GOLD SALTS (SODIUM AUROTHIOMALATE) 
(INTRAMUSCULAR INJECTION)

There are a very limited number of cases of gold exposure during pregnancy to be found in the literature, and many of these reports are old—probably reflecting the limited use of gold in the treatment of rheumatic diseases in the world outside of Canada, particularly with the increased use of methotrexate (MTX) over the last two decades.

Gold salts cross the human placenta and deposit within the placenta, fetal liver and kidney, 1-3,5,6 but the amount of the maternal dose that reaches the fetus is variable (57% to equal maternal serum concentrations and fetal-cord blood). 1,2

There is no evidence of increased teratogenicity or congenital malformations in fetuses that have been exposed to gold during pregnancy. 1-3,5,6

According to the Food and Drug Administration (FDA), gold salts fall under “category C” (see bottom of Table on page 8). Almost all reports of fetal exposure to gold have ended in uneventful deliveries of healthy infants. The relationship between the few infants reported with abnormalities and the exposure to gold during pregnancy is not clear. 1,2,5

Overall, it seems unlikely that gold causes any fetal abnormalities, however, more reports—including long-term studies—of gold use during pregnancy are needed to verify this statement. 1-3,5,6

Gold is most commonly used to treat rheumatoid arthritis (RA), although it is also used to treat other rheumatic diseases, especially psoriatic arthritis. In 70% to 75% of RA cases, the RA substantially improves or goes into remission during pregnancy, often negating the need for medication during this period; however, RA almost always flares post-partum. 9,10 Thus, gold may not be needed during most RA pregnancies, but will be needed post-partum.

Management of RA during pregnancy must be planned with the patient well in advance of her discontinuation of contraception, due to the long half-life of gold, and the finding in rats of gold in the yolk sac. This finding suggests that if gold does cause any teratogenicity, it may occur very early in the pre-embryonic stage of pregnancy. 11,12 It would therefore appear pointless to discontinue gold at the diagnosis of pregnancy, if the only reason is to protect the fetus from any potential risks due to gold (although the risks appear very low). If the patient and treating rheumatologist wish to avoid using gold during the patient’s pregnancy, it is recommended that it be discontinued three months prior to pregnancy. If gold is chosen to treat (or to help prevent) post-partum RA flares (which can be very severe), it should be restarted approximately one to three months prior to delivery, due to the long onset of action of gold (post-partum RA flares usually peak at two to three months post-partum, but can begin as early as two weeks post-partum). The use of gold in the third trimester would be estimated to be associated with even lower risk than in the first trimester.

The American Academy of Pediatrics (AAP) considers gold salts to be compatible with breastfeeding, 7 despite the fact that side effects have been reported. 8

METHOTREXATE (MTX)

Most of the data about the use of MTX prior to and during pregnancy is derived from cancer literature,
where the dose of MTX used is much higher than in
the rheumatic diseases. MTX is stored in
maternal tissues and crosses the placenta to the
fetus. Maternal ingestion of MTX prior to preg-
nancy (three months prior in the rheumatic diseases,
but up to six to seven months prior in treatment of
cancers) and during pregnancy has significant
potential to cause spontaneous abortions, and is
embryotoxic, causing multiple fetal anomalies and
intrauterine growth retardation (IUGR). The
pattern of malformations that occur in infants
exposed to MTX or any other folic-acid antagonists,
particularly in the first trimester, is called the
Aminopterin Syndrome. Newborn myelo-
suppression has been reported with MTX, but could
also be due to other immunosuppressives coadmin-
istered. One case of a normal female karotype
infant was found to have chromosomal anomalies
(gaps and a ring chromosome) with a theoretically
increased risk for cancer and genetic damage in the
next generation. When being used to treat rheumatic disease,
MTX is contraindicated for both women and men
for three months prior to discontinuation of contra-
ception. MTX is also contraindicated during preg-
nancy and breastfeeding. According to the
FDA, MTX falls under “category X.”

