PRACTICAL DRUG SAFETY

Drug Safety 1999 Oct; 21 (4): 311-323
0114-5916/99/0010-0311/$06.50/0

Treating Inflammatory Bowel Disease During Pregnancy

Risks and Safety of Drug Therapy

William Connell and *Ashley Miller*

St Vincent's Hospital, Victoria Parade, Fitzroy, Victoria, Australia

Contents

Abstract

The safety of drug therapy for inflammatory bowel disease during pregnancy is an important clinical concern. Current available information is largely derived from animal studies and clinical experience among patients with inflammatory bowel disease and autoimmune disorders and organ transplant recipients. However, these data are confounded by various factors including difficulty projecting the results of animal studies to humans, methodological deficiencies of some studies, insufficient experience with certain agents, difficulty distinguishing the fetal effects of underlying disease from drug therapy and a need to consider the

impact of background rates of adverse fetal outcomes which apply to all pregnancies.

In inflammatory bowel disease, the effects of active inflammation on the fetus are believed to be more harmful than those of drug treatment, and therapy is often justified to induce or maintain remission during pregnancy. The choice of appropriate treatment is determined by the severity of the disease and the potential for drug toxicity.

No causal relationship has been established between exposure to sulfasalazine or other 5-aminosalicylic acid drugs and the development of congenital malformations. These drugs may be used with relative safety during pregnancy and lactation. Considerable experience with corticosteroids have shown them to pose very small risk to the developing fetus. Current evidence indicates that maternal use of azathioprine is not associated with an increased risk of congenital malformations, though impaired fetal immunity, growth retardation or prematurity is occasionally observed. Preliminary evidence derived from patients with inflammatory bowel disease show no significant fetal toxicity following first trimester exposure to mercaptopurine, though its elective use in pregnancy is controversial. Cyclosporin is not teratogenic, but may be associated with growth retardation and prematurity. Pregnancy should be avoided in women treated with methotrexate because of its known abortifacient effects and risk of causing typical malformations. Although treatment with metronidazole or ciprofloxacin for short durations appear to be devoid of adverse fetal reactions, the effect of prolonged exposure as required in Crohn's disease remains unknown.

Inflammatory bowel disease is a chronic disorder that often affects young adults. Its management during pregnancy requires an understanding of possible drug toxicity, and a regard for the consequences of uncontrolled disease activity on mother and fetus.

Fertility in most women with ulcerative colitis is unaffected.[1] Two controlled trials observed subfertility in women with active Crohn's disease, but this may have been due to voluntary choice.[2,3] The majority of pregnant women with inactive disease can expect a normal pregnancy outcome, though individuals with active disease, especially at conception, may have a higher risk of growth retardation, spontaneous abortion or prematurity.[4,5]

Patients with active ulcerative colitis brought into remission with drug therapy during pregnancy have a similar outcome to those with quiescent disease at the start of pregnancy.[6] Provided that the condition is inactive at conception, disease exacerbations tend to occur at similar rates to nonpregnant women.[7] In contrast, both ulcerative colitis and Crohn's disease that is active at conception may be more difficult to control.[8,9] Because of the maternal and fetal advantages, it is preferable for women with inflammatory bowel disease to coincide conception with a time when the disease is relatively quiescent.[5,10]

An important principle in the management of inflammatory bowel disease during pregnancy is that disease activity is believed to play a more dominant role in determining fetal outcome than drug therapy.[11] Pharmacotherapy may be required to control disease activity before conception, and to maintain remission or treat flare-ups during and after pregnancy. Therapeutic options are best discussed with patients before conception, and the choice of treatment generally depends on individual preference, disease severity and potential for drug toxicity. Inevitably, most experience regarding the risks of drug treatment for inflammatory bowel disease in pregnancy has been derived for older therapies, including sulfasalazine and corticosteroids. Less information is available regarding the use of newer agents such as 5-aminosalicylic acid preparations, immunosuppressives and anti-

bacterials. The safety of these agents are best assessed from the results of animal studies, anecdotal reports and clinical experience in other disorders where they are more commonly used in pregnancy. The conclusions drawn for the inflammatory bowel disease patient from these methods must take into consideration the difficulties extrapolating animal data to humans, distinguishing the effects of drug therapy from the underlying condition for which it is required, the impact of concurrent medications, and the background rates of spontaneous abortions, prematurity or birth defects that apply in the general community.[12]

