The use of medications in pregnancy and lactation is one of the most difficult and troublesome areas in medicine, requiring the physician and patient to estimate the risk versus benefit with more scrutiny than in most other clinical situations—often with inadequate support from the medical literature (Table 1).

A priori, all medications must be considered to cross the placenta, and to circulate within the fetus. The placenta is a metabolically active organ, although not all medications are handled uniformly. The fetus is at greatest risk of teratogenicity during the first trimester, the time of embryo/fetal development and organogenesis.

Placental transfer of medications from mother to embryo and embryo to mother is established at approximately the fifth week of fetal life, when the mother may just be realizing that she is pregnant. Many anti-rheumatic drugs are long-acting, thus their discontinuation upon diagnosis of pregnancy will not necessarily protect the fetus from exposure. Pre-pregnancy counseling, planning and adjustment of medications well in advance of pregnancy is absolutely essential for patients with rheumatic diseases, if possible.

All rheumatic diseases, whether they improve during pregnancy or not, have a great potential to flare post partum. This creates potential difficulties in decision making for patients and their rheumatologists about breastfeeding versus the need for increased anti-rheumatic therapy.

Research on the use of medications during pregnancy and lactation is limited because, as a newly developing human being is involved, such research is considered by some to be unethical; as well, investigators of rheumatic drugs are generally unwilling to conduct double-blind, placebo-controlled trials on pregnant humans. As information about medications during pregnancy and lactation is acquired through inadvertent exposures, it stands to reason that the longer and more commonly the medication has been used, the more information there is available about its use during pregnancy and lactation. There is less reliable information on the new biologics, for example. Information about some anti-rheumatic drugs in pregnancy and lactation has also been obtained from solid-organ transplant patients and patients with other disorders (such as inflammatory-bowel disease), who have proceeded with pregnancies and sometimes breastfeeding.

Useful information about teratogenic effects has been acquired through the study of pregnant animals, but these results are not necessarily directly applicable to human pregnancies, due to differences among species. Many studies of pregnant animals also use far higher doses of anti-rheumatic drugs than are used clinically in humans. Further limitations on the interpretation of animal studies are due to the lack of specificity between cause and effect (which also applies in humans). All of these limitations should be kept in mind when reviewing the results of the animal studies listed in Table 2.

### CORTICOSTEROIDS

Exposure to high-dose prednisone in studies of rodent and rabbit fetuses is associated with cleft palate and/or cleft lip. These anomalies, however, have not been associated with prednisone exposure (at any dosage) in human fetuses. Aggressive behaviours reported in rodent fetuses also have not been reported in human fetuses. Low birth weight has been reported when both...
animal and human fetuses have been exposed to prednisone in utero, but in humans, it has never been clearly established whether the low birth weight in the infant was associated with prednisone therapy or with the disease for which the mother was receiving the prednisone.11

The human placenta metabolizes prednisone, and the prednisone that does reach the fetus is unable to be converted to the active metabolite by the fetal liver, so the human fetus is exposed to only 10% of the maternal dose.3,5,33 In large-population studies of pregnant women ingesting prednisone, there are no reports of teratogenicity—irrespective of dose, route of administration or gestational ingestion.11 There is one report of an infant born with congenital cataracts.4

Although there are no published reports of intravenous pulse methylprednisolone (15 mg/kg/pulse) being administered in pregnancy, some physicians have used this treatment for severe, life-threatening or vital-

