DRUG SAFETY CONCEPTS

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Treatment of Inflammatory Rheumatic Disorders in Pregnancy

What are the Safest Treatment Options?

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Abstract

The interaction of pregnancy and the rheumatic diseases varies, ranging from life-threatening conditions such as thromboembolic events and progressive renal disease in some autoimmune disorders, to minor flares of peripheral arthritis in inflammatory rheumatic disease. As a consequence, treatment strategy will vary according to the maternal or fetal compromise expected.

All nonsteroidal anti-inflammatory drugs (NSAIDs), including high dose aspirin (acetylsalicylic acid), can cause adverse effects during pregnancy related to the inhibition of prostaglandin synthesis. Prolongation of gestation and labour, constriction of the ductus arteriosus, persistent fetal circulation, impairment of renal function and bleeding are risks of third trimester exposure of pregnant women to all inhibitors of cyclo-oxygenase. Most of these adverse effects can be prevented by discontinuing NSAIDs 8 weeks prior to delivery. Low dose aspirin has not been associated with fetal or neonatal toxicity.

Some corticosteroids such as prednisone and prednisolone do not readily cross the placenta and can be safely used during pregnancy as immunosuppressive drugs. Maternal complications related to corticosteroids may occur and close monitoring is therefore mandatory. There is limited information on the safety of disease-modifying antirheumatic drugs including gold, antimalarials, penicillamine (D-penicillamine), sulfasalazine and cyclosporin. Of these agents, sulfasalazine has the best record for tolerability and can be used by pregnant patients. Gold compounds and penicillamine should be discontinued when pregnancy is recognised. Hydroxychloroquine has not been associated with congenital malformations and seems preferable to chloroquine in patients requiring treatment with antimalarials. Use of cyclosporin may be an alternative to other therapy in pregnant patients with severe rheumatic disease. Indications for treatment with colchicine during pregnancy are few, except for familial Mediterranean fever.

Azathioprine can be used when the maternal condition requires a cytotoxic drug during the first trimester. Cyclophosphamide, chlorambucil and methotrexate are contraindicated during pregnancy because of their teratogenic potential. Their use may be considered in late pregnancy if the mother has a life-threatening condition.

When women with inflammatory rheumatic disease become pregnant, management of peripheral arthritis and systemic disease becomes a challenge for the physician. The interaction of pregnancy and rheumatic diseases varies, ranging from life-threatening conditions such as thromboembolic events and progressive renal disease in some autoimmune disorders, to minor flares of peripheral arthritis in inflammatory rheumatic disease. As a consequence, treatment strategy will vary according to the maternal or fetal compromise expected. In the following text, the effect of pregnancy on the activity of inflammatory rheumatic diseases is reviewed; however, the reader interested in detailed surveys of pregnancy and the rheumatic diseases is referred to specialist literature in this field.[1,2]

1. The Interaction of Pregnancy and Rheumatic Disease

1.1 Rheumatoid Arthritis

About 75% of rheumatoid arthritis patients improve during pregnancy.[3,4] The reduction of disease activity develops early and is apparent in

about 70 to 75% of patients at the end of the first trimester, whereas amelioration is delayed until the second and third trimester in 25 to 30% of patients. Complete remission of all signs and symptoms leading to no need for medication has been described in about 65% of pregnancies which show improvement of disease activity.[3] Only about 20 to 30% of pregnant rheumatoid arthritis patients will need medications to control flares of arthritis or systemic disease.[4] Complications of pregnancy such as pre-eclampsia or premature labour have rarely been reported in rheumatoid arthritis.[3] As a rule, the disease does not compromise fetal outcome.[3,4]

1.2 Juvenile Chronic Arthritis and Adult Still's Disease

Juvenile chronic arthritis, defined by a disease onset before the age of 16, includes polyarticular, pauciarticular and systemic subgroup involvement. Complete remission of the signs and symptoms of juvenile chronic arthritis occurs in about 70% of the patients in early adulthood.[3] A small study found no reactivation of quiescent juvenile chronic arthritis by pregnancy.[5] Studying patients with persisting active juvenile chronic arthritis showed that improvement during pregnancy was most often seen in patients in the polyarticular subgroup, whereas it was less frequent in those with pauciarticular involvement and rare in patients with systemic juvenile chronic arthritis.[5] Complications of juvenile chronic arthritis requiring treatment during pregnancy have included active anterior uveitis, severe systemic disease and renal amyloidosis. No increase in adverse pregnancy outcomes has been reported.[5] The systemic form of juvenile chronic arthritis may have its symptom onset occur during adulthood. The few pregnancies reported in patients with adult Still's disease showed no consistent pattern with regard to disease activity. Acute flares occurred in several patients requiring high doses of salicylates or prednisone.[3]

1.3 Spondylarthropathies

Rheumatoid factor negative arthritis associated with the cell surface marker HLA-B27 with limited internal organ involvement includes disorders such as ankylosing spondylitis, psoriatic arthritis and Reiter's syndrome. Characteristics of ankylosing spondylitis are involvement of the spine, the sacroiliac and the large proximal girdle joints. Prospective and retrospective studies have documented that the signs and symptoms of ankylosing spondylitis are largely unaltered by pregnancy.[1] Exacerbations of spinal symptoms or peripheral arthritis are common around mid-gestation and may require treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in order to relieve pain and stiffness.[6] Complications during pregnancy are not increased in ankylosing spondylitis and fetal outcome is not compromised.[7]

In the only small prospective study of pregnancies in patients with psoriatic arthritis, improvement during pregnancy occurred in 80% of patients; of those patients showing improvement, complete resolution of all signs and symptoms occurred in half of them.[8] Amelioration was noted early in the first trimester and progressed during the latter half of gestation. Skin disease tended to subside during pregnancy.

Reactive arthritis following urogenital or gastrointestinal bacterial infections are not uncommon during the reproductive years. However, there have been no reports of pregnant patients with these conditions. The concurrence of pregnancy and inflammatory bowel disease is well recognised, but to date, no systematic study of the course of the associated arthritis has been performed in pregnant patients.

1.4 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) occurs predominantly in women of childbearing ages. Women with SLE frequently have symptoms of their disease during pregnancy and can have active disease *post partum*. The results of 6 recent studies are split 50 : 50 in their outcomes for SLE preg-

nancy: 3 support SLE flare during pregnancy,[9-11] and 3 groups have indicated that SLE flare is not increased in the setting of pregnancy.[12-14] Most series agree that SLE symptoms can occur during any trimester and *post partum*. Control of SLE symptoms in pregnant patients with medication is frequently needed prior to, during and after pregnancy.

Fetal outcome is adversely affected by maternal SLE. Approximately 50% of pregnancies in women with SLE result in a full term, healthy birthweight infant.[15] The adverse fetal outcomes in maternal SLE include fetal death, preterm birth (before 37 weeks gestation) and intrauterine growth retardation.[15,16] Maternal renal disease or hypertension, previous history of fetal death, or the presence of antiphospholipid antibodies adversely influence the risk of a poor fetal outcome in women with SLE.[17] The manifestations of neonatal SLE include transient rash within the newborn period, permanent heart block, or both.[18]

1.5 Scleroderma

Scleroderma or systemic sclerosis is a rare connective tissue disease with both inflammatory and vascular changes in the skin and internal organs. Early series described adverse maternal outcomes in pregnant patients with scleroderma.[19] In a recent comprehensive study, 69 patients with 133 pregnancies had no change in disease-related symptoms in 88% of pregnancies, 5% had improvement and 7% had an exacerbation of their disease.[20]

Renal crisis usually occurs in the setting of new onset disease or recent rapid progression of skin disease. Renal crisis is rare in the setting of pregnancy, and progression of skin disease is uncommon during pregnancy or *post partum*.

Women with scleroderma have an increased risk of preterm and small for dates infants. These patients are considered at high risk and treatment is directed at specific scleroderma-related symptoms.

Raynaud's disease is treated conservatively with avoidance of cold temperatures. Vasodilators such as nifedipine have been used successfully during pregnancy.[21] Gastroesophageal symptoms are managed with usual anti-reflux measures.[19] ACE inhibitors are contraindicated during pregnancy; however, in the unusual circumstance of renal crisis, their use may be considered life-saving for the mother.[19] There are no treatment modalities proven to be effective in modifying the overall course of the disease.

In the rare instance of early aggressive disease during pregnancy, the use of penicillamine (D-penicillamine), cytotoxic agents, or cyclosporin in the pregnant patient must be weighed against the risks to the fetus.[19]

1.6 Polymyositis and Dermatomyositis

Polymyositis is an inflammatory disease of unknown aetiology which affects striated muscle, while dermatomyositis includes both skin and muscle involvement. There are little data on pregnant women with polymyositis and dermatomyositis. The outcome for mother and fetus varies with the time of disease onset.[22] If the mother develops polymyositis or dermatomyositis during pregnancy or the puerperium, approximately 50% of pregnancies may result in fetal or neonatal death.[23] In contrast, most pregnancies in women with established disease have resulted in live births,[23-25] although most of these pregnancies were complicated by intrauterine growth retardation and/or preterm delivery. In 6 women who developed polymyositis or dermatomyositis during pregnancy or the puerperium, 3 of 6 (50%) had pregnancies complicated by fetal loss or neonatal death.[26] In 11 women with established disease, 12 of 15 pregnancies resulted in live births.[26] Of these 11 live births only 1 pregnancy was complicated by intrauterine growth retardation and 3 pregnancies were preterm.[24,25]

It is important to control disease prior to pregnancy and to control a disease flare if it occurs during pregnancy.[22,25] Therefore, medication management throughout a women's disease course is important.

1.7 Vasculitis

Vasculitis is a clinicopathological process characterised by inflammation and necrosis of blood vessels. The most common primary types of vasculitis are Wegener's granulomatosis, polyarteritis nodosa and Churg-Strauss vasculitis. There is limited information on pregnancy outcome and medication use in these patients because most of the primary vasculitides occur in older individuals and they are more common in men.

Maternal and fetal outcome was satisfactory in patients with Wegener's granulomatosis, polyarteritis nodosa and Churg-Strauss vasculitis when disease was controlled.[27-29] However, it is important to note that some of these women had disease onset or symptom recurrence *post partum*. Pregnancy may contribute to the appearance of disease for the first time during pregnancy and also contribute to disease flare during pregnancy or *post partum*. Therefore, it is important to treat such patients aggressively with immunosuppressive drugs during and after pregnancy if disease is active.[23] The practitioner also may want to have the patient continue medications during pregnancy if the risk of disease activity persists during this time or if the mother's life is threatened.

1.8 Other Disorders

Behçet's disease is a multisystem disorder characterised by recurrent aphthous stomatitis, genital ulcers, uveitis, cutaneous vasculitis, arthritis and other manifestations. Disease onset during childbearing age is frequent.[30] Case reports and small series have shown a variable course of Behçet's disease during pregnancy. A recent larger retrospective study reported that disease manifestations of Behçet's disease were not consistently worsened by pregnancy and that fetal outcome was good.[31]

Gout and acute gouty arthritis are uncommon in women in their reproductive years. In 6 case reports describing pregnancies in women with gout, acute gouty arthritis occurred in three.[32] Gouty nephropathy was present in 2 pregnant patients and required treatment. Attacks of pseudogout (chondrocalcinosis) have been reported in 4 pregnant women occurring during the second and third trimester of pregnancy.[33]

2. Data Collection

A comprehensive search of all biomedical literature from 1960 to 1997 was conducted using Medline. Terms included in the search were the rheumatic diseases discussed in this article and pregnancy, each drug, teratogenicity and immunosuppression. The bibliographies provided in previous review articles were reviewed for further relevant articles and included if appropriate. Since there were few data on antirheumatic drugs in human pregnancy, we decided to include all relevant publications if published in the following languages: English, French, German and Spanish.