1. Corticosteroids

Glucocorticoids are effective in inducing remission of disease activity in patients with ulcerative colitis and Crohn's disease.[13-17] Doses of prednisolone ≥40mg result in an overall remission in 67% of patients.[15] In patients with Crohn's disease, prednisolone 60 mg/day, tapering over 6 weeks, resulted in a 83% remission rate.[16] In a regional unselected group of newly patients with diagnosed Crohn's disease, the first corticosteroid treatment course achieved complete remission within 30 days in 48%, partial remission in 32% and no response in 20% of patients.[17] The choice of preparation used (oral, parenteral, topical or controlled release) depends on disease location and severity.

In the mother, glucocorticoids may theoretically aggravate recognised complications of pregnancy including glucose intolerance, hypertension, sodium retention and peripheral oedema.[18] It is appropriate to monitor patients receiving long term corticosteroid therapy for the development of these potential effects. Dose-dependent psychological disturbances may also occur. Abrupt cessation of prolonged, high dose corticosteroid therapy may induce maternal adrenal insufficiency, and supplemental therapy may be required during labour.

1.1 Animal Data

In animals, high dose prednisolone (up to 125 mg/kg) may be teratogenic.[19] The frequency of cleft palate is increased in the offspring of mice and rabbits exposed to prednisolone in a dose-dependent manner.[20,21] Other effects of high dose corticosteroids in animals include impaired fetal growth, abortion, low litter size, fetal islet cell degeneration and behavioural change.[22,23] An increased rate of skeletal anomalies, reduced litters and decreased fetal bodyweight occurred in rabbits receiving subcutaneous budesonide.[24]

1.2 Human Data

Different glucocorticoids undergo varying degrees of inactivation in the placenta. Following prednisolone usage, corticosteroid concentrations in the fetus approximate 10% that of the maternal circulation.[25] In contrast, dexamethasone and betamethasone cross the placenta more freely[26] and may theoretically result in adrenal suppression in the newborn. Although isolated cases of neonatal adrenal insufficiency and thymic hypoplasia have been reported, the general experience suggests that the concentrations of active corticosteroid in the newborn are unlikely to cause adrenal suppression when therapeutic doses of prednisolone are used.[10,27]

Corticosteroids do not appear to be teratogenic in humans. It is true that anecdotal cases of malformations have been reported in children of women treated with corticosteroids during pregnancy, and an early, uncontrolled study observed an increased frequency of cleft palate.[28] However, controlled data in patients with inflammatory bowel disease and other conditions do not show an increased risk of overall malformations in babies of women receiving corticosteroids during pregnancy.[10,29,30] In 468 exposed women, 2 cases of cleft palate were observed compared with 0.2 expected, but the authors found it impossible to tell if this increase was real.[30]

An increased incidence of growth retardation, stillbirths, placental insufficiency, fetal distress, and reduced neonatal birthweight may occur in women treated with prednisolone during pregnancy, though this could possibly be related to concurrent medical therapy or the effects of the under-

lying disease.[31-33] In contrast, several large series examining the outcome of corticosteroid exposure in pregnancy for asthma, inflammatory bowel disease, systemic lupus erythematosus and rheumatoid arthritis is reassuring.[11,30,34-36] In inflammatory bowel disease, fetal morbidity or mortality was not increased in a large series of women treated with corticosteroids alone or in combination with sulfasalazine. A small increase in fetal complications which was observed in women with Crohn's disease was attributed to the effects of the underlying disease.[10] There are no published data on the use of controlled-release budesonide preparations during pregnancy.