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<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Category*</th>
<th>Animal Studies</th>
<th>Human Experience</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (pred)</td>
<td>B</td>
<td>Cleft palate in those exposed to high-dose pred in pregnancy; Reduced birth weight; Aggressive behaviour</td>
<td>Appears safe; no congenital anomalies reported3,11</td>
<td>Appears safe;2,7,9,11 The American Academy of Pediatrics (AAP) considers prednisone compatible with breastfeeding.7</td>
</tr>
<tr>
<td>IV pulse methyl-</td>
<td>The FDA hasn’t assigned a category (ref.: personal communication).</td>
<td>No information</td>
<td>No published information; Has been used by some physicians at large centers; No obvious problems identified but use with extreme caution9,11</td>
<td>No published information; avoid</td>
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<tr>
<td>prednisolone (15</td>
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<tr>
<td>mg/kg/pulse)</td>
<td></td>
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<tr>
<td>ASA (high dose: 2-3</td>
<td>C (1st &amp; 2nd</td>
<td>Embryonic &amp; fetal demise, cleft lip &amp; palate, hydrocephaly, gastroschisis, skeletal dysplasia12</td>
<td>Avoid use during 1st &amp; 2nd trimesters (use other NSAIDs instead);11 Do NOT use during the 3rd trimester.11,13</td>
<td>Avoid large doses (low dose of 81 mg/d is safe).9</td>
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<tr>
<td>g/d)</td>
<td>trimesters)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>D (3rd trimester)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs: dicrofenac,</td>
<td>B (1st &amp; 2nd</td>
<td>Animal studies, usually involving mice, rats or rabbits, failed to reveal any embryotoxicity or teratogenic effects (even when given in maternal toxic doses), except indo- methacin, which caused skeletal abnormalities in mice but not rats. A 1990 study reported some degree of cleft palate. Given in the 3rd trimester, NSAIDs caused similar effects in humans but some studies also reported decreased fetal weight &amp; rat-pup survival.1</td>
<td>Safe during the 1st &amp; 2nd trimesters; no teratogenicity or congenital malformations reported.10,11,14</td>
<td>Safe, especially dicrofenac, ibuprofen, and naproxen; Only small amounts enter breast milk (approximately 1% of maternal serum level);1,2,9 The AAP considers these listed NSAIDs safe during breastfeeding (in full anti-inflammatory doses).9</td>
</tr>
<tr>
<td>ibuprofen, ketoprofen,</td>
<td>trimesters)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>naproxen, piroxicam,</td>
<td>D (6-8 weeks prior to delivery)</td>
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<tr>
<td>sulindac</td>
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</table>

Pred=prednisone, prednisolone, or methylprednisolone; ASA=acetylsalicylic acid; NSAIDs=nonsteroidal anti-inflammatory drugs; HCQ=hydroxychloroquine; CQ=chloroquine; SSZ=sulfasalazine

* The Food and Drug Administration (FDA) in the United States has established categories of risk factors for most drugs in pregnancy, based on the level of risk the drug poses to the fetus (risk factors A, B, C, D, and X):4

A - Controlled studies have revealed no risk to the fetus (virtually no drugs in this category)

B - No evidence of risk to the fetus has been reported in humans

C - Risk to the fetus cannot be ruled out, because either there is insufficient information available about the drug in animal or human pregnancies, or there are animal studies that have revealed adverse effects but no studies or reports in humans

D - There is positive evidence of human fetal risk, but the benefit may outweigh the risk

X - Contraindicated; benefit does not outweigh the risks; there is evidence of fetal risk based on human experience

Table continued on next page...
organ rheumatic-disease flares (usually in systemic lupus erythematosus [SLE]) without any obvious adverse outcomes.11 Bolus doses of methylprednisolone can cause vascular spasm and hypertension in the mother, which could jeopardize the pregnancy,11 but the pregnancy is usually already in jeopardy due to the serious disease flare necessitating this treatment. It is mandatory to carefully weigh the risks versus the benefits of this treatment in pregnancy. Bolus doses of methylprednisolone do reach the fetus, but no known deleterious effects have been definitively noted.11 The severe maternal disease activity may have more potential indirect effects on the fetus if the disease is not treated maximally.

The major risks of prednisone use in pregnancy are those of exacerbation of pregnancy-induced maternal complications, including hypertension, pre-eclampsia, gestational diabetes and osteoporosis.3,5,11 There are very few data specifically on the use of prednisone in pregnancy. The Główny wynik na tej stronie dokumentu. Wysokość: 792.0, szerokość: 612.0
rare reports of neonatal adrenal insufficiency and perinatal infection.