3. Drug Treatment During Pregnancy

Virtually all drugs given to pregnant women will be passed to the fetus. Factors involved in placental drug transfer have been reviewed elsewhere.[34,35] Lipid-soluble nonionic small molecules of 0.6 to 1kD will readily cross the placenta. Only the unbound, nonionised fraction of a drug is available for transplacental transfer. The placental transfer rate is highly dependent on maternal and fetal placental blood flow rates.[36] After transplacental passage, drug equilibration with fetal tissues occurs.[37] Both drug protein binding and hepatic metabolism in the fetus differ from those in the mother, and depend on the stage of fetal development.

Placental transfer has been demonstrated for the majority of the antirheumatic drugs. The fetal to maternal drug concentration ratio varies greatly for different drugs and can be found to be less than, equal to, or can exceed maternal serum concentrations. Critical factors for fetal exposure are dosage, the type of the drug, duration of treatment and timing.[38] The first 12 and last 4 weeks of pregnancy are particularly vulnerable periods of antenatal drug exposure, the latter because of possible drug effects on the neonate, and the former because of early fetal development. Toxic effect of drugs

given during fetal organogenesis will cause malformations (teratogenesis) while drugs given at the later stages of fetal development can cause functional abnormalities. Long term effects of antenatal drug exposure are in general unknown.

Pharmaceutical companies usually recommend patients take no antirheumatic drugs during pregnancy due to a lack of intensive investigation in such women. To date, few controlled studies have been conducted on the safety of most antirheumatic drugs during pregnancy. In the absence of controlled studies, reporting bias favours the reporting of negative events, particularly in case reports and small series.

4. Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are the mainstay of antirheumatic therapy. Pregnancy-related conditions such as premature labour, polyhydramnios and pregnancy-induced hypertension have also been indications for treatment with NSAIDs. With the exception of low dose aspirin (acetylsalicylic acid) most of the currently available NSAIDs are nonselective inhibitors of cyclo-oxygenase (COX) with an effect both on the housekeeping COX 1 and on COX 2, which is induced by inflammation.[39] Thus, nonselective COX inhibitors inhibit not only inflammatory but also gastric, platelet and renal prostaglandin production.[39] It has to be pointed out that nearly all reports on NSAIDs in human pregnancy covered in this review relate to indications other than rheumatic disease for maternal treatment. Particular indications such as tocolysis may exaggerate some adverse effects of NSAIDs and possibly minimise others which might occur when treating rheumatic patients.

4.1 Animal Data

High, nonpharmacological doses of aspirin and indomethacin have caused malformations in some animal species.[40] For the other NSAIDs surveyed in this review, no congenital abnormalities have been observed in animals treated with pharmacological or higher doses.[40,41] Adverse fetal effects such as premature closure of the ductus arteriosus and prolongation of gestation and labour has been observed following third trimester exposure to NSAIDs.[42,43]

4.2 Aspirin (Acetylsalicylic Acid)

Aspirin is the drug most frequently ingested during pregnancy worldwide. It has been estimated that about 60% of pregnant women occasionally take aspirin during pregnancy.[42]

Reports on exposure to high dosages of aspirin (>1 g/day) for between 1 week through to daily use throughout pregnancy comprise more than 16 000 pregnancies.[41] In 1975, Collins and Turner[44] published their experience with 144 mother-child pairs in which the mother ingested salicylates during gestation. They found a significantly decreased mean birthweight, as well as a 5-fold increase in stillbirths compared with control participants. Several studies found an association between aspirin ingestion during pregnancy and fetal malformations.[42,45] A study published in 1985[46] reported an association between first trimester use of aspirin and congenital heart defects, but this was not supported by 2 other controlled studies which enrolled >3000 infants.[42,47] Several case reports have described fetal abnormalities including cerebral haemorrhage, constricted ductus arteriosus, neonatal acidosis and neonatal salicylate toxicity occurring in infants exposed to high doses of aspirin antenatally.[40,42]

The Collaborative Perinatal Project in the US studied 14 864 mothers-infant pairs prospectively.[48] Heavy exposure to aspirin (more than 7 days in 1 month) during the first 4 months of pregnancy was reported in 5128 patients and intermediate exposure (less than 7 days in 1 month) was reported in 9736 patients. The study failed to show aspirin as a cause of stillbirth or reduced birthweight, and was there were no increases in the rate of congenital malformations.[48] The Michigan Medicaid Surveillance Study which investigated first trimester exposure to aspirin in 1709 pregnancies also failed to show an increase in congenital abnormalities.[40]

Effects of high dose aspirin given near term have been investigated in several studies. Significant prolongation of gestation and labour was found in 103 pregnant women treated with more than 3 g/day aspirin for rheumatoid arthritis during the last 6 months of pregnancy.[49] Increased maternal blood loss at delivery was found, although no neonatal bleeding was reported. However, high dose aspirin given near to delivery has been shown to cause bleeding tendencies and CNS haemorrhage in neonates.[50,51] Rumack[51] found that among premature infants, 71% had signs of ventricular haemorrhage compared with 44% of control infants not exposed to aspirin. Clotting abnormalities have been detected in newborns exposed to a total of aspirin 325 to 650mg within 1 week prior to delivery.[40,41] Clotting abnormalities in the newborn have not been reported for low dose aspirin (≤80 mg/day) even when given up to term.[42] One small study found no effect of low dose aspirin on neonatal platelet aggregation.[52] Two studies have shown treatment with aspirin 40 to 80 mg/day to selectively inhibit thromboxane, but not prostacyclin production, in the mother.[53,54]

Several large studies have addressed the use of low dose aspirin during gestation (<325 mg/day) to prevent pregnancy-induced hypertension and pre-eclampsia, and for fetal indications such as intrauterine growth retardation.[55,56] Low (10 mg/μl), but not high (>10 mg/μg) doses of aspirin increase the production of interleukin-3, a cytokine which positively affects pregnancy and fetal development.[57] More than 10 000 pregnancies exposed to 60 to 80 mg/day of aspirin during the second and third trimester up to term have been reported without any increase in maternal and fetal adverse effects.[55,56,58] Two follow-up studies comparing 2573 children exposed to aspirin 60 mg/day during the second and third trimester of pregnancy with 2580 children not exposed revealed no significant differences between the groups with respect to congenital malformations, development and health status up to 18 months.[59,60] No adverse effect of low dose aspirin on fetal renal function, the fetal ductus or clotting ability of the newborn has been demonstrated.[52] Doppler investigation of fetuses aged 15 to 40 weeks exposed to aspirin 60 mg/day during the second and third trimester did not reveal any effect on the ductus arteriosus.[61]

4.3 Indomethacin

Prenatal transplacental transfer of indomethacin is unrelated to gestational age in the human fetus.[62] In several retrospective and prospective studies, short courses of 1 to 3 days with 100 to 400 mg/day of indomethacin, given to suppress premature labour, showed good maternal and fetal tolerance, with no increase in the risk of congenital malformations, premature closure of the ductus arteriosus, pulmonary hypertension, or renal impairment of the neonate.[63-65] Adverse fetal effects have been reported involving numerous case reports and retrospective studies involving more than 1000 pregnancies.[40,66] Duration of therapy over 3 weeks and administration close to delivery appeared to be major risk factors for neonatal complications.[66]

Several studies using fetal echocardiography have analysed the effect of indomethacin on the constriction of the ductus arteriosus. Constriction was related to gestational age, and the occurrence of constriction was rare before week 27, and occurred with an incidence of about 60% after week 30.[67] Constriction was independent of the fetal serum concentration of indomethacin.[68] Constriction resolved in all fetuses within 48 hours of stopping indomethacin, and none of the neonates showed persistent fetal circulation after delivery.[69] Pulmonary hypertension has been reported in neonates exposed to indomethacin within 24 hours of delivery.[70-72] In several of these premature infants the complication proved fatal.[73]

A marked decline in fetal urine output has been observed within 5 hours of indomethacin treatment with oligohydramnios developing in 70 to 82% of patients during the first week of treatment, but oligohydramnios disappeared after discontinuation of the drug.[74,75] Development of oligohydramnios has been shown to be dose-dependent.[76] One study found no impairment of renal

function in offspring of 9 mothers treated with a mean dosage of indomethacin 117 mg/day for an average of 40 days.[77] Transient anuria,[78] but also fatal persistent anuria in neonates exposed to indomethacin within the 24 hours after delivery, has been reported.[79,80]

Other reported adverse effects after antenatal exposure to indomethacin have included necrotising enterocolitis[81] and intracranial haemorrhage in the neonate.[82] The latter finding contrasts with data suggesting that indomethacin may protect against neonatal intraventricular haemorrhage when given postnatally.[83]

4.4 Sulindac

Sulindac is a prodrug which is reduced by hepatic enzymes to the active sulfide metabolite. Transplacental passage of sulindac, and to a lesser degree its active sulfide metabolite, has been demonstrated.[84] The ability to reduce sulindac to the active sulfide is decreased in the human fetus.[84] First trimester exposure did not result in an increased malformation rate in 69 neonates.[40] When comparing a dosage of sulindac 400 mg/day with indomethacin 150 mg/day in 20 women treated 2 or 4 days for preterm labour, sulindac produced significantly less fetal adverse effects and did not produce complications in the neonates.[85,86] In a placebo-controlled study, treatment with sulindac 200 mg/day in 34 women for 1 week did not produce fetal renal or cardiac adverse effects.[87] Treatment with sulindac 400 mg/day for 4 to 8 weeks reduced amniotic fluid volume in 3 sets of twins, but did not affect the ductus arteriosus.[88] A case report described localised ileal perforation in a premature infant exposed to dexamethasone and sulindac within the 24 hours before delivery.[89]

4.5 Naproxen

Transplacental passage of naproxen has been documented.[90] Fetal serum concentrations were found to reach maternal serum concentrations after repeated dosages of naproxen 250mg every 8 hours. First trimester exposure to naproxen in 1448 pregnant patients studied[40] has not been found to increase fetal malformation rate. Healthy children were born to 23 women treated for arthritis with an average dosage of naproxen 560 mg/day during the first and second trimester of pregnancy.[6] Antenatal exposure to naproxen 750mg to 1g, and in 1 patient to 5g within the 48 hours before delivery caused primary pulmonary hypertension, increased blood clotting time, hyperbilirubinaemia and impaired renal function in 4 preterm infants.[91,92] One infant died 4 days after birth and was found to have a short constricted ductus arteriosus.

4.6 Ibuprofen

Data from the Michigan Medicaid Surveillance Study, including 3178 first trimester exposures to ibuprofen, indicated no teratogenicity of the drug.[40] Ibuprofen, 1200 to 2400 mg/day, has been used as a tocolytic agent in 115 human pregnancies.[6,93] Mild constriction of the ductus arteriosus was found in 4 of 61 fetuses exposed to ibuprofen, but resolved after discontinuation of the drug.[94] The same study did not detect oligohydramnios by ultrasonography, whereas 2 other reports found a decrease in amniotic fluid following tocolytic therapy with 1200 to 2400 mg/day.[75,95] Amniotic fluid volume normalised after discontinuation of the drug.