Corticosteroids enter breast milk in amounts between 5 and 25% of maternal drug concentration.[37,38] These concentrations are not thought to represent any clinically significant risk to breastfed infants, and women requiring prednisolone should not be discouraged from breast feeding.[39]

2. Aminosalicylates

2.1 Sulfasalazine

Sulfasalazine consists of 5-aminosalicylic acid (5-ASA) conjugated to sulfapyridine. In the colonic lumen, the azo bond joining these 2 molecules is disrupted by bacteria releasing 5-ASA, the active moiety, and sulfapyridine, an inert carrier molecule which is responsible for many of the drug's adverse effects. Sulfasalazine is useful in the induction and maintenance of remission in patients with mild to moderately active ulcerative colitis.[40]

Up to one-third of patients taking sulfasalazine develop adverse effects, most of which are dose-dependent and occur in slow acetylators of the drug. Among these, the commonest are nausea, epigastric pain, vomiting, headache and hepatitis. Other reactions such as fever, rash, arthralgia and lymphadenopathy are due to drug hypersensitivity. Haematological disorders are rare but potentially serious, and include haemolytic anaemia, folate malabsorption, agranulocytosis and aplastic anaemia.[41] Reversible oligospermia and poor sperm motility may cause male infertility during therapy.[42]

2.2 Animal Data

There is no evidence of teratogenicity from sulfasalazine in animals.

2.3 Human Data

A small number of children of mothers taking sulfasalazine for inflammatory bowel disease have been born with cleft lip, cleft palate, hydrocephalus,[43] congenital heart defects[44,45] and reversible congenital neutropenia.[46] A questionnaire mailed to patients with inflammatory bowel disease in Leicestershire, England, showed an increased frequency of congenital malformations among the children of men and women using sulfasalazine at the time of pregnancy. Details of concurrent medical therapy, disease severity and the nature of the anomalies were not described.[47] These reports contrast with other substantial experience over several decades which have shown the drug can be used with relative safety during pregnancy. Retrospective and case-controlled reviews have shown no increase in rates of spontaneous abortion, premature delivery, or congenital malformations for women with either ulcerative colitis or Crohn's disease taking sulfasalazine.[9,11,48,49] The rate of congenital defects in infants of 531 mothers treated with sulfasalazine for inflammatory bowel disease was lower than the general population.[10] In this study, fetal morbidity and mortality in 287 pregnant women treated with sulfasalazine or prednisolone were no different than that observed in 244 pregnant women with inflammatory bowel disease who were untreated.[10]

Both sulfasalazine and sulfapyridine cross the placental barrier,[50,51] and cord blood concentrations of sulfasalazine and sulfapyridine are equal or slightly lower than in the mother.[52,53] Although sulfonamides may cause kernicterus, it has not been reported with sulfasalazine. Neither sulfasalazine nor sulfapyridine have been shown to significantly displace bilirubin from albumin.[52]

Folic acid deficiency may be associated with neural tube defects.[54] Since sulfasalazine competitively inhibits both the metabolism and transport of folic acid, supplementation with folic acid 1mg twice daily is advised in women receiving sulfasalazine prior to and during pregnancy.[8,55]

Concentrations of sulfasalazine and sulfapyridine in breast milk are low, and unlikely to result in kernicterus.[56] In general, sulfasalazine does not cause any problems to the nursing infant,[48,51] but in view of a single case report of bloody diarrhoea occurring in an breast-fed infant whose mother required sulfasalazine,[57] caution regarding its use in nursing mothers has been advised.[58]

2.4 5-Aminosalicylic Acid Preparations

Various formulations of 5-ASA have been developed as alternatives to sulfasalazine to deliver salicylates to the distal small bowel and colon without the need for the sulfapyridine moiety. These include 5-ASA dimers (olsalazine, balsalazide), pH-dependent preparations of mesalazine and mesalazine microspheres. These drugs may be used to treat acute episodes and to maintain remission in both ulcerative colitis and Crohn's disease.[59-62] Acute management of mild-to-moderate ulcerative colitis requires dosages higher than 2 g/day, and for maintenance treatment, 1.5 to 2 g/day can be used.[59] In acute Crohn's ileitis, 4 g/day of mesalazine capsules was superior to lower doses,[61] though the optimal dose for maintenance therapy or for preventing postoperative recurrence remains unclear. 5-ASA drugs are well tolerated, with occasional reports of hypersensitivity reactions, myocarditis, pancreatitis or renal toxicity associated with the pH-dependent agents.[63] Olsalazine may cause diarrhoea in a dose-dependent manner.[64]