Despite the rarity of these problems, some recommend monitoring the prednisone-exposed infant in a specialized neonatal nursery—at least overnight (which, due to the rarity of these problems, the author does not do, although a pediatric or neonatology specialist is consulted to review the infant at delivery). Chronic daily use of prednisone or high-dose use of prednisone in pregnancy can be associated with a premature rupture of amniotic membranes. 3,5

"Stress doses" of steroid (such as 100 mg of hydrocortisone intravenously every eight hours for three doses) should be administered beginning at the time of late-stage labour or Caesarean section to any patients who have been treated chronically with steroids within one year of delivery. 3,5

The fluorinated steroids, such as dexamethasone and betamethasone, freely cross the placenta and should only be used in pregnancy to treat the fetus in utero (such as for fetal congenital heart block or to induce fetal lung maturation when premature delivery is anticipated). 3,5

Only trace amounts of prednisone have been found in breast milk in human studies. 1 For maternal doses of 20 mg daily or less, the infant would be exposed to minimal prednisone. 11 Even at maternal doses of 80 mg/day, the infant would ingest less than 0.1% of the dose (corresponding to less than 10% of the infant's endogenous cortisol production). 1,11 It is recommended, however, that if the maternal dose of prednisone is "high" (1 mg/kg/day), the mother should wait four hours before breastfeeding. 1,11

If it were not for the maternal side effects seen with prednisone, this would be the anti-rheumatic drug of choice in pregnancy and lactation (which it still often is, especially for the treatment of life-threatening maternal rheumatic disease, or very-low-dose daily oral prednisone for mildly active disease). 3,3

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Acetylsalicylic acid (ASA). ASA is the most frequently ingested medication in pregnancy worldwide, either alone or in combination with other drugs. 1,13 Eight surveys have revealed that approximately 61% of women ingest ASA at some time during pregnancy, but the true incidence is likely higher, as women having normal pregnancy outcomes do not recall or realize that they have ingested ASA during pregnancy. 1

ASA readily crosses animal and human placentas. 5,12 Low-dose ASA (60-81 mg/day) causes irreversible inactivation of platelet cyclooxygenase, resulting in greater inhibition of thromboxane A2 synthesis than of prostacyclin, which is useful in preventing placental thrombolysis, in treating fetuses with intrauterine growth retardation (IUGR) and probably in prophylaxis against maternal pregnancy-induced hypertension and pre-eclampsia in patients at risk. 1,9,15 Low-dose ASA in the third trimester selectively inhibits maternal platelet cyclooxygenase without affecting neonatal platelet aggregation or pulmonary circulation. 12 and there is no increased risk of neonatal hemorrhage. 12,13

Low-dose ASA is rapidly de-esterified, so that when ASA use is stopped, maternal blood levels fall to zero within two hours, and fetal levels fall to zero within six hours. 12 Low-dose ASA appears to be safe throughout all trimesters of pregnancy, and likely provides beneficial effects for certain patients. 1,9,12-15

Maternal ingestion of high-dose ASA (2-3 g/day) is controversial in the first and second trimesters. There are some retrospective case series that noted increased rates of stillbirth, low birth weight and oral clefts in human fetuses exposed to ASA. 5 A 1985 study found a possible association between the use of ASA in early pregnancy and congenital heart disease, particularly a two-fold increase in septation of the truncus arteriosus compared to nonexposed controls. 1,5 The Collaborative Perinatal Project, however, which monitored over 50,000 mother-child pairs (14,864 mothers having ingested ASA in the first trimester) revealed no fetal malformations. 1,5,13