4.7 Ketoprofen

No increase in the fetal malformation rate has been observed after first trimester exposure to ketoprofen in 112 pregnancies.[40] Daily doses of ketoprofen 200 to 300mg administered for 3 to 8 days to prevent preterm labour in 270 pregnancies did not produce maternal or fetal adverse effects.[96-98] Several case reports and small series have described toxicity due to antenatal exposure to ketoprofen. Of 48 prematurely delivered infants, 20 had renal insufficiency, 6 had pulmonary hypertension, and 5 infants died.[79,98-100] A selective accumulation of the pharmacologically active enantiomer of ketoprofen was demonstrated in 6 premature neonates with renal insufficiency. They were the children of mothers treated with ketoprofen 100 to 200 mg/day for preterm labour.[101]

4.8 Diclofenac

Studies in pregnant mice and rats have shown that diclofenac and its metabolites cross the placenta.[102] Antenatal exposure of mature rat fetuses to diclofenac caused constriction of the ductus arteriosus in a dose-dependent fashion.[43] Administration of diclofenac during the last trimester of pregnancy caused pulmonary hypertension in 1 patient.[103] In another study, 9 patients with premature labour were treated with diclofenac 75 to 150 mg/day for 3 to 45 days without any fetal or neonatal adverse effects observed.[104]

4.9 Piroxicam

First trimester exposure to piroxicam in 161 pregnancies did not increase the fetal malformation rate in the Michigan Medicaid Surveillance Study.[40] No harmful effect on mother or neonate was reported in 6 pregnancies treated with dosages of piroxicam 20 mg/day during the first or second trimester.[6] One case report described renal maldevelopment and oligohydramnios in an infant exposed to piroxicam around mid-gestation.[105] However, no details on dose or duration of treatment were provided.

In conclusion, the occurrence of adverse events related to gestational use of NSAIDs in humans has been investigated in depth only for aspirin and indomethacin. Experience is limited for most other NSAIDs. However, the NSAIDs discussed in this review have shared at least 1 of the adverse fetal effects described for indomethacin. It has to be suspected that all NSAIDs which are inhibitors of prostaglandin synthesis can cause adverse effects during pregnancy. The dose, duration and period of gestation are important determinants of these effects.

Constriction of the fetal ductus arteriosus which may result in primary pulmonary hypertension in the newborn is a risk. Maternal consumption of NSAIDs and aspirin has been shown to increase by a factor of 5 to 6 the risk of pulmonary hypertension.[106] Most studies of NSAIDs used as tocolytics have indicated that the fetus is relatively resistant to premature closure of the ductus before week 32 of gestation. It is not clear if this also applies for NSAID effects on fetal renal function. High dose aspirin and indomethacin, which have the most extensive record of adverse effects, are less frequently used to treat rheumatic disorders than the newer NSAIDs,[107] and should truly be avoided during pregnancy. However, it is unknown whether more selective COX 2 inhibitors such as salicylate, meloxicam and nimesulide have less fetal effects. A case report of a woman treated with nimesulide 200 mg/day from gestational week 16 to 36 showed no adverse effect on the fetal ductus arteriosus.[108]

Many of the serious adverse effects reported in newborns after intrauterine exposure to NSAIDs have occurred in infants delivered preterm and exposed to the drug near delivery as a result of attempted tocolysis. It is important to bear in mind that prematurity and low birthweight are associated with complications such as intracranial haemorrhage,[42] respiratory distress syndrome,[109] and necrotising colitis[110] whether or not the infant has been exposed to a NSAIDs.

Complications such as persistent fetal circulation, impaired renal function and haemorrhage in neonates, as well as prolongation of gestation and labour and maternal bleeding, can be prevented by discontinuation of the NSAIDs 6 to 8 weeks prior to delivery. One study has found this a safe approach in pregnant, rheumatic patients in need of NSAIDs treatment.[6]

5. Corticosteroids

Corticosteroids are frequently used during pregnancy. The dose, frequency of administration and route of administration of corticosteroids varies with the severity and type of clinical manifestation of the particular maternal disease to be treated. Transplacental passage varies between different corticosteroids but is limited for prednisone and prednisolone which are most frequently used during pregnancy.[111] High doses of corticosteroids consistently cause cleft palate in rodents and rabbits.[112-114] If mice are only exposed to cortico-

steroids during the latter part of gestation, they have reduced birthweight, but not cleft palate.[115]

5.1 Human Studies

There are many reports describing successful pregnancies among women exposed to corticosteroids before and throughout pregnancy.[116] In early studies, there were isolated reports of 2 infants with cleft palate and 1 infant with adrenal cortical failure out of 260 exposed pregnancies.[117-119] In more recent studies, cleft palate defects were not noted in human fetuses exposed to corticosteroids *in utero*.[120] Clinical observations have suggested an increased incidence of low birthweight among offspring exposed to corticosteroids *in utero*,[10,16] but concurrent medications and the underlying maternal disease may also contribute to intrauterine growth retardation. Maternal use of corticosteroids may also be associated with preterm delivery.[121] Cataracts are observed in adults receiving corticosteroids and congenital subcapsular cataracts have been noted in an infant exposed to prednisone throughout pregnancy.[122]

Lymphopenia and reduced immunoglobulin concentrations are rarely observed in infants exposed to corticosteroids and azathioprine.[123] Immunosuppression lasting 15 weeks after birth was noted in 1 infant exposed to high doses of prednisone and azathioprine *in utero*.[124] Perinatal infections, fortunately, are not a frequent complication in infants exposed to corticosteroids *in utero*.[125]

In conclusion, some corticosteroids such as prednisone and prednisolone, do not readily cross the placenta. At low dosages they can be safely used as anti-inflammatory agents in arthritis or as immunosuppressive drugs at high doses in pregnant patients with severe systemic disease. Other corticosteroids, e.g. dexamethasone and betamethasone, cross the placenta and are reserved for special fetal indications. One example of a fetal indication for corticosteroid use is to hasten fetal lung maturity for imminent delivery of a preterm infant.

The available data support the use of corticosteroids in pregnant women with rheumatic diseases.[126,127] However, maternal complications related to corticosteroid use may occur, and it is necessary to monitor for the following toxicities associated with corticosteroids: (i) cataracts; (ii) infection; (iii) avascular necrosis of bone; (iv) osteopenia; (v) glucose intolerance; (vi) hypertension; (vii) premature rupture of membranes; and, (viii) pre-eclampsia. Calcium and vitamin D supplementation should be considered in these patients. In addition, treatment for hyperglycaemia and hypertension is indicated.

6. Disease-Modifying Antirheumatic Drugs

6.1 Gold Compounds

Sodium aurothiomalate, aurothioglucose and auranofin (oral gold) are used for the treatment of rheumatoid arthritis, psoriatic arthritis and juvenile chronic arthritis. The transplacental passage of gold has been studied in rats and rabbits, and congenital anomalies have been detected in rat fetuses.[128,129] Gold has been detected in the placenta, the liver and the kidney of human fetuses exposed to gold *in utero*.[130,131] Cord serum concentrations equalled maternal serum concentrations in a neonate born to a mother treated with sodium aurothiomalate 100mg monthly throughout pregnancy.[132]

Uneventful pregnancies concluding in the delivery of healthy children have been reported in women receiving gold therapy.[133] Except for 2 children with hip abnormalities, no congenital malformations were observed in 102 children born to patients who had terminated gold therapy in early to mid-pregnancy, or in the children of 26 patients treated with gold throughout pregnancy.[134] One case of multiple fetal malformations in a mother who received sodium aurothiomalate 20 mg/week during the first 20 weeks of pregnancy has been reported, but a relation to gold therapy has been disputed.[135] To date, little is known about the effect of auranofin on the human fetus. Six women who received auranofin while pregnant delivered healthy children.[136]

In conclusion, information on the safety of gold during pregnancy is insufficient.[137] Most rheumatologists would hesitate to start injectable gold during pregnancy whereas continuation of therapy, at least in patients on monthly injections, is advocated by some. Gibbons[138] has suggested a restarting of sodium aurothiomalate in late pregnancy in order to suppress the common postpartum flare of rheumatoid arthritis, but documentation on the efficacy of this regimen is lacking.[138] Because of the lack of human data, statements on peroral gold cannot be made. Auranofin has immunosuppressive-like properties and contains triethylphosphine.[139] It seems wise to stop therapy when pregnancy is diagnosed and not to start auranofin during gestation.

6.2 Antimalarial Drugs

Antimalarial drugs containing 4-aminoquinoline compounds are used to treat rheumatoid arthritis, SLE (particularly when associated with antiphospholipid antibodies), and discoid SLE. Chloroquine, the drug of choice for the prophylaxis of sensitive malaria species, has been studied for its safety during pregnancy. Chloroquine crosses the placenta and accumulates preferentially in melanin-containing structures in the fetal uveal tract and inner ear.[140,141] Abnormalities of the eye have been detected in rat fetuses exposed to chloroquine antenatally.[142]

A cohort study comparing 169 pregnancies exposed to chloroquine 300 mg/week throughout gestation for malaria prophylaxis, to 450 pregnancies not exposed found no difference in rates of congenital malformations between groups.[143] In the rheumatic literature, 93 pregnancies exposed to chloroquine or hydroxychloroquine during the first trimester were located. No congenital malformation were reported in children of 37 pregnant patients treated with chloroquine 250 mg/day and 56 pregnant patients treated with hydroxychloroquine 200 to 400 mg/day.[144-148] No congenital malformations were reported in children exposed antenatally to standard doses of antimalarials.[149,150] Negative experiences in 2 reports were related to women treated with higher than the recommended doses of chloroquine throughout pregnancy. Malformations of the inner ear and other abnormalities were reported after intrauterine exposure to chloroquine 500 mg/day in 3 siblings born of a mother with SLE.[151] In another report, a woman had taken chloroquine 200 to 300 mg/day over 3 years and throughout 2 pregnancies for malaria prophylaxis. Her 2 children had retinal degeneration.[152]

In conclusion, although antimalarials have been used safely in pregnant patients without producing congenital abnormalities,[153] their long elimination half-life and their tendency to accumulate in certain tissues including the retina, restricts their gestational use. Documentation of the safety of chloroquine and hydroxychloroquine throughout pregnancy is currently limited. Since discontinuation of antimalarials in pregnant SLE patients may precipitate a flare with harmful consequences for mother and child,[154] it seems reasonable to continue antimalarials in SLE pregnancies.[146] Hydroxychloroquine in dosages of ≤6.5 mg/kg/bodyweight has not been associated with fetal toxicity and seems preferable to chloroquine.[150]

6.3 Penicillamine

Penicillamine is used as a second line drug in the treatment of several inflammatory rheumatic diseases including rheumatoid arthritis, juvenile chronic arthritis, psoriatic arthritis and scleroderma. Experience from its use in human pregnancy relates mainly to treatment of pregnant women with Wilson's disease, cystinuria and rheumatoid arthritis.[155] In rats, hamsters and mice, high doses of penicillamine given during gestation caused a variety of malformations including loose skin.[156]

Transplacental passage of penicillamine was documented by the detection of the drug in the urine of a neonate whose mother had been treated for cystinuria with penicillamine 1.2 mg/day throughout pregnancy.[157] Reports on about 100 pregnancies treated with penicillamine for Wilson's disease, cystinuria, or rheumatoid arthritis

for 1 to 9 months and in dosages varying from 0.5 to 2.25 g/day have been located.[40,155,158] Five infants with congenital collagen defects after antenatal exposure to penicillamine have been reported.[159-163] Two of the neonates had generalised abnormalities of connective tissue and died of sepsis.[159,160] In other infants the cutis laxa observed at birth was transient.[162,163] By contrast, no abnormalities were detected in 51 children born of 28 mothers with Wilson's disease[164-166] and 7 with cystinuria treated with penicillamine 0.5 to 2 g/day.[40,167] In a further report on 19 pregnant rheumatoid arthritis patients treated with penicillamine, the only congenital abnormality observed was a ventricular septum defect.[168]

In conclusion, the use of penicillamine is crucial for a successful outcome of pregnancy in patients with Wilson's disease. In these patients, the benefit of continued treatment seems to outweigh the small risk of teratogenicity associated with gestational use of penicillamine. According to the literature about 5% of children exposed to penicillamine antenatally will have a congenital collagen defect. This risk may not be acceptable to a woman with inflammatory rheumatic disease where the benefit of continued treatment is less obvious and other treatment modalities exist.[137] As a consequence, penicillamine should be stopped before a patient with rheumatic disease tries to conceive, or it should be withdrawn immediately when pregnancy is diagnosed.[169]