2.5 Animal Data

There is no convincing evidence that mesalazine or olsalazine are teratogenic.[65] Rats exposed to 5-ASA *in utero* develop dose-dependent renal glomerular and tubular damage.[66] In rats and rabbits, the 'no observed adverse effect' level occurred at dose regimens far higher than used in humans.[67] Exposure to high doses of olsalazine have been associated with decreased fetal weight, retarded ossification, and immaturity of fetal visceral organs.[68]

2.6 Human Data

5-ASA crosses the placental barrier, but fetal concentrations are lower than in maternal plasma.[69] Renal insufficiency was reported in a newborn child exposed to high dosage 5-ASA (oral mesalazine 4 g/day) during the second trimester.[70] Provided 5-ASA is used at the recommended doses, however, other clinical series have now demonstrated the overall safety of oral or topical 5-ASA during pregnancy.[65,71-73]

Negligible amounts of 5-ASA are excreted into breast milk.[74] However, acute diarrhoea has been reported in breast-fed babies whose mothers required 5-ASA therapy, suggesting a possible allergic reaction.[75,76] The drug should be used with caution in nursing mothers.[58]

Para-aminosalicylic acid (4-ASA) is also used in the treatment of ulcerative colitis and Crohn's disease.[77,78] There are no published reports of adverse events during pregnancy.

3. Immunosuppressives

3.1 Azathioprine and Mercaptopurine

Azathioprine and its metabolite mercaptopurine are purine antimetabolites that are effective in the treatment of chronic active ulcerative colitis and Crohn's disease, and exert corticosteroid sparing effects.[79,80] Complications associated with azathioprine and mercaptopurine include pancreatitis, myelotoxicity, hypersensitivity reactions, hepatotoxicity and opportunistic infections.[79] Although information regarding the use of these drugs in pregnant women with inflammatory bowel disease is limited, experience with azathioprine in transplant recipients and various connective tissue disorders provides valuable information about its effects on the developing fetus.

3.2 Animal Data

Azathioprine is mutagenic in several bacterial test systems, but not in humans.[81] In animal studies, azathioprine or mercaptopurine may be associated with embryonic resorption, growth retardation, cleft palate, hydrocephalus, skeletal defects, and ocular anomalies.[81-85] Impaired ovarian function has been observed in surviving female offspring of mice given low dose mercaptopurine during pregnancy.[86]

3.3 Human Data

Azathioprine and mercaptopurine readily cross the placenta and predominantly circulate in the fetus as the inactive metabolite thiouric acid.[18,87] The fetus is theoretically protected from the adverse effects of azathioprine in early pregnancy as its liver lacks the enzyme, inosinate pyrophosphorylase, that converts azathioprine to its active metabolites.[88]

Fertility does not seem to be affected in humans treated with azathioprine, though the effect of mercaptopurine is not known.[88] Many successful pregnancies have been reported in transplant and nontransplant patients requiring azathioprine.[89-93] Sporadic congenital anomalies have been observed, but not in any characteristic pattern.[88] The frequency of malformations in early series of renal transplant recipients requiring azathioprine during pregnancy was up to 9%,[94] but the effects of high therapeutic doses, small sample size, other medical treatment, hypertension and renal dysfunction may have contributed. In contrast, several other transplant and nontransplant series[95-100] have shown the frequency of malformations following exposure to azathioprine in pregnancy to be similar to the reported rate of 3.9% in the general population.[101]

Fetal growth retardation and prematurity may occur at a slightly higher rate among renal transplant recipients treated with azathioprine during pregnancy than those who are untreated.[102,103] It is unclear if these complications are drug-related or due to the effects of the underlying disease. In systemic lupus erythematosus, adverse fetal effects were no more common in women treated with azathioprine than those who were not.[93]