High-dose ASA (2-3 g/day) should not be ingested by the mother in the third trimester due to premature closure of the patent ductus arteriosus, and renal failure in the fetus with oligohydramnios; potential stillbirth; neonatal central-nervous-system (CNS) hemorrhage; acidosis and salicylate toxicity; and prolongation of gestation and labour. 1,5,9,10,12-14 In the week prior to premature delivery of small infants, ASA dosages of even 325 mg/day to 1,500 mg/day ingested by the mother have been associated with neonatal bleeding. 15

NSAIDs (nonselective cyclooxygenase [COX] inhibitors). Most of the human experience with NSAIDs in pregnancy is derived from their use as tocolytics for 24 hours to 48 hours in the third trimester. 13 While there is a greater amount of information available in the literature about ASA and indomethacin use, there are reports of increasing use of many other NSAIDs in pregnancy, especially since the 1990s. 14 Various NSAIDs cross the placenta in varying concentrations. 13

Animal studies indicate that NSAIDs block blastocyst implantation, and this effect is suspected in humans. 1,9

continued on page 16
possibly interfering with conception in some women.

Several surveillance studies\(^\text{13}\) and a prospective study of NSAIDs\(^\text{14}\) failed to reveal any increase in congenital malformations or teratogenicity, particularly with the use of ASA, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Diclofenac, also, has not been associated with any congenital anomalies.\(^\text{1}\) These NSAIDs all appear to be safe to use in the first and second trimesters of pregnancy in their usual, non-pregnancy, anti-inflammatory doses. It is recommended that high-dose ASA and indomethacin be avoided in favour of the other above-listed NSAIDs for treatment of rheumatic disease in pregnancy, because of the increased risks of neonatal bleeding (including CNS hemorrhage, in the case of premature delivery).\(^\text{5,9,13}\)

NSAIDs should not be administered to the mother in the third trimester of pregnancy because of the risk to the fetus of premature closure of the ductus arteriosus, with the potential development of the following: pulmonary hypertension; impaired renal function with oligohydramnios; neonatal hemorrhage; and prolonged gestation and labour.\(^\text{1,9,10,12-14}\) These NSAID effects on the fetus appear to reverse quickly (within 24 hours of discontinuation of the NSAID).\(^\text{14}\)

From studies using NSAIDs as tocolytics, it appears that constriction of the ductus arteriosus is rare prior to 27 weeks gestation, and increases to about 60% after week 30, independent of the fetal-serum NSAID concentration.\(^\text{13}\) Most fetuses, however, appear to be relatively resistant to these NSAID effects in utero until 32 weeks gestation;\(^\text{9,10,12-14}\) thus, the recommendations in the literature are to discontinue NSAID therapy six to eight weeks prior to the anticipated date of delivery.\(^\text{9,10,12-14}\) At the tertiary-referral high-risk pregnancy center where this author works, use of all regular NSAID therapy is discontinued from page 8

\[ \text{continued from page 8} \]

there are many reports where the CQ has been ingested without any fetal anomalies.\(^\text{22,24,26,27}\)

Antimalarial drugs (e.g., HCQ and CQ) containing the 4-aminoquinolone radical do cross the placenta and bind avidly to pigmented (melanin-containing) tissues in the fetus.\(^\text{5,22}\) HCQ appears to be safer in pregnancy than CQ, since HCQ binds less avidly to tissues and has a lesser ability to cross the placenta (i.e., approximately 50% of maternal concentration with HCQ versus 100% with CQ).\(^\text{23,24}\) There are, however, concerns about fetal retinal toxicity and ototoxicity related to the ingestion of HCQ and CQ, both of which are known to have a potential for retinal deposition, which may lead to visual impairment. This effect is dose-dependent\(^\text{23}\) (although, as stated above, this has never been reported in any fetuses exposed to HCQ). Concerns regarding CQ ingestion in pregnancy arise from isolated case reports of auditory toxicity with high-dose CQ (250 mg twice daily); retinal and cochlear deposition in animal models;\(^\text{6,24}\) and a report published 30 years ago about one mother who ingested a high dose of CQ (250 mg/day to 500 mg/day) during three of her pregnancies, resulting in congenital anomalies in those infants (i.e., Wilm’s tumour at age four in one child, left-sided hemihypertrophy in one child and cochleovestibular paresis in two of the infants).\(^\text{1,24,26}\) This same mother had two other normal infants who had not been exposed to CQ in pregnancy.\(^\text{1,26}\) These concerns influence some physicians to recommend HCQ during pregnancy instead of CQ.\(^\text{10}\)