6.4 Sulfasalazine

Reports regarding the use of sulfasalazine during and after pregnancy originate exclusively from experience in patients with inflammatory bowel disease. Animal studies in fetal rats and rabbits exposed to doses of sulfasalazine up to 6 times the human dose have not shown an increase in congenital anomalies.[170]

Sulfasalazine and its principle metabolites cross the placenta[171] and achieve fetal blood concentrations close to maternal concentrations.[172] However, the bilirubin-displacing ability of sulfasalazine and its metabolites has been demonstrated to be small.[173]

More than 1300 pregnancies in patients with ulcerative colitis and nearly 800 patients with Crohn's disease treated either with sulfasalazine alone or in combination with corticosteroids at some time during pregnancy have been reported.[40] No increase in birth defects, pathological jaundice, or small for gestational age babies was detected. Two studies examining the effect of sulfasalazine and corticosteroids on fetal outcome in pregnant women with inflammatory bowel disease did not disclose an increase in adverse pregnancy outcome in the infants exposed antenatally to sulfasalazine and corticosteroids compared with infants not exposed.[174,175]

There have been isolated reports on children born with congenital malformations to mothers treated with sulfasalazine during pregnancy.[176,177] However, a causal relationship to the drug treatment was not established. A questionnaire-based study including 639 women and 472 men with inflammatory bowel disease found a significant correlation between congenital abnormalities and use of sulfasalazine both in male and female patients.[178] The study gave no details regarding sulfasalazine treatment and stage of pregnancy, cumulative dose or additional medications used during gestation. One case report described reversible, profound neutropenia in a premature infant whose mother was treated with sulfasalazine 3 g/day for Crohn's disease during pregnancy.[179]

In conclusion, previous reviews have regarded the gestational use of sulfasalazine as acceptable.[180] There is a theoretical risk of kernicterus when sulfasalazine is taken near term; however, severe neonatal jaundice has not been reported following maternal treatment.[40] The bilirubin-displacing ability of sulfasalazine and its metabolites has been demonstrated to be small.[181] Furthermore, bilirubin binds to different serum protein receptors than sulfasalazine.[181] Thus, sulfasalazine may be continued throughout pregnancy when strictly indicated, preferable at a dosage <3 g/day. There is no evidence supported by the literature to

discontinue the drug near term. Sulfasalazine may induce folate deficiency and folic acid supplementation is therefore recommended in pregnant patients treated with the drug.[182]

6.5 Cyclosporin

Cyclosporin is used primarily as an immunosuppressive drug to prevent rejection of organ transplantation.[183] The efficacy of cyclosporin has been demonstrated in patients with rheumatoid arthritis[184,185] and SLE[186] whose conditions have not responded to conventional therapy. When cyclosporin was administered at 10 mg/kg/day to pregnant rats throughout gestation, the drug was not toxic to the exposed fetuses. However, it was embryotoxic at dosages of 25 to 100 mg/kg/day.[187]

Cyclosporin crosses the placenta, but the concentration of drug in the newborn falls rapidly to zero within a few days.[188-190] Renal and liver function were normal in 166 exposed infants in 159 women, and the majority of these mothers were treated to prevent allograft rejection with both cyclosporin and corticosteroids.[191] Growth retardation and prematurity developed in 40% of the neonates and minor laboratory abnormalities including thrombocytopenia, leucopenia, hypoglycaemia and mild disseminated intravascular coagulation, were observed in several babies. Other series of transplant recipients have also noted lower birthweight,[192] increased risk of spontaneous abortion,[193] and preterm labour.[194] One neonate exposed to cyclosporin *in utero* died at age 3 days. On postmortem examination, the corpus callosum was absent. Additional problems noted in individual neonates exposed to cyclosporin *in utero* were a hydrocele, bilateral cataracts, mild hypoparathyroidism and hypoplasia of the bones, muscles and subcutaneous tissue of the right leg and foot.[40,195,196] Three patients with SLE nephritis treated with cyclosporin during pregnancy had no significant disease flares, no drug toxicity and their pregnancies resulted in live births.[197,198]

There is limited experience with long term follow-up of children exposed to cyclosporin *in utero*. In several studies, physical and mental development were normal in 10 children followed from 1 to 13 months.[190,199] In 1 follow-up study (mean 39 months), 22 infants had normal renal function after exposure to cyclosporin *in utero*.[200]

In conclusion, cyclosporin is not an animal teratogen and the few available human pregnancies indicate that it is unlikely to be a human teratogen. No consistent pattern of congenital defects have been seen in the few newborns with anomalies. Use of cyclosporin may be an alternative to other therapy in the setting of severe disease in the pregnant patient with rheumatic disease. The long term effects of cyclosporin exposure *in utero* are unknown.

7. Colchicine

Colchicine is used for the treatment of gout and familial Mediterranean fever. Colchicine has been found to be teratogenic in mice and rabbits.[201] The transplacental passage of colchicine has been described.[202] Several case reports and a retrospective series of 36 pregnancies described the use of colchicine during the first trimester.[203] No congenital malformations occurred in the newborns. A large study of 225 pregnancies in patients with familial Mediterranean fever included 91 patients treated with colchicine throughout pregnancy, 40 patients treated during the first trimester and 94 untreated control participants.[204] There was no increase in the rate of congenital malformations, and no growth or developmental disturbances were noted in the children who were followed up for more than 10 years. No chromosomal aberrations were found in the offspring of 11 patients treated for familial Mediterranean fever during pregnancy.[205]

8. Cytotoxic Drugs

8.1 Azathioprine and Mercaptopurine

Azathioprine is an immunosuppressant drug that is usually used in conjunction with other immunosuppressant drugs to treat rheumatic diseases and vasculitis or to prevent organ rejection. Aza-

thioprine has caused skeletal defects and impaired fetal growth in rodents[206,207] and multiple anomalies in rabbit fetuses exposed during gestation.[208]

Azathioprine readily crosses the placenta and, as expected, only trace amounts of its active metabolite, mercaptopurine, have been found in fetal blood.[209] The fetal liver lacks the enzyme, inosinate pyrophosphorylase, which converts azathioprine to its active metabolites.

Azathioprine has not been associated with congenital defects in humans; however, sporadic anomalies have been reported. No definitive association between the drug and the observed anomalies has been firmly established. Azathioprine has been used extensively during pregnancy in women who require this drug to maintain a renal allograft.[210,211] No predominant or frequent birth defects were found. Azathioprine has also been used to treat active disease or maintain remissions in patients with SLE.[212,213]

Forty percent of patients with renal transplants requiring treatment during pregnancy with azathioprine and corticosteroids were noted to have infants with intrauterine growth retardation even though the patients had normal renal function during the pregnancy.[214,215] In contrast, the authors of the latter study were unable to assess the individual contribution of each drug, or of the mother's underlying disease, to the observed decrease in fetal growth. Monitoring for adequate fetal growth and the status of maternal disease in these high risk mothers is strongly recommended.

In conclusion, patients with renal transplants or SLE who were treated during pregnancy with azathioprine and corticosteroids have had successful pregnancies.[216] Although increases in the rates of birth defects, miscarriages and stillbirths have not been established in association with this drug, the number of reported patients with adequate follow-up may not be sufficient to detect a small increase in these rates or to detect late-occurring abnormalities. Neonatal immunosuppression[217] and cytomegalovirus infection[218] have been noted in exposed infants.

8.2 Chlorambucil

Chlorambucil is an alkylating agent that is most frequently used as an antineoplastic agent. Chlorambucil has been used to treat patients with rheumatoid arthritis, juvenile chronic arthritis, dermatomyositis, scleroderma, SLE and Behçet's syndrome. Chlorambucil is mutagenic and carcinogenic.[219-221] Agenesis of the left kidney and ureter has been noted in rats exposed to chlorambucil *in utero*.[222] In addition, tail and limb abnormalities have been observed in mice and rats exposed to this drug.[223]

The use of chlorambucil during pregnancy has resulted in both healthy and deformed infants.[224-227] Two reports have documented unilateral agenesis of the left kidney and ureter in male fetuses after first trimester exposure to the drug.[225,226] A full term infant exposed to chlorambucil during the tenth week of gestation died at 3 days of age of multiple cardiovascular anomalies.[228] Using the available data from 6 exposed fetuses, the estimated risk of congenital malformations during exposure to chlorambucil *in utero* was 33% (95% confidence interval 6.8 to 96.4).[227] A recently reported retrospective study of 57 juvenile arthritis patients with reactive amyloidosis who were treated with chlorambucil showed that women treated with chlorambucil previously can have successful pregnancies.[229]

In conclusion, chlorambucil exposure during the first trimester may cause renal anomalies in the fetus. The teratogenic effect of the drug is enhanced by caffeine.[137] Alternative immunosuppressive drugs are recommended if the patient requires treatment during pregnancy.

8.3 Cyclophosphamide

Cyclophosphamide is an alkylating agent and is used in the rheumatic diseases for severe cases of vasculitis, SLE, juvenile chronic arthritis and rheumatoid arthritis. Cyclophosphamide is administered orally or intravenously. This agent produces birth defects in all animal species tested. Some teratogenic effects consistently observed in ani-

mals are facial clefts and limb reduction defects,[230-232] and exposures later in gestation induced craniofacial dysmorphisms.[233]

Both healthy and malformed newborns have been reported following the use of cyclophosphamide during pregnancy.[234,235] It is important to note that the observations on the risk of malformations in infants exposed to cyclophosphamide *in utero* are in mothers with cancer who were also treated with additional therapies such as radiation or other antineoplastic drugs. Five women with SLE received cyclophosphamide during 6 pregnancies. In the first instance, the mother received 20 mg/day of prednisone throughout her pregnancy and 2 intravenous doses of 200mg each between 15 and 46 days' gestation. Multiple congenital anomalies were reported in this infant.[235] The outcome of the other 5 pregnancies included 2 miscarriages, 1 elective termination of pregnancy, 1 infant with shortness of the arms and legs, and 1 healthy child.[236,237]

The congenital defects observed in the exposed infants of mothers with cancer or SLE include facial anomalies (flattened nasal bridge, palate defects, dysmorphic facies, bilateral blepharophimosis with left microphthalmos, abnormally shaped low-set ears and borderline microcephaly), skin and musculoskeletal anomalies (skin tag, 4 toes on each foot, hypoplastic middle phalanx on the fifth finger, haemangioma, bilaterally absent thumbs, dystrophic nails and hypotonia), visceral organ anomalies (imperforate anus, rectovaginal fistula and single coronary artery), growth retardation and possible developmental delay at 10 months of age.[227,238-243] The risk of congenital malformations from cyclophosphamide exposure has been estimated at between 16 to 22%.[227,236]

Fetal exposure to cyclophosphamide in the second and third trimesters is not as devastating as exposure during the first trimester, but pancytopenia has been observed in those neonates exposed during the latter part of gestation.[236] Treatment with a combination of cyclophosphamide and corticosteroids in the second and third trimester in patients with vasculitis[244,245] and Henoch-Schönlein purpura resulted in healthy infants without any haematological abnormalities.[246] The long term effects of *in utero* exposure to cyclophosphamide are unknown. There is 1 case report of a male twin who developed thyroid papillary cancer at age 11 and neuroblastoma at age 14. His twin did not develop cancer.[247]

In conclusion, cyclophosphamide is contraindicated during pregnancy; however, its use may be considered in the latter stages of pregnancy if the mother has a life-threatening illness.