Although only isolated cases of neonatal myelotoxicity and immunosuppression are reported,[104] they are potentially serious. Lethal pancytopaenia and severe combined immune deficiency, nonfatal lymphopenia, hypogammaglobulinaemia, thymic hypoplasia, neonatal infections and reversible neonatal immunosuppression have all been described.[8,105-107] It has been advised to limit the dosage in pregnancy to 2 mg/kg/day or less to avoid these possible adverse reactions.[108] This dose, however, may be insufficient to achieve a therapeutic effect. Alternatively, the dose of azathioprine may be modified in the third trimester depending on the mother's white blood cell count. In a study of 10 pregnant renal transplant recipients, no cases of neonatal leucopenia or thrombocytopenia were observed when the dose of azathioprine was halved at 32 weeks gestation if the maternal leucocyte count was lower than 8.6×10^9/L.[107]

An unusual but potentially serious complication of antenatal azathioprine exposure concerns the risk of chromosomal anomalies. A woman who was treated with azathioprine during pregnancy for systemic lupus erythematosus delivered a baby with 2 separate *de novo* constitutional chromosomal anomalies.[109] Transient chromosomal aberrations have been detected in the lymphocytes of infants born to renal transplant mothers, although these disturbances disappeared within 5 to 32 months.[110] There is a theoretical risk that abnormalities in other tissues not studied, such as germ cells, could increase the likelihood that these disturbances be passed on to future generations. No studies have specifically assessed the risk of neoplasia in exposed infants. Current experience does not indicate this to be a problem in clinical practice, though little long term data are available.[90]

In inflammatory bowel disease, a retrospective review of 16 pregnancies in 14 women taking azathioprine (2 mg/kg), observed no congenital abnormalities or subsequent health problems in the children for up to 16 years.[89]

Published data concerning the safety of mercaptopurine in human pregnancy are limited to the experience from one centre treating patients with inflammatory bowel disease. The use of mercaptopurine prior to conception and during pregnancy was not associated with increased prematurity, spontaneous abortion, congenital abnormalities, neonatal and childhood infections, or neoplasia.[111] Updated data from this series noted a prematurity rate of 3% and congenital malformation rate of 5% in women who conceived while they were receiving mercaptopurine.[112] Although these preliminary data are reassuring for patients who inadvertently conceive while taking mercaptopurine, the elective use of this drug during pregnancy remains controversial.

Outcomes of pregnancy when fathers are treated with mercaptopurine are even less understood. A single neoplasm was observed in a 4-year-old boy whose father had been receiving mercaptopurine at the time of conception.[112] Among the offspring of 12 men receiving mercaptopurine within 3 months of fertilisation, the frequency of perinatal complications was increased.[113] In a study of babies born to male transplant recipients treated with azathioprine at the time of conception, 58 of 60 were normal.[94]

Azathioprine and mercaptopurine are transferred to breast milk in small quantities.[114] Because of the potential for immunosuppression and myelotoxicity, its use is not recommended in nursing mothers.

4. Cyclosporin

Cyclosporin is a lipid-soluble metabolite of soil fungi that inhibits interleukin-2 production by T helper cells. Intravenous cyclosporin is effective in patients with severe, corticosteroid-refractory ulcerative colitis,[115] but in practice is rarely required during pregnancy for this purpose.

Maternal complications of cyclosporin include hypertension, nephrotoxicity, severe opportunistic infections, neurotoxicity and hepatotoxicity.[116]

4.1 Animal Data

Cyclosporin is neither teratogenic, mutagenic or myelotoxic in animals.[94,117] Embryotoxicity and growth retardation have occurred with high doses of cyclosporin.[118,119] Reduced fertility was observed in male rats and ovarian toxicity occurred in female rabbits following exposure to cyclosporin *in utero*.[120,121]

4.2 Human Data

Cyclosporin crosses the placenta, and umbilical cord drug concentrations are approximately 50% of that in the maternal circulation.[108] The drug is rapidly eliminated within the fetus.[103]

Fertility is not adversely affected by cyclosporin therapy. Although sporadic congenital anomalies have been reported in infants exposed to cyclosporin antenatally,[88] the drug is not thought to be teratogenic in humans. A 3% rate of congenital malformations was no different from that expected in the general population according to 2 large series of transplant recipients receiving cyclosporin during pregnancy.[122,123]