For men and women receiving MTX treatment
for rheumatic disease who wish to pursue preg-
nancy, months of pre-pregnancy planning is
required. The patient needs to be tapered off the
MTX (to avoid a post-MTX arthritis flare), and the
MTX should be switched to a DMARD that is safe
during pregnancy (discussed above and below and
also in Part 1 of this article). A change from MTX
to another DMARD therapy must be accomplished
at least three months prior to discontinuation of
contraception. In women with rheumatic
diseases such as connective-tissue disorders
e.g., Systemic Lupus Erythematosus [SLE]) and the
rare patient with one of the serious vasculidities
e.g., Polyarteritis Nodosa, Churg-Strauss or
Wegener’s Granulomatosis), the DMARD switch is
recommended six months prior to pursuing preg-
nancy, to ensure that the multisystem disease is
quiescent and stable on the new DMARD for six
months before pregnancy.

When discontinuing MTX prior to pursuing
pregnancy in either men or women it is
recommended that folic-acid supplementation
be continued pre-pregnancy and throughout the
pregnancy, as MTX is a folic-acid antagonist and folic acid is extremely important in preventing neural-tube defects in the
embryo. When discontinuing MTX prior to pursuing
pregnancy in either men or women it is
recommended that folic-acid supplementation
be continued pre-pregnancy and throughout the
pregnancy, as MTX is a folic-acid antagonist and folic acid is extremely important in preventing neural-tube defects in the
embryo.

AZATHIOPRINE (AZA)
AZA readily crosses the placenta, but the fetal liver
lacks the enzyme to convert AZA to its active
metabolite (6-mercaptopurine), which appears to
protect the fetus from teratogenic effects. Only trace amounts of 6-mercaptopurine (derived
from AZA in the maternal circulation) cross the
placenta.

AZA has been used extensively in pregnancies in
patients who have undergone solid-organ
transplantation and in patients with inflammatory-
bowel disease, with no reports of any congenital
defects that have been definitely associated with
the AZA. AZA is now successfully
used in SLE pregnancies, and appears to be safer in
these pregnancies than in solid-organ-transplant
pregnancies. Various sporadic anomalies have
been reported, but these have not been felt to be
associated with AZA use during pregnancy.

Spontaneous abortions, IUGR and prematurity
have been reported, but it is unclear whether these are related to: 1) AZA; 2) other simultaneously ingested medications that most of these patients also require; or 3) the underlying disease/condition for which the patient required the AZA.1-3,5,14,30,32-34

Newborn immunosuppression of various severities (e.g., cytopenias and/or low immunoglobulin M, A and/or G levels) have been reported1,2,5,13,14 with in utero exposure to AZA. Most of these cases seem to have resolved without incident, but one infant

<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>Leflunomide (LF)</td>
<td>X</td>
<td>Animal data have shown an increased rate of malformations &amp; terogenicity as well as fetal death in various species.1,44</td>
<td>LF is a relatively new drug for treatment of RA, available in the USA since late 1998; thus, there is no information about its use in pregnancy. LF is currently contraindicated in pregnancy &amp; considered to have teratogenic potential in humans (a terogenicity registry is underway). Due to LF’s long elimination half-life, it is recommended that women &amp; men wishing a pregnancy should discontinue LF 2 yrs. prior to pursuing pregnancy or undergo a “drug-elimination” procedure with either cholestyramine (8 g po TID x 11 days) or activated charcoal (50 g po QID x 11 days) followed by two blood tests, 14 days apart, to verify LF plasma levels of &lt;0.02 mg/L, or repeat treatment.1,4,44-47</td>
<td>No information available and, thus, considered contraindicated during breastfeeding.</td>
</tr>
<tr>
<td>D-Penicillamine (d-Pen)</td>
<td>D</td>
<td>Studies in pregnant rats, administered 6x the maximum dose in humans, experienced fetal resorptions &amp; fetal anomalies consisting of skeletal defects &amp; cleft palates.1 Skin laxity in animals has also been reported.5</td>
<td>Data on d-Pen use is sparse &amp; conflicting &amp; comes from the use of d-Pen in patients with RA, Systemic Sclerosis (SSc), Wilson’s disease &amp; cystinuria in pregnancy. D-Pen crosses the placenta, but there are reports of normal infants who were exposed to d-Pen for part or all of a pregnancy, especially in Wilson’s disease. There are also, however, reports of fetal anomalies. It is, thus, recommended that d-Pen be used in pregnancy only when absolutely necessary, such as in Wilson’s disease, cystinuria or SSc, in the lowest possible effective dose. There are safer medications to treat RA during pregnancy than d-Pen. Thus, d-Pen should not be used to treat RA in pregnancy &amp; should be stopped beforehand or immediately at the beginning in the case of an unplanned pregnancy.1,3,6,48</td>
<td>There are no reports of d-Pen in lactation or on whether it is excreted in breast milk. D-Pen has a short plasma half-life &amp; is extensively protein-bound; thus, one would theorize that only small amounts should be present in breast milk. Due to the lack of information, breastfeeding mothers ingesting d-Pen should be advised against breastfeeding.3,40</td>
</tr>
</tbody>
</table>