8.4 Methotrexate

Methotrexate is a folic acid antagonist which impairs dihydrofolate reductase and interferes with production of purines. Methotrexate has been used for psoriasis, rheumatoid arthritis, and in some patients with SLE, juvenile chronic arthritis, polymyositis and vasculitis. Folic acid 1 mg/day is recommended to avoid folate depletion. Intrauterine exposure to methotrexate is associated with birth defects in chicks,[248] mice[249] and rats,[250] but not in rabbits[251] or monkeys.[252] The congenital anomalies observed in animals exposed to methotrexate *in utero* often involve the CNS and the palate.[253]

Experience with methotrexate in human pregnancy has been derived from patients treated for cancer or when methotrexate was used to terminate a pregnancy. Toxicity to fetal tissues has been demonstrated when this drug has been used to terminate ectopic pregnancies.[254] Three infants exposed during the first trimester to methotrexate *in utero* had multiple cranial anomalies.[40] In 7 patients, methotrexate was given during late pregnancy; 6 healthy children were born and 1 child had pancytopenia. There is a small case series of 10 pregnancies in 8 patients with rheumatoid arthritis who were receiving low dose methotrexate during the first trimester of pregnancy.[255] Two elective and 3 spontaneous abortions occurred. Five full term children were born without malformations and no long term problems were identified (mean follow-up 11.5 years). A recent report described an infant with multiple congenital abnor-

malities who was exposed to approximately 100mg of methotrexate in total during the first 8 weeks of gestation in a mother with juvenile chronic arthritis.[256] The abnormalities were consistent with those reported as part of the 'aminopterin syndrome'. Another report described a healthy infant born after first trimester exposure to weekly low doses of methotrexate in a mother with psoriatic arthritis.[257]

No increased risk of congenital malformations have been noted in infants of women treated with methotrexate prior to conception[258] with the exception of a rare pulmonary disorder, desquamating fibrosing alveolitis, which occurred in 2 offspring of 1 mother.[259] In the first infant, the mother discontinued methotrexate 2 months prior to conception and the second infant born 3 years later also had the same disorder. However, a third child born 4 years after the drug was stopped developed normally. The relationship between this congenital anomaly in 2 of 3 siblings and the maternal use of methotrexate is unclear. Four healthy pregnancies (including 1 set of twins) in 3 other women have been reported following recent termination of methotrexate treatment.[257,260-262]

Severe myelosuppression has been reported in 2 infants after methotrexate and other neoplastic agents were used during pregnancy.[40] Low birthweight may also be associated with the drug, but the contribution of concurrent medications and the underlying maternal disease may contribute to this problem.

In conclusion, methotrexate is contraindicated during pregnancy. There is a risk of congenital malformations even when low dose methotrexate is used in the treatment of rheumatic diseases. Pregnancy should be avoided if either partner is receiving the drug.[137] Male patients should wait a minimum of 3 months and female patients at least 1 ovulatory cycle after discontinuation of therapy before attempting conception.[263] Folic acid supplementation must be given during the preconception period because folate deficiency has been associated with neural tube defects.[264] Folic acid supplementation should continue until after the pregnancy is completed.

9. Conclusions

None of the drugs surveyed can be regarded as absolutely safe during pregnancy. Even a drug with no recorded adverse effects during pregnancy does not mean that that drug will be safe for all fetuses. Adverse drug effects during pregnancy may occur only in a few of the exposed individuals and depend on largely unknown fetal and maternal factors. To detect rare adverse effects would require large prospective, controlled studies which are difficult to perform in pregnant patients, particularly in those with rare disorders.

The decision to treat must involve an assessment of the known risks of the underlying disease on maternal and fetal outcome versus the risks and benefits of the drug in question. In conditions with life-threatening complications such as serious cases of SLE, antiphospholipid syndrome, scleroderma, polymyositis and dermatomyositis, the use of medication in pregnant patients can hardly be disputed. The benefit of drug treatment has also been shown by improving pregnancy outcome in diseases such as SLE, antiphospholipid syndrome and familial Mediterranean fever. In more benign disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile chronic arthritis, only drugs with a favourable history of use in pregnant patients should be used when necessary. In any case, the risks and benefits of medication should be explained to the patient and she should be actively involved in therapeutic decisions.

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References

1. Østensen M, Husby G. Ankylosing spondylitis and pregnancy. Rheum Dis Clin North Am 1989; 15: 241-54
2. Petri M. Pregnancy and rheumatic disease. Rheum Dis Clin North Am 1997; 23: 1-218

3. Nelson JL, Østensen M. Pregnancy and rheumatoid arthritis. Rheum Dis Clin North Am 1997; 23: 195-212
4. Griffin J. Rheumatoid arthritis: biological effects and management. In: Scott JS, Bird HA, editors. Pregnancy, autoimmunity and connective tissue disorders. Oxford: Oxford University Press, 1990: 140-62
5. Østensen M. Pregnancy in patients with a history of juvenile rheumatoid arthritis. Arthritis Rheum 1991; 34: 881-7
6. Østensen M, Østensen H. Safety of nonsteroidal antiinflammatory drugs in pregnant patients with rheumatic disease. J Rheumatol 1996; 23: 1045-9
7. Østensen M, Østensen H. Ankylosing spondylitis – the female aspect. J Rheumatol 1998; 25: 120-4
8. Østensen M. Pregnancy in psoriatic arthritis. Scand J Rheumatol 1988; 17: 67-70
9. Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. Arthritis Rheum 1991; 34: 1538-45
10. Wong KL, Chan FY, Lee CP. Outcome of pregnancy in patients with systemic lupus erythematosus: results of a multidisciplinary approach. J Rheumatol 1986; 13: 732-9
11. Ruiz-Irastorza G, Lima F, Alves J, et al. Increased rate of lupus flare during pregnancy and the puerperium. Br J Rheumatol 1996; 35: 133-5
12. Mintz G, Nix J, Gutierrez G, et al. Prospective study of pregnancy in systemic lupus erythematosus: results of a multidisciplinary approach. J Rheumatol 1986; 13: 732-9
13. Lockshin MD, Reinitz E, Druzin ML, et al. Lupus pregnancy: case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. Am J Med 1984; 77: 893-8
14. Urowitz MB, Gladman DD. Farewell VT, et al. Lupus and pregnancy studies. Arthritis Rheum 1993; 36: 1392-7
15. Petri M, Allbritton J. Fetal outcome of lupus pregnancy: a retrospective case-control study of the Hopkins Lupus Cohort. J Rheumatol 1993; 20: 650-6
16. Julkunen T, Jouhikainen T, Kaaja R, et al. Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. Lupus 1993; 2: 125-31
17. Ramsey-Goldman R, Kutzer JE, Kuller LH, et al. Pregnancy outcome and anti-cardiolipin antibody in women with systemic lupus erythematosus. Am J Epidemiol 1993; 138: 1057-69
18. Lee LA. Neonatal lupus erythematosus. J Invest Dermatol 1993; 100 Suppl.: 9S-13S
19. Steen VD. Scleroderma and pregnancy. Rheum Dis Clin North Am 1997; 23: 133-47
20. Steen VD, Conte C, Day N, et al. Pregnancy in women with systemic sclerosis. Arthritis Rheum 1989; 32: 151-7
21. Wilson AGM, Kirby JDT. Successful pregnancy in a woman with systemic sclerosis while taking nifedipine. Ann Rheum Dis 1990; 49: 51-2
22. Rosenzweig BA, Rotmensch S, Binette SP, et al. Primary idiopathic polymyositis and dermatomyositis complicating pregnancy: diagnosis and management. Obstet Gynecol Surv 1989; 44: 162-70
23. Friedman SA, Bernstein MS, Kitzmiller JL. Pregnancy complicated by collagen vascular disease. Crit Care Obstet 1991; 18: 213-36
24. Houck W, Melnyk C, Gast MJ. Polymyositis in pregnancy. J Reprod Med 1987; 32: 208-10
25. Ohno T, Imai A, Tamaya T. Successful outcomes of pregnancy complicated with dermatomyositis. Gynecol Obstet Invest 1992; 33: 187-9
26. Satoh M, Ajmani AK, Hirakata M, et al. Onset of polymyositis with autoantibodies to threonyl-t RNA synthetase during pregnancy. J Rheumatol 1994; 21: 1564-6
27. Pauzner R, Mayan H, Hershko E, et al. Exacerbation of Wegener's granulomatosis during pregnancy: report of a case with tracheal stenosis and literature review. J Rheumatol 1994; 21: 1153-6
28. Owen J, Hauth JC. Polyarteritis nodosa in pregnancy: a case report and brief literature review. Am J Obstet Gynecol 1989; 160: 606-7
29. Ogasawara M, Kajiura S, Inagaki H, et al. Successful pregnancy in a Churg-Strauss Syndrome patient with a history of intrauterine fetal death. Int Arch Allergy Immunol 1994; 108: 200-2
30. Hamza M, Elleuch M, Zribi A. Behçet's disease and pregnancy. Ann Rheum Dis 1988; 47: 350-2
31. Marsal S, Falga C, Simeon CP, et al. Behçet's disease and pregnancy relationship study. Br J Rheumatol 1997; 36: 234-8
32. Kelsall JT, O'Hanlon DP. Gout during pregnancy. J Rheumatol 1994; 21: 1365-6
33. Regan M, Clarke AK, Doherty M. Pseudogout provoked by pregnancy. Br J Rheumatol 1993; 32: 245-7
34. Levy G, Hayton WL. Pharmacokinetic aspects of placental drug transfer. In: Borens L, editor. Fetal pharmacology. New York: Raven Press, 1973: 29-39
35. Bourget P, Roulot C, Fernandez H. Models for placental transfer studies of drugs. Clin Pharmacokinet 1995; 28: 161-80
36. Bassily M, Ghabrial H, Smallwood RA, et al. Determinants of placental drug transfer: studies in the isolated perfused human placenta. J Pharm Sci 1995; 84: 1054-60
37. Bogaert MC, Thiery M. Pharmacokinetics and pregnancy. Eur J Obstet Gynecol Reprod Biol 1983; 16: 229-35
38. Redmond GP. Physiological changes during pregnancy and their implications for pharmacological treatment. Clin Invest Med 1985; 8: 317-22
39. Frölich JC. A classification of NSAIDs according to the relative inhibition of cyclooxygenase isoenzymes. Trends Pharm Sci 1997; 18: 30-4
40. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 4th ed. Baltimore: Williams and Wilkins, 1994
41. Schoenfeld A, Bar Y, Merlob P, et al. NSAIDs: maternal and fetal considerations. Am J Reprod Immunol 1992; 28: 141-7
42. Herz-Picciotto I, Hopenhayn-Rich C, Golub M, et al. The risks and benefits of taking aspirin during pregnancy. Epidemiol Rev 1990; 12: 108-48
43. Momma K, Takeuchi H. Constriction of the fetal ductus arteriosus by non-steroidal anti-inflammatory drugs. Prostaglandins 1983; 26: 631-43
44. Collins E, Turner G. Maternal effects of regular salicylate ingestion in pregnancy. Lancet 1975; 2: 335-7
45. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton (MA): Littleton Publishing Sciences Group, 1977: 286-95
46. Zierler S, Rothman KJ. Congenital heart disease in relation to maternal use of bendectin and other drugs in early pregnancy. N Engl J Med 1985; 313: 347-52
47. Werler MM, Mitchell AA, Shapiro S. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. N Engl J Med 1989; 321: 1639-42
48. Slone D, Heinonen OP, Kaufman DW, et al. Aspirin and congenital malformations. Lancet 1976; I: 1373-5
49. Lewis RB, Schulman JD. Influence of acetylsalicylic acid, an inhibitor of prostaglandin synthesis, on the duration of human gestation and labour. Lancet 1973; 2: 1159-61