In contrast, fetal growth retardation and prematurity occur in approximately 50% of cases, though the mechanism by which this occurs is unknown.[122-124] Some neonates exhibit minor laboratory abnormalities including thrombocytopenia, leucopenia, and hypoglycaemia.[125] Of 26 infants born to mothers treated with cyclosporin during pregnancy for renal transplantation, no evidence of abnormal renal function was seen for up to 39 months of follow-up.[126] The need for carefully collected long term follow-up of individuals exposed to cyclosporin antenatally has been highlighted by a recent case in which a hepatoblastoma developed in a 2-year-old child born to a liver transplant recipient who was receiving cyclosporin and prednisolone.[127]

When urgent colectomy is required for fulminant colitis in pregnancy, the mortality rate is high for mother and fetus.[128] In such exceptional circumstances, short term cyclosporin may be justified to avoid emergency surgery. A single report

described the successful outcome following 10 days intravenous cyclosporin succeeded by oral therapy in a 29-week pregnant woman with severe, corticosteroid refractory colitis.[129]

Cyclosporin is excreted into breast milk at concentrations similar to blood.[130] Although no untoward effect occurred within 2 years in an infant who was breast fed for 14 months by a woman treated with cyclosporin,[131] the drug is not advised in nursing mothers because of potential nephrotoxicity and immunosuppression.[58]

4.3 Methotrexate

Methotrexate is a folic acid antagonist that inhibits the synthesis of purines. It may be useful in patients with severe refractory Crohn's disease.[132] Adverse reactions of methotrexate include hypersensitive pneumonitis, hepatic fibrosis, myelotoxicity, nausea, increased hepatic enzyme activity, skin rash and reversible oligospermia.[85,116]

Elective use of methotrexate is contraindicated in pregnancy because of the embyrotoxic and teratogenic effects it exerts in animals and humans.[18,88] Indeed, its abortifacient properties have been used therapeutically.[133] There is no reported experience of methotrexate in pregnant women with inflammatory bowel disease.

Administration of methotrexate during the first trimester may be associated with the development of characteristic malformations including abnormal head shape, large fontanelles, craniosynostosis, ocular hypertelerism and skeletal deformities.[134,135] The critical period of exposure is between 6 and 8 weeks of gestation when parietal bone genesis occurs.[136] Although it is possible that low dose methotrexate therapy is less likely to be associated with harmful fetal effects,[95,136] in 1 study there was 3 spontaneous abortions among 8 patients with rheumatoid arthritis taking <10 mg/wk in the first trimester,[137] and in another report multiple congenital anomalies developed in a baby whose mother received 10 to 12.5 mg/wk during early pregnancy.[138]

Methotrexate may also be associated with fetal growth retardation,[139] severe neonatal bone marrow suppression,[140] and possible chromosomal aberrations.[141] Methotrexate is excreted into breast milk and is contraindicated during breast feeding.[58,142] Studies suggest methotrexate is not teratogenic >1 year after it has been discontinued.[95] As such, women should stop taking methotrexate for at least 12 months prior to attempting pregnancy.

5. Antibacterials

5.1 Metronidazole

Metronidazole, a synthetic nitroimidazole, is commonly used for the treatment of perianal Crohn's disease, and may be beneficial in the prevention of pre-anastomotic recurrence following ileal resection for Crohn's disease.[143,144] The drug may cause adverse reactions in mothers including nausea, anorexia, metallic taste, glossitis and peripheral neuropathy.

5.2 Animal Data

The reduced form of metronidazole is mutagenic in bacteria, but mammals are not thought to be at risk because they are unable to reduce metronidazole. In high doses, the drug is carcinogenic in rodents, but not in other animals. It has not been shown to be teratogenic in animal studies.[145]

5.3 Human Data

Metronidazole crosses the placenta, and cord blood concentrations approximate those in maternal serum.[146] Although there are no clear adverse fetal effects, it is currently recommended for use in the second and third trimesters only.[145] Sporadic midline facial defects have been observed in infants exposed to metronidazole during the first trimester,[147] but 2 large meta-analyses concluded that short courses (7 to 10 days) of metronidazole during the first trimester were not associated with an increased risk of malformations.[147,148] Furthermore, this therapy is not associated with an increased frequency of still births, growth retardation, or prematurity.[149] There are no published data available on the safety of prolonged metroni-

dazole therapy, as is usually required in inflammatory bowel disease, during early pregnancy.