HCQ and CQ both have long half-lives, so discontinuing these drugs upon diagnosis of pregnancy still exposes the fetus to HCQ or CQ throughout the first trimester, during organogenesis.\(^\text{22}\)

Discontinuation of HCQ has been shown, furthermore, to precipitate disease flares in patients with SLE.\(^\text{28,29}\) It is now well-known that controlling SLE disease activity during pregnancy is related to improved pregnancy outcome.\(^\text{23}\) One double-blind, placebo-controlled study has shown that SLE patients who ingested HCQ throughout pregnancy had improved pregnancy outcomes, with lower SLE disease-activity scores, compared with those SLE patients who did not ingest HCQ during pregnancy.\(^\text{24}\) There were no reports of any adverse effects in the mothers or fetuses in this study.

Dr. Ann Parke has reported a 20-year follow-up of 16 pregnancies in 12 mothers with SLE who ingested HCQ throughout pregnancy; no abnormalities have ever been detected to date in this cohort of infants (now grown) who were exposed to HCQ in pregnancy.\(^\text{23}\) It is strongly recommended that HCQ not be discontinued during the pregnancy of women with SLE.\(^\text{31}\)

\[ \text{ANTI-MALARIAL MEDICATIONS} \]

Hydroxychloroquine (HCQ) is considered safe in pregnancy, with no reports of animal or human congenital anomalies or teratogenicities when ingested in a daily dosage of equal to or less than 6.5 mg/kg of pre-pregnancy maternal weight.\(^\text{5,9,10,22-27}\) There are a few isolated case reports of congenital anomalies occurring after exposure to chloroquine (CQ) in pregnancy (usually high daily doses of greater than 4 mg/kg pre-pregnancy maternal weight), but

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SULFASALAZINE
Information regarding the use of sulfasalazine (SSZ) in pregnancy originates from experience with the use of this medication in the treatment of inflammatory-bowel disease in pregnancy.\textsuperscript{1,9,32,34,37} Approximately 30\% of an oral dose of SSZ is absorbed in the small intestine, with the remainder being cleaved into 5-ASA and sulfapyridine in the colon.\textsuperscript{9} SSZ and sulfapyridine freely cross the placenta, demonstrating the same maternal and fetal blood levels.\textsuperscript{1,9,32} 5-Aminosalicylic acid has a very limited placental transfer.\textsuperscript{9} There have been three isolated reports involving five infants described with congenital malformations after exposure to SSZ, but it could not be determined whether these observed anomalies were related to maternal disease, the SSZ or a combination of both.\textsuperscript{1,32} The increase in congenital anomalies for gestational-age fetuses of mothers ingesting SSZ during pregnancy is considered insignificant.\textsuperscript{1,9,32-37}

Sulfasalazine is a folic-acid antagonist that could potentially cause neural-tube defects and other folic-acid-related defects (e.g., cardiovascular and oral clefts) in fetuses. Recent studies have examined data from an ongoing case-control study of birth defects in the United States and Canada.\textsuperscript{38,39} No definite increase in the adjusted-odds ratios for these events were found to be related to SSZ ingestion in pregnancy;\textsuperscript{38,39} however, it is strongly advised that all women of reproductive age ingesting SSZ also ingest a minimum of 1 mg/day of folic acid.