50. Stuart MJ, Gross SJ, Elrad H, et al. Effects of acetylsalicylic-acid ingestion on maternal and neonatal hemostasis. N Engl J Med 1982; 307: 909-12
51. Rumack CM, Guggenheim MA, Rumack BH, et al. Neonatal intracranial hemorrhage and maternal use of aspirin. Obstet Gynecol 1981; 58 Suppl.: 52S-6S
52. Sibai BM, Mirro R, Chesney CM, et al. Low-dose aspirin in pregnancy. Obstet Gynecol 1989; 74: 551-7
53. Kaaja R, Julkunen H, Viinikka L, et al. Production of prostacyclin and thromboxane in lupus pregnancies: effect of small dose of aspirin. Obstet Gynecol 1993; 82: 327-31
54. Martin C, Varner MW, Branch DW, et al. Dose-related effects of low dose aspirin on hemostasis parameters and prostacyclin/thromboxane ratios in late pregnancy. Prostaglandins 1996; 51: 321-30
55. Writing Group of the Italian Study of Aspirin in Pregnancy. Low dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. Lancet 1993; 341: 396-400
56. Writing Group for the Collaborative Low-dose Aspirin Study in Pregnancy. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of preeclampsia among 9364 women. Lancet 1994; 343: 619-29
57. Fishman P, Falach-Vaknin E, Sredni B, et al. Aspirin–interleukin-3 interrelationships in patients with anti-phospholipid syndrome. Am J Reprod Immunol 1996; 35: 80-4
58. Leitich H, Egarter C, Husslein A, et al. A meta-analysis of low dose aspirin for the prevention of intrauterine growth retardation. Br J Obstet Gynaecol 1997; 104: 450-9
59. Parazzini F, Bortolus R, Chatenoud L, et al. Follow-up of children in the Italian study of aspirin in pregnancy [letter]. Lancet 1994; 343: 1235
60. Low-dose Aspirin Study in Pregnancy Collaboration Group. Low dose aspirin in pregnancy and early childhood development: follow-up of the collaborative low dose aspirin study in pregnancy. Br Obstet Gynecol 1995; 102: 861-8
61. Di Sessa TG, Moretti ML, Khoury A, et al. Cardiac function in fetuses and newborns exposed to low-dose aspirin during pregnancy. Am J Gynecol 1994; 171: 891-900
62. Parks BR, Jordan RL, Ranson JE, et al. Indomethacin: studies of absorption and placental transfer. Am J Obstet Gynecol 1977; 129: 464-5
63. Zuckerman H, Reiss U, Rubinstein I. Inhibition of human premature labor by indomethacin. Obstet Gynecol 1974; 44: 787-92
64. Niebyl JR, Black DA, White RD, et al. The inhibition of premature labor with indomethacin. Am J Obstet Gynecol 1980; 136: 1014-9
65. Dudley DKL, Hardie MJ. Fetal and neonatal effects of indomethacin used as a tocolytic agent. Am J Obstet Gynecol 1985; 151: 181-4
66. Marpeau L, Bouillie J, Barrat J, et al. Obstetrical advantages and perinatal risks of indomethacin: a report of 818 cases. Fetal Diagn Ther 1994; 9: 110-5
67. Tulzer G, Gudmundsson S, Tews G, et al. Incidence of indomethacin-induced fetal ductal constriction. J Matern Fetal Invest 1992; 1: 267-9
68. Veyver van den IB, Moise KJ, Ou CN, et al. The effect of gestational age and fetal indomethacin levels on the incidence of constriction of the fetal ductus arteriosus. Obstet Gynecol 1993; 82: 500-3
69. Moise KJ, Huhta JC, Sharif DS, et al. Indomethacin in the treatment of preterm labor; effects on the fetal ductus arteriosus. N Engl J Med 1988; 319: 327-31
70. Gerson A, Abbasi S, Johnson A, et al. Safety and efficacy of long-term tocolysis with indomethacin. Am J Perinatol 1990; 7: 71-4
71. Besinger RE, Niebyl JR, Keyes WG, et al. Randomized comparative trial of indomethacin and ritodrine for the long-term treatment of preterm labor. Am J Obstet Gynecol 1991; 164: 981-8
72. Morales WJ, Madhav H. Efficacy and safety of indomethacin compared with magnesium sulfate in the management of preterm labor: a randomized study. Am J Obstet Gynecol 1993; 169: 97-102
73. Csaba JF, Sulyok E. Ertl T. Clinical note: relationship of maternal treatment with indomethacin to persistence of fetal circulation [letter]. J Pediatr 1978; 92: 484
74. Kirshon B, Moise KJ, Wasserstrum N, et al. Influence of short-term indomethacin therapy on fetal urine output. Obstet Gynecol 1988; 72: 51-3
75. Hickok DE, Hollenbach KA, Reilley SF, et al. The association between decreased amniotic fluid and treatment with nonsteroidal anti-inflammatory agents for preterm labor. Am J Obstet Gynecol 1989; 160: 1525-31
76. Goldenberg RL, Davis RO, Baker RC. Indomethacin-induced oligohydramnios. Am J Obstet Gynecol 1989; 160: 1196-7
77. Wurtzel D. Prenatal administration of indomethacin as a tocolytic agent: effect on neonatal renal function. Obstet Gynecol 1990; 76: 689-92
78. Cantor B, Tyler T, Nelson RM, et al. Oligohydramnios and transient neonatal anuria. J Reprod Med 1980; 24: 220-3
79. Simeoni U, Messer J, Weisburd P, et al. Neonatal renal dysfunction and intrauterine exposure to prostaglandin synthesis inhibitors. Eur J Pediatr 1989; 148: 371-3
80. Van den Heijden BJ, Carlus C, Narcy F, et al. Persistent anuria, neonatal death, and renal microcystic lesions after prenatal exposure to indomethacin. Am J Obstet Gynecol 1994; 171: 617-23
81. Major CA, Lewis DF, Harding JA, et al. Tocolysis with indomethacin increases the incidence of necrotizing enterocolitis in the low-birth-weight neonate. Am J Obstet Gynecol 1994; 170: 102-6
82. Norton ME, Merril J, Cooper BAB, et al. Neonatal complications after the administration of indomethacin for preterm labor. N Engl J Med 1993; 329: 1602-7
83. Ment LR, Duncan CC, Ehrenkranz RA, et al. Randomized low-dose indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight neonates. J Pediatr 1988; 112: 948-55
84. Kramer WB, Saade G, Ou CN, et al. Placental transfer of sulindac and its active sulfide metabolite in humans. Am J Obstet Gynecol 1995; 172: 886-90
85. Carlan SJ, O'Brian WF, O'Leary TD, et al. Randomized comparative trial of indomethacin and sulindac for the treatment of refractory preterm labor. Obstet Gynecol 1992; 79: 223-8
86. Räsanen J, Jouppila P. Fetal cardiac function and ductus arteriosus during indomethacin and sulindac therapy for threatened preterm labor: a randomized study. Am J Obstet Gynecol 1995; 173: 20-5
87. Carlan SJ, O'Brian WF, Jones MH, et al. Outpatient oral sulindac to prevent recurrence of preterm labor. Obstet Gynecol 1995; 85: 769-74
88. Peek MJ, McCarthy A, Kyle P, et al. Medical amnioreduction with sulindac to reduce cord complications in monoamniotic twins. Am J Obstet Gynecol 1997; 176: 334-6

89. Ng PC, Fung H, Yeung CK. Localised ileal perforation associated with antenatal sulindac and dexamethasone treatment. Pediatr Surg Int 1995; 10: 557-8
90. Wilkinson AR. Naproxen levels in preterm infants after maternal treatment. Lancet 1980; II: 591-2
91. Wilkinson AR, Aynsley-Green A, Mitchell MD. Persistent pulmonary hypertension and abnormal prostaglandin levels in preterm infants after maternal treatment with naproxen. Arch Dis Child 1979; 54: 942-5
92. Alun-Jones E, Williams J. Hyponatremia and fluid retention in a neonate associated with maternal naproxen overdose. Clin Toxicol 1986; 24: 257-60
93. Barry WS, Meinziger MM, Howse CR. Ibuprofen overdose an exposure *in utero*: results from a postmarketing voluntary reporting system. Am J Med 1984; 77 (1A): 35-9
94. Hennessy MD, Livingston EC, Papagianos J, et al. The incidence of ductal constriction and oligohydramnios during tocolytic therapy with ibuprofen [abstract]. Am J Obstet Gynecol 1992; 166: 324
95. Wiggins DA, Elliott JP. Oligohydramnios in each sac of a triplet gestation caused by Motrin – fulfilling Kock's postulates. Am J Obstet Gynecol 1990; 162: 460-1
96. Tramontana S, Allocca G. Caserta R, et al. The use of ketoprofen in threatened premature labor [letter; in Italian]. Minerva Gynecol 1979; 4: 291
97. Dubecq JP, Gonnet JM, Horovitz J, et al. Prevention of threatened premature delivery by ritodrine and ketoprofen association [in French]. Proceedings of the 10th Journee de Medicine perinatale, Deauville 1980; 383-5
98. Llanas B, Cavert MH, Apere H, et al. Les effets secondaires du ketoprofene apres exposition intra-uterine: interet du dosage plasmatique. Arch Pediatr 1996; 3: 248-53
99. Netter JC, Choulot JJ, Dagues-Bie M, et al. Oligohydramnios and persistent pulmonary arterial hypertension after use of ketoprofen during pregnancy. Sem Hop 1990; 66: 1953-4
100. Gouyon JB, Petion AM, Sandra D, et al. Renal insufficiency in a preterm infant after intrauterine exposure to ketoprofen. Arch Fr Pediatr 1991; 48: 347-8
101. Labat L, Llanas B, Dermotes-Mainard F, et al. Accumulation of S-Ketoprofen in neonates after maternal administration of the racemate [abstract]. Fundam Clin Pharmacol 1995; 9: 94
102. Sioufi A, Stierlin H, Schweizer A, et al. Recent findings concerning clinically relevant pharmacokinetics of diclofenac sodium. In: Kass E, editor. Voltarin – new findings. Vienna: Hans Huber, 1982: 19-30
103. Mignot G, Bavoux F. En fin de grosesse, les AINS sont dangereux pour le foetus. Rev Prescrire 1991; 11: 363-6
104. Valente MG, Graca LM, Doria JM. Imbicao do trabalho de parto prematuro pelo diclofenac. Medico 1978; 87: 245-7
105. Voyer LE, Drut R, Mendez JH. Fetal renal maldevelopment with oligohydramnios following maternal use of piroxicam. Pediatr Nephrol 1994; 8: 592-4
106. Van Marter LJ, Leviton A, Allred EN, et al. Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. Pediatrics 1996; 97: 658-63
107. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs - differences and similarities. N Engl J Med 1991; 324: 1716-25
108. Sawdy R, Slater D, Fisk N, et al. Use of a cyclooxygenase type-2-selective non-steroidal anti-inflammatory agent to prevent preterm delivery. Lancet 1997; 350: 265-6
109. Luerti M, Parazzine F, Agarossi A, et al. Risk factors for respiratory distress syndrome in the newborn. Acta Obstet Gynecol Scand 1993; 72: 359-64
110. Kanto WP, Wilson R, Breat GL. Perinatal events and necrotizing enterocolitis in premature infants. Am J Dis Child 1978; 141-67
111. Østensen M. Optimisation of antirheumatic drug treatment in pregnancy. Clin Pharmacokinet 1994; 27: 486-503
112. Walker B. Induction of cleft palate in rats with antiinflammatory drugs. Teratology 1971; 4: 39-42
113. Pinsky L, DiGeorge AM. Cleft palate in the mouse: a teratogenic index of glucocorticoid potency. Science 1965; 147: 402-3
114. Walker E. Induction of cleft palate in rabbits by several glucocorticoids. Proc Soc Exp Biol Med 1967; 125: 1281-4
115. Reinisch JM, Simon NG. Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science 1978; 202: 436-8
116. Bongiovanni AM, McPadden AJ. Steroids during pregnancy and possible fetal consequences. Fertil Steril 1960; 11: 181-6
117. Serment H, Charpin J, Tessier G, Felce A. Corticothérapie et grossesse. Bulletin Fed Soc Gynécol Obstét Franc 1968; 20: 159-61
118. Popert AJ. Pregnancy and adrenocortical hormones. BMJ 1962; 1: 967-72
119. Fine LG, Barnett EV, Danovitch GM. Systemic lupus erythematosus in pregnancy. Ann Intern Med 1981; 94: 667-77
120. Scott JR. Fetal growth retardation associated with maternal administration of immunosuppressives. Am J Obstet Gynecol 1977; 128: 668-76
121. Cowchock FS, Reece EA, Balaban D, et al. Repeated fetal losses associated with antiphospholipid antibodies; a collaborative randomized trial comparing prednisone with low-dose heparin treatment. Am J Obstet Gynecol 1992; 166: 1318-23
122. Kraus AM. Congenital cataract and maternal steroid injection. J Pediatr Ophthalmol Strabismus 1975; 12: 107-8
123. Cederqvist LL, Merkatz IR, Litwin SD. Fetal immunoglobulin synthesis following maternal immunosuppression. Am J Obstet Gynecol 1977; 129: 687-90
124. Coté CJ, Meuwissen HJ, Pickering RJ. Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy. J Pediatr 1974; 85: 324-8
125. Schmidt PL, Sims ME, Strassner HT, et al. Effect of antepartum glucocorticoid administration upon neonatal respiratory distress syndrome and perinatal infection. Am J Obstet Gynecol 1984; 178: 178-86
126. Ramsey-Goldman R. Pregnancy in systemic lupus erythematosus. Rheum Dis Clin North Am 1988; 14: 169-85
127. Grigor RR, Shervington PC, Hughes GRV, et al. Outcome of pregnancy in systemic lupus erythematosus. Proc Soc Exp Biol Med 1977; 70: 99-100
128. Fuchs U, Lippert TH. Goldtherapie und Schwangerschaft. Dtsch Med Wochenschr 1986; 111: 31-4
129. Szabo KT, Guerriero J, Kang YJ. The effects of gold containing compounds on pregnant rats and their fetuses. Vet Pathol 1978; 15 Suppl. 5: 89-96
130. Møller-Madsen B, Danscher G, Uldbjerg N, Allen JG. Autometallographic demonstration of gold in human fetal liver and placenta. Rheumatol Int 1987; 7: 47-8
131. Rocker I, Henderson WJ. Transfer of gold from mother to fetus [letter]. Lancet 1976; 2: 1246
132. Cohen D, Orzel J. Infants of mothers receiving gold therapy. Arthr Rheum 1981; 24: 104-5