* 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
was born with pancytopenia and severe combined immune deficiency, and died of complications at age 28 days. These reports of newborn immunosuppression seem to be related to the maternal dose of AZA. One study revealed a significant correlation between the maternal white-blood-cell count (WBC) at 32 weeks’ gestation and the umbilical-cord WBC at delivery. The investigators in this case halved the maternal dose of AZA at 32 weeks’ gestation if the maternal WBC count was at or below one standard deviation for normal pregnancy; since commencing this protocol, this institution has had no episodes of newborn immunosuppression. There are two reports of newborn cytomegalovirus infection. There has been one case report of a child with a balanced translocation and partial deletion of chromosome 7 following in utero exposure to AZA, but it is unclear whether this was related to the AZA therapy. There are also reports of other reversible chromosomal aberrations.

Table (cont’d)

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<tr>
<td>Tetracyclines (Doxycycline; minocycline)</td>
<td>D</td>
<td>Doxycycline administered to pregnant rats resulted in a delay in skeletal differentiation in the long bones. Tetracyclines are generally contraindicated during pregnancy and should not be used to treat rheumatic disease during pregnancy because tetracyclines are associated with dental staining and interference with bone growth in exposed fetuses in utero; thus, in treatment of rheumatic diseases during pregnancy, there are safer medications that can be used. When needed as an antibiotic, there are conflicting reports regarding association of tetracyclines with congenital anomalies. Tetracyclines are excreted into breast milk in low concentrations &amp; serum levels of tetracyclines in exposed infants have been undetectable. There are theoretical concerns regarding dental staining &amp; inhibition of bone growth that could occur in breastfed infants of mothers ingesting tetracyclines. There is also potential concern regarding modification of bowel flora in the breastfed infant, &amp; interference with the interpretation of culture results in the investigation of an exposed infant with a fever. The AAP, however, considers tetracyclines to be compatible with breastfeeding.</td>
<td>Infants with and without congenital anomalies have been reported after exposure to CTX in utero. First-trimester exposure to CTX appears to be teratogenic. Exposure in 2nd &amp; 3rd trimesters does not appear to be associated with birth defects or neurologic abnormalities, but these infants are at risk for bone-marrow suppression at birth &amp; low birth weight (but the latter could also be due to the disease for which the CTX is required as well as to other simultaneously administered meds). Long-term effects in humans from exposure to CTX during pregnancy are unknown. CTX should be considered teratogenic &amp; contraindicated during pregnancy unless absolutely required to treat maternal life-threatening rheumatic-disease flares in 2nd or 3rd trimesters of pregnancy. CTX should be discontinued three months prior to discontinuing contraception.</td>
<td>CTX is excreted into breast milk. The AAP &amp; others consider CTX contraindicated during breastfeeding, with risks including infant neutropenia &amp; adverse effects related to immune suppression, growth &amp; potential carcinogenesis.</td>
</tr>
<tr>
<td>Cyclophosphamide (CTX), an antineoplastic alkylating agent</td>
<td>D</td>
<td>Clearly embryofetotoxic, teratogenic &amp; mutagenic in animals. Teratogenicity in mice, in one study, was dose-related.</td>
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AAP=American Academy of Pediatrics
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<td>Chlorambucil; an antineoplastic alkylating agent</td>
<td>D</td>
<td>In rats, chlorambucil has shown to be 3x more potent as a teratogenic agent (on a mg/kg basis) than cyclophosphamide (CTX).^14</td>
<td>Very similar to CTX during pregnancy but less data available. Reports of normal infants &amp; infants with congenital anomalies exposed to chlorambucil in utero. Two reports of left-kidney &amp; ureter agenesis following 1st-trimester exposure^10 &amp; cardiovascular anomalies.^3 Chlorambucil is contraindicated during pregnancy.^1,3,14</td>
<td>No reports of chlorambucil in breastfeeding but because of its potential for severe adverse effects, breastfeeding is considered contraindicated for mothers ingest chlorambucil.^1,3,14</td>
</tr>
<tr>
<td>Mycophenolate mofetil (MMF)</td>
<td>C</td>
<td>Studies using MMF in subtherapeutic human dosages in pregnant rats &amp; rabbits revealed fetal resorptions &amp; malformations.^3</td>
<td>There are minimal data on the use of MMF during human pregnancy, all of which arise from use of MMF in pregnant solid-organ-transplant patients. MMF is theorized to cross the placenta, as MMF &amp; its metabolite are of low molecular weight and, also, presumed to cross because of the results of animal studies.^1 There is one case report of a mother who had undergone renal transplant who ingested MMF throughout the entire pregnancy (in addition to tacrolimus &amp; prednisone); a premature (35 &amp; 3/7 weeks gestation) but otherwise healthy female infant was delivered, &amp; the only anomalies found were hypoplastic nails &amp; short 5th fingers.^4 A report from one transplant registry noted “no structural malformations” among offspring exposed to MMF (five mothers, 29 fathers);^5 although the same authors in another paper stated that “there are concerns about the reproductive safety of MMF.”^6 A European transplant group does “not recommend” MMF during pregnancy “based on current information available.”^7 Due to lack of sufficient data &amp; results from animal studies, there is concern re: the safety of MMF during pregnancy, &amp; the manufacturer of MMF recommends that patients ingesting MMF use contraception, &amp; that pregnancy not be pursued until 6 weeks after stopping MMF.^1</td>
<td>MMF is excreted into the breast milk of rats but there are no reports of the use of MMF in human lactation. Due to lack of available data &amp; the potential for risk to the infant if exposed to MMF, breastfeeding should be considered contraindicated for mothers who are ingesting MMF.^1</td>
</tr>
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It is unclear whether these isolated reports of immunoglobulin deficiency, chromosomal abnormalities and malformations in fetuses exposed to AZA in utero are any more common than the rate occurring in the normal healthy obstetrical population.\^14 There remain unanswered, potential, long-term affects on offspring exposed to AZA in utero, such as the child’s future fertility and risk of carcin-
According to the FDA, AZA falls under “category D.” At present, the greatest known risk to infants exposed to AZA in utero is IUGR and prematurity, and this risk is unlikely related to AZA exposure alone.\(^2,14,30-35\)