There is a potential concern for hyperbilirubinemia in fetuses exposed to SSZ close to term, although there are no cases of kernicterus or severe neonatal jaundice reported in infants exposed to SSZ in utero up to the time of delivery.\textsuperscript{1} Caution is also advised in the use of sulfonamides administered to mothers near term, as jaundice has been reported in newborns who were exposed in utero.\textsuperscript{1} This fact may be of clinical importance only in preterm neonates; because of this potential neonatal risk, however, the author discontinues maternal administration of SSZ two weeks prior to delivery, particularly for anticipated preterm deliveries.

SSZ is considered safe during pregnancy and two authors\textsuperscript{9} feel that, of all the disease-modifying anti-rheumatic medications, SSZ is probably the drug of first choice for treating pregnant patients who have the rheumatic diseases for which SSZ is indicated.\textsuperscript{1,9,32-37}

It should be noted that SSZ ingestion by adult males can cause oligospermia, impaired sperm motility, and an increase in the number of abnormal spermatozoa, all of which can result in reversible male infertility.\textsuperscript{1,9}

CONCLUSION
It is always safest for the fetus when mothers can avoid the use of any medications during pregnancy. In rheumatology, however, patients frequently have chronic diseases, and abstinence from all medications is not always possible. In some rheumatic diseases, such as the connective-tissue disorders, Behcet’s syndrome, sarcoidosis and the vasculidities (rarely seen in pregnancy), control of disease activity is directly related to pregnancy outcome. If the disease flares out of control and the mother dies, or an IUGR fetus has to be delivered prematurely (due to severe maternal morbidity and unsatisfactory uterine environment for the fetus), then the careful use of the lowest dosage of the safest and most appropriate anti-rheumatic therapy(ies) clearly outweighs the potential risks to the fetus. In disorders such as severe rheumatoid arthritis (RA) where the patient is one of the 30\% of RA patients who continue to suffer progressive, erosive disease through pregnancy, medications that are considered reasonably safe in pregnancy are indicated to control disease activity. The same principles apply to the spondyloarthropathies and juvenile idiopathic arthritis.

Of all pregnancies (including pregnancies in healthy mothers), 5\% of infants are born with some type of congenital problem. Sometimes, the cause of the congenital problem is not diagnosable, leaving the mother and the rheumatologist to wonder if the anti-rheumatic medication used in pregnancy played any role. Pre-pregnancy planning is essential in minimizing medication use during pregnancy by timing the pregnancy with the time of rheumatic-disease remission or low-level, controlled disease activity, requiring minimal or no medication.

Although breastfeeding is important, management of rheumatic disease during lactation is much more flexible than during pregnancy because the mother does not have to breastfeed the infant. If the rheumatic disease is uncontrolled \textit{post partum}, and medications incompatible with breastfeeding are necessary to control the rheumatic disease, most patients realize that the infant is better off with a healthier mother than with an ill, breastfeeding mother.

\textit{Please look for Part 2 of this article in the Winter issue (December 2002) of the CRAJ.}

References
John loved to teach and was a mentor to numerous trainees. His first trainee, Marty Atkinson, subsequently became Director of the Rheumatic Disease Unit at the University of Calgary. Up until fairly recently, every rheumatologist in Edmonton had trained with John. He also had a notable reputation in the training of foreign medical graduates—most notably from Australia, Thailand and Saudi Arabia—many of whom subsequently played a leading role in the development of rheumatology in their own countries. He really took pride in the achievements of all the people who trained under him.

John was also a leading light in the Arthritis Society during one of its most formative periods, and was an advisor and confidant of Mr. Edward Dunlop, a notable President of the National Arthritis Society. John was an effective champion and advocate for patients with rheumatic diseases, and always truly believed that the patient comes first.

Over the years, John was always a challenging friend and colleague, and it was never boring to be in his company (although often humbling to be the butt of his incisive wit)! Nobody could be ambivalent about John, and he would not have wanted it any other way.

The Faculty of Medicine at the University of Alberta—and Canadian rheumatology at large—has lost one of its long-term, devoted colleagues and characters. And his absence is palpable.