133. Patterson M, Traeger CH. Report, meeting of New York Rheumatism Association: 1951. In: McCarty, editor. Arthritis and allied conditions. 9th ed. Philadelphia (PA): Lea & Febiger, 1972: 479
134. Miyamoto T, Miyaji S, Horiuchi Y, et al. Gold therapy in bronchial asthma – special emphasis upon blood levels of gold and its teratogenicity. Nippon Naika Gakkai Zasshi 1974; 63: 1190-7
135. Rogers JG, Anderson R, Chow CW, et al. Possible teratogenic effects of gold. Aust Paediatr J 1980; 16: 194-5
136. Tozman ECS, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. Med Toxicol 1987; 2: 177-89
137. American College of Rheumatology ad hoc Committee on clinical guidelines: guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996; 39: 723-31
138. Gibbons RB. Complications of chrysotherapy. Arch Intern Med 1979; 139: 343-6
139. Kean WF, Hart L, Buchanan WW. Auranofin. Br J Rheumatol 1997; 36: 560-72
140. Ullberg S, Lindquist NJ, Sjøstrand SE. Accumulation of chorioretinotoxic drugs in the fetal eye. Nature 1970; 227: 1257-8
141. Dencker L, Lindquist NG. Distribution of labeled chloroquine in the inner ear. Arch Otolaryngol 1975; 101: 185-8
142. Mgbodile MU. Effects of perinatal exposure of albino rats to chloroquine. Biol Neonate 1987; 51: 273-6
143. Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. BMJ 1985; 290: 1466-7
144. Fraga A, Mintz G, Orozco J, et al. Sterility and fertility rates, fetal wastage and maternal morbidity in systemic lupus erythematosus. J Rheumatol 1974; 1: 293-8
145. Mac Kenzie AH. Antimalarial drugs for rheumatoid arthritis: (oral gold symposium). Am J Med 1983; 75: 48-58
146. Suhonen R. Hydroxychloroquine administration in pregnancy [letter]. Arch Dermatol 1983; 119: 185
147. Buchanan NMM, Toubi E, Khamashta M, et al. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Ann Rheum Dis 1996; 55: 486-8
148. Levy M, Buskila D, Gladman DD, et al. Pregnancy outcome following first trimester exposure to chloroquine. Am J Perinatol 1991; 8: 174-8
149. Parke AL. Antimalarial drugs, systemic lupus erythematosus and pregnancy. J Rheumatol 1988; 15: 607-10
150. Parke AL, West B. Hydroxychloroquine in pregnant patients with systemic lupus erythematosus. J Rheumatol 1996; 23: 1715-8
151. Hart CN, Naunton RF. The ototoxicity of chloroquine phosphate. Arch Otolaryngol Head Neck Surg 1964; 80: 407-12
152. Paufique L, Magnard P. Retinal degeneration in 2 children following preventive antimalarial treatment of mother during pregnancy. Bull Soc Opththalmol Fr 1969; 69: 466-7
153. Phillips-Howard PA. The safety of antimalarial drugs in pregnancy. Drug Saf 1996; 14: 131-45
154. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med 1992; 324: 150-4
155. Endres W. D-penicillamine in pregnancy - to ban or not to ban? Klin Wochenschr 1981; 59: 535-7
156. Rosa FW. Teratogen update: penicillamine. Teratology 1986; 33: 127-31
157. Crawhall JC, Scowen EF, Thompson CJ. Dissolution of cystine stones during D-penicillamine treatment of a pregnant patient with cystinuria. BMJ 1967; 1: 216-8
158. Hartard C, Kunze K. Pregnancy in a patient with Wilson's disease treated with D-penicillamine and zinc sulfate: a case report and a review of the literature. Eur Neurol 1994; 34: 337-40
159. Mjølnerød OK, Rasmussen K, Dommerud SA, et al. Congenital connective tissue defect probably due to D-penicillamine treatment in pregnancy. Lancet 1971; 1: 673-5
160. Laver M, Fairley KF. D-penicillamine treatment in pregnancy. Lancet 1971; 1: 1019-20
161. Solomon L, Abrams G, Dinner M, et al. Neonatal abnormalities associated with D-penicillamine treatment during pregnancy. N Engl J Med 1977; 296: 54-5
162. Harpey JP, Jaudon MC, Clavel JP, et al. Cutis laxa and low serum zinc after antenatal exposure to penicillamine [letter]. Lancet 1983; II: 858
163. Linares A, Zarranz JJ, Rodriguez-Alarcon J, et al. Reversible cutis laxa due to maternal D-penicillamine treatment [letter]. Lancet 1979; II: 43
164. Scheinberg IH, Sternlieb I. Pregnancy in penicillamine-treated patients with Wilson's disease. N Engl J Med 1975; 293: 1300-2
165. Maracek Z, Graf M. Pregnancy in penicillamine treated patients with Wilson's disease. N Engl J Med 1976; 295: 841-2
166. Biller J, Swiontoniowski M, Brazis PW. Successful pregnancy in Wilson's disease: a case report and a review of the literature. Eur Neurol 1985; 24: 306-9
167. Gregory MC, Mansell MA. Pregnancy and cystinuria. Lancet 1983; II: 1158-60
168. Lyle WH. Penicillamine in pregnancy [letter]. Lancet 1978; I: 606
169. Jaffe I. Therapeutic strategy in rheumatoid arthritis: a roundtable discussion. J Rheumatol 1981; Suppl. 7: 124-45
170. Xiong JM, Liang B, Mo YQ, et al. Teratologic studies of methyl-5-aminosalicylate and salicylazopyridine. Acta Pharmacol Sin 1992; 13: 265-7
171. Hensleigh PA, Kauffman RE. Maternal absorption and placental transfer of sulfasalazine. Am J Obstet Gynecol 1977; 127: 443-4
172. Järnerot G, Into-Malmberg MB, Esbjoerner E. Placental transfer of sulphasalazine and sulfapyridine and some of its metabolites. Scand J Gastroent 1981; 16: 693-7
173. Järnerot G, Andersen S, Esbjoerner E, et al. Albumin reserve for binding of bilirubin in maternal and cord serum under treatment with sulphasalazine. Scand J Gastroent 1981; 16: 1049-55
174. Mogadam M, Dobbins WO, Korelitz BI, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981; 80: 72-6
175. Nielsen OH, Andreasson B, Bondesen S, et al. Pregnancy in ulcerative colitis. Scand J Gastroenterol 1983; 18: 735-42
176. Hoo JJ, Hadro TA, Von Behrens P. Possible teratogenicity of sulfasalazine [letter]. N Engl J Med 1988; 318: 1128
177. Rasenack J, Schölmerich J. Entzündliche Darmerkrankungen und Schwangerschaftsverlauf. Gynäkologie 1990; 23: 11-7
178. Moody GA, Probert C, Jayanti V, et al. The effects of chronic ill health and treatment with sulphasalazine on fertility amongst men and women with inflammatory bowel disease in Leicestershire. Int J Colorect Dis 1997; 12: 220-4
179. Levi S, Liberman M, Levi AJ, et al. Reversible congenital neutropenia associated with maternal sulphasalazine therapy [letter]. Eur J Pediatr 1988; 148: 174-5
180. Byron M. Prescribing in pregnancy: treatment of rheumatic diseases. BMJ 187; 294: 236-8