It should be noted that there are several reports of renal-transplant patients ingesting AZA who have conceived pregnancies with intrauterine contraceptive devices (IUDs) in situ. It is felt that AZA may interfere with the contraceptive action of IUDs; it is therefore recommended to advise patients of this, and to advise them to consider using either another form of contraception or an additional form of contraception.\(^1\)

**Overall, it appears that AZA, in the lowest effective dose, is relatively safe in pregnancy, when the benefits of this medication outweigh the possible risks to the fetus/newborn.**\(^2-5,13,21,30-34\) If
AZA is necessary to control SLE disease activity during pregnancy, its use has been associated with improved pregnancy outcome compared to those who were not treated.\textsuperscript{4,28} Of all the immunosuppressive agents, it would appear that AZA is the safest to use during pregnancy, if an immunosuppressive agent is required.\textsuperscript{13}

Motherisk, in Toronto, Canada, and others\textsuperscript{3,14} state that AZA is excreted into breast milk in low concentrations. The AAP considers breastfeeding not recommended when mothers are ingesting AZA due to lack of information and data on long-term outcome.\textsuperscript{3,13,14}

CYCLOSPORINE A (CsA)
The use and experience of CsA during pregnancy is very similar to that of AZA and, in fact, these immunosuppressive agents have frequently been used together in the same patients, along with prednisone (particularly in management of pregnant patients who have undergone solid-organ transplantation).\textsuperscript{2,14,30-40} CsA has been used to treat a limited number of autoimmune patients with severe RA, psoriasis, SLE and other connective-tissue disorders, inflammatory bowel disease and chronic inflammatory demyelinating polyneuropathy during pregnancy.\textsuperscript{2,3,14,30-40} There are no reports in humans of any fetal malformations associated with the use of CsA during pregnancy. Similar to AZA, there was a high rate of spontaneous abortions (approximately 35\%), IUGR (average about 50\%) and prematurity (54\%).\textsuperscript{2,14,30,32-40}

CsA has a lower bone-marrow toxicity and lower carcinogenic potential compared to other immunosuppressive agents and, overall, complications in newborns have been slightly lower than complications in newborns exposed to other immunosuppressive agents.\textsuperscript{2,14}

