disease (HD) is during the age range of 20 to 40 years, its association with pregnancy is not uncommon, occurring in 1:1000 to 1:6000 deliveries.33 To date, the majority of published studies have been case reports of small series due to the relative rareness of the combination of HD and pregnancy. Therefore, the guidelines for evaluation and treatment of HD in pregnancy are not well established. Because tomographic scans and isotope studies are not recommended during pregnancy, and the current trend is to administer chemotherapy initially even in early stages (stages I and II) of Hodgkin’s disease, a limited initial staging workup is suggested.

The workup should include history, physical examination, routine blood tests, bone marrow biopsies, chest X-ray with abdominal shielding, abdominal ultrasound, and possibly magnetic resonance imaging (MRI).34 The clinical behavior of HD during pregnancy does not appear to differ from that outside of this setting, and pregnant women are not more likely to present at a higher stage than women of reproductive age in general. Also, the histologic subtypes of HD in pregnancy are not different from those of nonpregnant women younger than 40 years.35 Due to the limited availability of treatment information, it is not feasible to make specific recommendations regarding patient management. In general, it is recommended to avoid chemotherapy during the first 12 to 16 weeks of pregnancy if possible, and to postpone radiotherapy until after the delivery. If combination chemotherapy is considered, probably the recommended protocol is “ABVD”: adriamycin, bleomycin, vinblastine, and dacarbazine.

Prognosis and Fetal Consequences. There is no effect of pregnancy on survival of women with HD.36 Infants born to women with HD during pregnancy do not have a higher risk for prematurity or intrauterine growth retardation.36 In the cases reported by Anselmo et al.,37 pregnant women affected by HD safely carried their pregnancies to term and gave birth to healthy children. The association of HD with pregnancy is not, on its own, an indication for a therapeutic abortion. Recommendations regarding abortion should be individualized based on potential harm of staging procedures, chemotherapy, or radiotherapy to the fetus.

The induction of labor should be performed when there is a viable fetus and the mother’s blood counts are not compromised by a recent cytotoxic treatment. Breastfeeding is contraindicated during active treatment of HD. There are no reports of HD metastases to the placenta or to the fetus.

Leukemia

The occurrence of leukemia during pregnancy is very rare, with an estimated incidence of 1:100,000 pregnancies annually.38 It has been estimated that during pregnancy most leukemias are acute: two thirds are myeloid (AML) and one third are lymphatic (ALL). Chronic myeloid leukemia (CML) is found in less than 10% of leukemias during pregnancy, and chronic lymphocytic leukemia...
(CLL) is extremely rare. The survival of pregnant and nonpregnant women with acute leukemia has improved with the availability of modern chemotherapy and supportive care. Remission rates of 70% to 75% are currently reported for pregnant women, while survival is dependent on many factors, including the type of acute leukemia and the presence of cytogenetic abnormalities. These figures are not different from those achieved in nonpregnant women with acute leukemia.

Acute leukemia can affect pregnancy and the fetus. Intruterine growth retardation has been reported in mothers not treated with chemotherapy. In addition, preterm labor, induced and spontaneous abortion, and stillbirth are common in acute leukemia. Although there is an estimated teratogenic risk rate of 10% when chemotherapy is administered in the first trimester, Aviles and Niz reported no fetal malformations and no late side effects in children born to mothers who were treated for acute leukemia during early pregnancy.39 It is generally believed that pregnant women should be treated in the same manner as nonpregnant women. Therapeutic abortion should be considered in early gestation, but if the woman decides to continue the pregnancy, then certain drugs, such as methotrexate, should be replaced. Standard anti-leukemic treatment can be safely administered during the second and third trimesters. Delivery should be accomplished when fetal survival can be ensured and the mother is in complete remission. There are rare reports of leukemia blasts infiltrating the placenta, and a single case of infantile AML caused by vertical transmission of the mother’s leukemia cells.

Five cases of relapse of ALL in pregnancy have been reported in the English-language medical literature. The mechanisms attributable to the immunologic and hormonal changes of pregnancy have been reviewed.40 All five patients were treated with cytotoxic chemotherapy in the first trimester, and all survived and the mother is in complete remission. There are rare reports of leukemia blasts infiltrating the placenta, and a single case of infantile AML caused by vertical transmission of the mother’s leukemia cells.

CML during pregnancy should be treated as it is in nonpregnant patients. Because the disease has an initial chronic phase, it is usually managed conservatively during pregnancy, while an aggressive approach, such as bone marrow transplantation, may be considered after delivery. A limited number of studies have described successful treatment modalities of CML during pregnancy, including leukapheresis, hydroxyurea, and interferon. With tyrosine kinase inhibitors and imatinib becoming the standard of care for CML, their fetal safety will have to be addressed as well.

Pregnancy complicated by hairy cell leukemia is extremely rare. Splenectomy is a safe and effective treatment option during the second trimester for this rare condition. Single cases have been treated with interferon during pregnancy.

Disclosure
Conflict-of-interest disclosure: The authors declare no competing financial interest. Off-label drug use: None disclosed.

Correspondence
Gidean Koren, MD, Division of Clinical Pharmacology/Toxicology, Hospital for Sick Children, 555 University Ave., Toronto, ON, Canada MSG 1X8; Phone: (416) 813-5781; Fax: (416) 813-7562; e-mail: gkoren@sickkids.ca

References