181. Esbjörner E, Järnerot G, Wranne L. Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. Acta Pediatr Scand 1987; 76: 137-42
182. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Morb Mortal Wkly Rep 1992; 41: 1-7
183. Britton S, Palacios R. Cyclosporin A – usefulness, risks and mechanism of action. Immunol Rev 1982; 65: 5-22
184. Tugwell P, Bombardier C, Geut M, Et al. Low-dose cyclosporin versus placebo in patients with rheumatoid arthritis. Lancet 1990; 335: 1051-5
185. Yocum DE, Klippel JH, Wilder RL, et al. Cyclosporin A in severe, treatment refractory rheumatoid arthritis. Ann Intern Med 1988; 109: 863-9
186. Tokuda M, Kurata N, Mizoguchi A, et al. Effect of low-dose cyclosporin A on systemic lupus erythematosus disease activity. Arthritis Rheum 1994; 37: 551-8
187. Mason RJ, Thomson AW, Whiting PH, et al. Cyclosporine-induced fetotoxicity in the rat. Transplantation 1985; 39: 9-12
188. Lewis GJ, Lamont CAR, Lee HA, et al. Successful pregnancy in a renal transplant recipient taking cyclosporin A [letter]. BMJ 1983; 286: 603
189. Flechner SM, Katz AR, Rogers AJ, et al. The presence of cyclosporine in body tissues and fluids during pregnancy. Am J Kidney Dis 1985; 5: 60-3
190. Burrows DA, O'Neil TJ, Sorrells TL. Successful twin pregnancy after renal transplant maintained on cyclosporine A immunosuppression. Obstet Gynecol 1988; 72: 459-61
191. Arellano F, Monka C, Krupp P. Treatment with cyclosporine A in pregnancy [in Spanish]. Med Clin (Barcelona) 1991; 96: 194
192. Armenti VT, Ahlswede KM, Ahlswede BA, et al. National transplantation pregnancy registry: outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients. Transplantation 1994; 57: 502-6
193. Gaughan WJ, Moritz MJ, Radomski JS, et al. National Transplantation Pregnancy Registry: report on outcomes in cyclosporine-treated female kidney transplant recipients with an interval from transplant to pregnancy of greater than five years. Am J Kidney Dis 1996; 28: 266-9
194. Haugen G, Fauchald P, Sodal G, et al. Pregnancy outcome in renal allograft recipients in Norway: the importance of immunosuppressive drug regiment and health status before pregnancy. Acta Obstet Gynecol Scand 1994; 73: 541-6
195. Cockburn I, Krupp P, Monka C. Present experience of Sandimmun in pregnancy. Transplantation Proc 1989; 21: 3730-2
196. Pujals JM, Figueras G, Puig JM, et al. Osseous malformation in baby born to Woman on cyclosporin [letter]. Lancet 1989; I: 667
197. Hussein MM, Mooij JMV, Roujouleh H. Cyclosporine in the treatment of lupus nephritis including two patients treated during pregnancy. Clin Nephrol 1993; 40: 160-3
198. Doria A, Di Leonardo L, Vario S, et al. Cyclosporin A in a pregnant patient affected with systemic lupus erythematosus. Rheumatol Int 1992; 12: 77-8
199. Calne RY, Brons IGM, Williams PF, et al. Successful pregnancy after paratropic segmental pancreas and kidney transplantation [letter]. BMJ 1988; 296: 1709
200. Shaheen FAM, Al-Sulaiman MH, Al-Khader AA. Long-term nephrotoxicity after exposure to cyclosporine *in utero*. Transplantation 1993; 56: 224-5
201. Shepard TH. Catalog of teratogenic agents. 6th ed. Baltimore (MD): The John Hopkins University Press, 1989; 164-6
202. Amoura Z, Schermann JM, Wechsler B, et al. Transplacental passage of colchicine in familial Mediterranean fever [letter]. J Rheumatol 1994; 21: 383
203. Ehrenfeld M, Brzezinski A, Levy M, et al. Fertility and obstetric history in patients with familial Mediterranean fever on long-term colchicine therapy. Br J Obst Gynaecol 1987; 94: 1186-91
204. Rabinovitch O, Zemer D, Kukia E, et al. Colchicine treatment in conception and pregnancy: two hundred thirty-one pregnancies in patients with familial Mediterranean fever. Am J Reprod Immunol 1992; 28: 245-6
205. Livneh A, Cabili S, Zemer D, et al. Effect of pregnancy on renal function in amyloidosis of familial Mediterranean fever. J Rheumatol 1993; 20: 1519-23
206. Fujii TM, Kowa Y. Teratogenesis of azathioprine (Imuran) in mice and rats [letter]. Oyo Yakuri 1968; 2: 401
207. Githens JH, Rosencrantz JG, Tunnock SM. Teratogenic effects of azathioprine (Imuran). J Pediatr 1965; 66: 962-3
208. Tuchmann-Duplessis H, Mercier-Parot L. Production in rabbits of malformations of the extremities by administration of azathioprine and 6-mercaptopurine. C R Seances Soc Biol Fil 1966; 160: 501-6
209. Saarikoski S, Seppala M. Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus. Am J Obstet Gynecol 1973; 115: 1100-6
210. Rudolph JE, Schweizer RT, Bartus SA. Pregnancy in renal transplant patients. Transplantation 1979; 27: 26-9
211. The Registration Committee of the European dialysis and transplant association. Successful pregnancies in women treated by dialysis and kidney transplantation. Br Obstet Gynaecol 1980; 87: 839-45
212. Felson DT, Anderson J. Evidence for the superiority of immunosuppressive drugs and prednisone over prednisone alone in lupus nephritis. Results of a pooled analysis. N Engl J Med 1984; 311: 1528-33
213. Ramsey-Goldman R, Mientus JM, Kutzer JE, et al. Pregnancy outcome in women with systemic lupus erythematosus treated with immunosuppressive drugs. J Rheumatol 1993; 20: 1152-7
214. Marushak A, Weber T, Bock J, et al. Pregnancy following kidney transplantation. Acta Obstet Gynecol Scand 1986; 65: 557-9
215. Davison JM, Lindheimer MD. Pregnancy in renal transplant recipients. J Reprod Med 1982; 27: 613-21
216. Haagsma EB, Visser GHA, Klompmaker IJ, et al. Successful pregnancy after orthotopic transplantation. Obstet Gynecol 1989; 74: 442-3
217. Davison JM, Dellagrammatikos H, Parkin JM. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. Br J Obstet Gynaecol 1985; 92: 233-9
218. Sharon E, Jones J, Diamond H, et al. Pregnancy and azathioprine in systemic lupus erythematosus. Am J Obstet Gynecol 1974; 118: 25-8
219. Lawler SD, Lele KP. Chromosomal damage induced by chlorambucil and chronic lymphocytic leukemia. Scand J Haematol 1972; 17: 197-204
220. Westin J. Chromosome abnormalities after chlorambucil therapy of polycythemia vera. Scand J Haematol 1976; 17: 197-204
221. Kahn MF, Arlet J, Block-Michel H, et al. Leucemies aigues après traitement par agents cytotoxigues en rheumatologies: 19 observations chex 2006 patients. Nouv Presse Med 1979; 8: 1393-7

222. Monie IW. Chlorambucil-induced abnormalities of urogenital system of rat fetuses. Anat Rec 1961; 139: 145-9
223. Brummett ES, Johnson EM. Morphological alterations in the developing fetal rat limb due to maternal injection of chlorambucil. Teratology 1979; 20: 279-88
224. Sokal JE, Lessmann EM. Effects of cancer chemotherapeutic agents on the human fetus. JAMA 1960; 172: 1765-71
225. Shotton D. Monie IW. Possible teratogenic effect of chlorambucil on a human fetus. JAMA 1963; 186: 74-5
226. Steege JF, Caldwell DS. Renal agenesis after first trimester exposure to chlorambucil. South Med J 1980; 73: 1414-5
227. Roubenoff R, Hoyt I, Petri M, et al. Effects of antiinflammatory and immunosuppressive drugs on pregnancy and fertility. Semin Arthritis Rheum 1988; 18: 88-110
228. Thompson J, Conklin KA. Anesthetic management of a pregnant patient with scleroderma. Anesthesiology 1983; 59: 69-71
229. David J, Vouyiouka O, Ansell BM, et al. Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. Clin Exp Rheumatol 1995; 11: 85-90
230. Hackenberger I, Kreybig T. Vergleichende teratologische Untersuchungen bei der Maus und der Ratte. Arzneimittel Forschung 1965; 15: 1456-60
231. Chaube S, Kury G, Murphy ML. Teratogenic effects of cyclophosphamide in the rat. Cancer Chemother Biol Response Modif 1967; 51: 363-76
232. Fritz H, Hess R. Effects of cyclophosphamide on embryonic development in the rabbit. Agents Actions 1971; 2: 83-6
233. Wilk AL, McClure HM, Horigan EA. Induction of craniofacial malformations in the rhesus monkey with cyclophosphamide [abstract]. Teratology 1978; 17 Suppl.: 24A
234. Nicholson HO. Cytotoxic drugs in pregnancy: review of reported cases. J Obstet Gynaecol Br Commonw 1968; 75: 307-12
235. Kirshon B, Wasserstrum N, Willis R, et al. Teratogenic effects of first-trimester cyclophosphamide therapy. Obstet Gynecol 1988; 72: 462-4
236. Martinez-Rueda JO, Arce-Salina CA, Kraus A, et al. Factors associated with fetal losses in severe systemic lupus erythematosus. Lupus 1996; 5: 113-9
237. Matsukawa Y, Nishinari S, Horie T, et al. Successful child bearing during intravenous cyclophosphamide therapy in a patient with systemic lupus erythematosus. Br J Rheumatol 1998; 37: 342-3
238. Pizzuto J, Aviles A, Noriega, et al. Treatment of acute leukemia during pregnancy: presentation of nine cases. Cancer Treat Rep 1980; 64: 679-83
239. Greenberg LH, Tanaka KR. Congenital anomalies probably induced by cyclophosphamide. JAMA 1964; 188: 423-6
240. Toledo TM, Harper RC, Moser RH. Fetal effects during cyclophosphamide and irradiation therapy. Ann Intern Med 1971; 74: 87-91
241. Coates A. Cyclophosphamide in pregnancy. Aust J Obstet Gynaecol 1970; 10: 33-4
242. Murray CL, Reichert JA, Anderson J, et al. Multimodal cancer therapy for breast cancer in the first trimester of pregnancy. JAMA 1984; 252: 2607-8
243. Sweet DL, Kinzie J. Consequences of radiotherapy and antineoplastic therapy for the fetus. J Reprod Med 1976; 17: 241-6
244. Luisiri P, Lance NJ, Curran JJ. Wegener's granulomatosis in pregnancy. Arthritis Rheum 1997; 40: 1354-60
245. Barry C, Davis S, Garrad P, et al. Churg-Strauss disease: Deterioration in a twin pregnancy: successful outcome following treatment with corticosteroids and cyclophosphamide. Br J Obstet Gynecol 1997; 104: 746-7
246. Nguyen Tan Lung R, Granier M, Gaudry E, et al. Cyclophosphamide en cours de grossesse: une prescription acceptable. J Gynecol Obstet Biol Reprod (Paris) 1995; 2: 314-8
247. Zemlickis D, Lishner M, Erlich R, et al. Teratogenicity and carcinogenicity in a twin exposed *in utero* to cyclophosphamide. Teratog Carcinog Mutagen 1993; 13: 139-43
248. Zamenhof S. Differential effects of antifolate on the development of brain parts in chick embryos. Growth 1985; 49: 28-33
249. Skalko RG, Gold MP. Teratogenicity of methotrexate in mice. Teratology 1974; 9: 159-64
250. Schmid BP. Monitoring of organ formation in rat embryos after *in vitro* exposure to azathioprine, mercaptopurine, methotrexate, or cyclosporine A. Toxicology 1984; 31: 9-21
251. Adams CE, Hay MF, Lutwak-Mann C. The actions of various agents on the rabbit embryo. J Embryol Exp Morphol 1961; 9: 468-91
252. Wilson JG, Scott WJ, Ritter EJ, et al. Comparative distribution and embryotoxicity of methotrexate in pregnant rats and Rhesus monkeys. Teratology 1979; 19: 71-80
253. Milunsky A, Graef JW, Gaynor MF. Methotrexate-induced congenital malformations. J Pediatr 1968; 72: 790-5
254. Chotiner HC. Nonsurgical management of ectopic pregnancy associated with severe hyperstimulation syndrome. Obstet Gynecol 1985; 66: 740-3
255. Kozlowski RD, Steinbrunner JV, MacKenzie AH, et al. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. Am J Med 1990; 88: 589-92
256. Buckley LM, Bullaboy CA, Leichtman L, et al. Multiple congenital anomalies associated with weekly low-dose methotrexate treatment of the mother. Arthritis Rheum 1997; 40: 971-3
257. Østensen M. Treatment with low dose methotrexate during early pregnancy. Rheumatology Eur 1997; 26 Suppl. 2: 40
258. Rustin GJS, Booth M, Dent J, et al. Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours. BMJ 1984; 288: 103-6
259. Walden PAM, Bagshawe KD. Pregnancies after chemotherapy for gestational trophoblastic tumours [letter]. Lancet 1979; II: 1224
260. Turchi JJ, Villasis C. Anthracyclines in the treatment of malignancy in pregnancy. Cancer 1988; 61: 435-40
261. Barnes AB, Link DA. Childhood dermatomyositis and pregnancy. Am J Obstet Gynecol 1983; 146: 335-6
262. Sivanesaratnam V, Sen DK. Normal pregnancy after successful treatment of choriocarcinoma with cerebral metastases: a case report. J Reprod Med 1988; 33: 402-3
263. Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. Med J Aust 1989; 150: 613-9
264. Morris LF, Harrod MJ, Menter MA, et al. Methotrexate and reproduction in men: case report and recommendations. J Am Acad Dermatol 1993; 29: 913-6

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