Maternal morbidity was significant in those who ingested CsA, including hypertension (56\%), pregnancy-induced hypertension (29\%), pre-eclampsia and gestational diabetes. These maternal morbidities were reported, however, in renal-transplant patients—patients who are already at higher risk for development of these complications than most patients with autoimmune diseases who receive CsA during pregnancy.\textsuperscript{2,14,34}

Two studies have followed offspring long-term, who were exposed to CsA in utero (usually also with prednisone and/or AZA), up to 11 years and 18 years of age, respectively.\textsuperscript{35,39} No health problems developed in any of the offspring that were more than those developed in the average population, except possibly the development of “urinary-tract abnormalities on ultrasound” in four out of 40 (10\%) in the second study only.\textsuperscript{39} Both studies came to the same conclusions that, despite the high incidence of pre-term delivery and low birth weight, the offspring of renal-transplant recipients were doing well.\textsuperscript{35,39} Long-term studies are still needed to determine whether there will be any effects other than, possibly, urinary-tract abnormalities.

CsA appears to be a safe immunosuppressive agent to use in a pre-pregnant or pregnant autoimmune-disease patient who requires such therapy.\textsuperscript{2,14,30,32-40} According to the FDA, CsA falls under “category C.”

The AAP considers CsA contraindicated in breastfeeding due to the potential immune suppression, neutropenia, unknown effect on infant growth and possible long-term risk of carcinogenesis.\textsuperscript{7}

CONCLUSION
It is most important to avoid the use of any and all medications during pregnancy, as the long-term effects on the fetus/infant are often unknown. In any pregnancy, there is a small chance (5\%) of a spontaneous congenital anomaly occurring, leaving the physician(s) to wonder whether medication(s) ingested by the mother played a role or not, and usually always leaving the mother with strong feelings of guilt (no matter how necessary the medication was during the pregnancy). In the rheumatic diseases in pregnancy, often, medications cannot be avoided and are absolutely necessary for the best pregnancy outcome for both mother and infant. Medications often are required to control the rheumatic disease through pregnancy, especially
when guiding mothers through a pregnancy with SLE and other related connective-tissue disorders, Behcet’s Syndrome, sarcoidosis or the vasculidities. If the rheumatic disease becomes active or flares through pregnancy, the pregnancy outcome can be severely compromised, usually with premature delivery of an IUGR infant who must spend time in a special-care nursery, potentially developing morbidities related to prematurity (or suffering an intrauterine death); there is also significant maternal morbidity and occasionally maternal death. Thus, the risks of leaving some of these rheumatic disorders untreated during pregnancy, for fear of adverse drug effects, are far outweighed by the benefits of careful use of medication during pregnancy. Of course, with these particular rheumatic disorders, pregnancy should never be considered unless the disease is well controlled or, most preferably, in remission, requiring minimal or no medication use during pregnancy.

In other rheumatic diseases, where maternal vital-organ involvement and appropriate fetal development are not at risk directly due to the rheumatic disorder (e.g., RA, psoriatic arthritis, spondylarthropathies, juvenile idiopathic arthritis), the potential risks of medications must be carefully weighed against the progression of joint damage through pregnancy, as well as maternal pain and function.

When counseling a breastfeeding mother, the same risks versus benefits must be carefully balanced. It is sometimes necessary to advise the breastfeeding mother that the necessity for certain medications for her own health clearly outweighs the benefits to the infant of being breastfed, and that the decision to discontinue breastfeeding to allow optimal treatment of the rheumatic disease is the best decision for mother and infant. An ill, dysfunctional, depressed, breastfeeding mother who is unable to do anything else for that infant is of much less benefit to the appropriate development of the infant than is a much healthier, non-breastfeeding mother.

Fortunately, as discussed in this article and in Part 1 (see Summer 2002 issue of the CRAJ), there are many medication choices that are now felt to be safe during pregnancy (especially in the short term or for part of a pregnancy) and lactation. The use of these medications in these situations must be clearly justified, with the benefits definitely outweighing any potential risks. These medications have allowed pregnancies in women with rheumatic diseases, when, only a decade ago, these women were strongly advised against pregnancy. Pre-pregnancy counseling and pregnancy planning in the rheumatic diseases is imperative to a successful pregnancy outcome.

References