Metronidazole passes into breast milk, reaching maximal concentration 2 to 4 hours after administration.[150] One breast-fed infant developed diarrhoea and secondary lactose intolerance.[151] Due to *in vitro* mutagenicity, the American Academy of Paediatrics considers the effects of metronidazole on nursing infants to be unknown and maybe of concern.[58]

5.4 Ciprofloxacin

Ciprofloxacin is a quinolone antibacterial that acts by inhibiting bacterial DNA gyrase and hence DNA metabolism. It may be used as an alternative to metronidazole in patients with Crohn's disease. Quinolones readily cross the placenta and concentrate in the amniotic fluid.[152] These drugs have a high affinity for bone tissue, and juvenile animals may develop arthropathy following exposure in pregnancy.[153] Studies on cynomolgus monkeys did not reveal evidence of teratogenicity or embryotoxicity.[154] In humans, a prospective, observational study of 38 women receiving ciprofloxacin or norfloxacin during the first trimester for urinary tract infections demonstrated no increased risk of malformations or musculoskeletal problems.[152] There are no data concerning the use during pregnancy of ciprofloxacin as primary treatment for inflammatory bowel disease.

Quinolones are found in high concentrations in breast milk.[155] Due to the potential risks of arthropathy, ciprofloxacin is not recommended during pregnancy and lactation.

6. Emerging Therapies

There are no data available regarding the use in pregnancy of newer treatments for inflammatory bowel disease such as tissue necrosis factor-α, mycophenolate mofetil, interleukin-10, short chain fatty acids and tacrolimus. Because the effect of these drugs on the fetus is currently unknown, pregnancy is contraindicated in patients taking these medications.

7. Conclusions

Most women with inflammatory bowel disease can expect an uneventful pregnancy, especially when the condition is controlled at the time of conception. Although there is an understandable reluctance to use any drugs during pregnancy, treatment may be required to minimise the adverse fetal effects of uncontrolled disease activity, such as growth retardation, prematurity, and spontaneous abortion. For this reason, the impact of pregnancy on inflammatory bowel disease and the potential fetal toxicity of medication should be discussed prior to conception. The choice of therapy can then be tailored according to the individual's circumstances. Women who are unwilling to risk possible fetal drug toxicity should avoid pregnancy during therapy.

Clinical studies support the safety of sulfasalazine and moderate doses of 5-ASA formulations in pregnancy. The large experience with corticosteroids in pregnancy shows them to be free of significant fetal effects, although it is possible that a small increase in oral cleft may be associated with their use in the first trimester. This possibility should be discussed in advance of treatment, and weighed up against the therapeutic effects on maternal inflammation. Although azathioprine is seldom associated with significant fetal toxicity, such effects may be serious, and its elective use should be restricted to patients with severe disease in whom this drug is the best agent capable of maintaining remission. Data from a small series suggest that exposure to mercaptopurine is unlikely to be associated with an increased risk of congenital anomalies, but further information is required before its elective use can be widely recommended during pregnancy. Termination of pregnancy is not mandatory in women who inadvertently become pregnant while taking either azathioprine or mercaptopurine. In exceptional cases, cyclosporin may be used to avoid emergency surgery in pregnant women with inflammatory bowel disease. Because of its embryotoxic and teratogenic effects, women of reproductive years requiring methotrexate should be advised to avoid pregnancy during ther-

apy and for 12 months after its discontinuation. The safety of prolonged treatment with metronidazole or ciprofloxacin has not been confirmed.

References

1. Hudson M, Flett G, Sinclair TS, et al. Fertility and pregnancy in inflammatory bowel disease. Int J Gynecol Obstet 1997; 58 (2): 222-37
2. Baird DD, Narendranathan M, Sandler RS. Increased risk of preterm birth for women with inflammatory bowel disease. Gastroenterology 1990; 99 (4): 987-94
3. Mayberry JF, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease: a case control study by European collaborative group. Gut 1986; 27 (7): 821-5
4. Willoughby CP, Truelove SC. Ulcerative colitis and pregnancy. Gut 1980; 21: 469-74
5. Woolfson K, Cohen Z, McLeod RS. Crohn's disease and pregnancy. Dis Colon Rectum 1990; 33 (10): 869-73
6. Hanan IM, Kirsner JB. Inflammatory bowel disease in the pregnant woman. Clin Perinatol 1985; 12: 682-99
7. Miller JP. Inflammatory bowel disease in pregnancy: a review. J R Soc Med 1986; 79: 221-5
8. Modigliani R. Drug therapy for ulcerative colitis during pregnancy. Eur J Gastroenterol Hepatol 1997; 9 (9): 854-7
9. Khosla R, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. Gut 1984; 25 (1): 52-6
10. Mogadam M, Dobbins WO, Korelitz BI, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981; 80 (1): 72-6
11. Baiocco PJ, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. J Clin Gastroenterol 1984; 6 (3): 211-6
12. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998; 338: 1128-37
13. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. BMJ 1955; II: 1041-8
14. Summers RW, Switz DM, Sessions JT, et al. The National cooperative Crohn's disease study: results of drug treatment. Gastroenterology 1979; 77: 847-69
15. Kjeldsen J. Treatment of ulcerative colitis with high doses of oral prednisolone: the rate of remission, the need for surgery, and the effect of prolonging the treatment. Scand J Gastroenterol 1993; 28 (9): 821-6
16. Malchow H, Ewe K, Brandes JW, et al. European cooperative Crohn's disease study (ECCDS): results of drug treatment. Gastroenterology 1984; 86 (2): 249-66
17. Munkholm P, Langholz E, Davidsen M, et al. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut 1994; 35 (3): 360-2
18. Esplin MS, Branch DW. Immunosuppressive drugs and pregnancy. Obstet Gynecol Clin North Am 1997; 24 (3): 601-16
19. Albengres E, Le Louet H, Tillement JP. Immunosuppressive drugs and pregnancy: experimental and clinical data. Transplant Proc 1997; 29: 2461-6
20. Pinski L, DiGeorge AM. Cleft palate in the mouse: a teratogenic index of glucocorticoid potency. Science 1965; 147: 402-3
21. Walker BE. Induction of cleft palate in rabbits by several glucocorticoids. Proc Soc Exp Biol Med 1967; 125: 1281-4
22. Ballard PD, Hearney EF, Smith MB. Comparative teratogenicity of selected glucocorticoids applied ocularly in mice. Teratology 1977; 16: 175-80
23. Rayburn WF. Glucocorticoid therapy for rheumatic diseases: maternal, fetal, and breast-feeding considerations. Am J Reprod Immunol 1992; 28 (3-4): 138-40
24. Kihlstrom I, Lundberg C. Teratogenicity study of the new glucocorticosteroid budesonide in rabbits. Arzneimittel Forschung 1987; 37 (1): 43-6
25. Beitins IZ, Bayard F, Ances IG, et al. The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone near term. Pediatr Res 1973; 7: 509-19
26. Blanford AT, Murphy BEP. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. Am J Obstet Gynecol 1977; 127: 264-7
27. Kenny MJ, Preeyasombat C, Spaudling JS, et al. Cortisol production rate in infants born of steroid-treated mothers and of diabetic mothers. Pediatrics 1966; 37 (6): 960-6
28. Harris JWS, Ross IP. Cortisone therapy in early pregnancy: relation to cleft palate. Lancet 1956; I: 1045-7
29. Schatz M. Asthma treatment during pregnancy: what can be safely taken? Drug Saf 1997; 16 (5): 342-50
30. Fraser FC, Sajoo A. Teratogenic potential of corticosteroids in humans. Teratology 1995; 51 (1): 45-6
31. Reinisch JM, Simon NG, Karow WG, et al. Prenatal exposure to prednisolone in humans and animals retards intrauterine growth. Science 1978; 202 (4366): 436-8
32. Scott JR. Fetal growth retardation associated with maternal administration of immunosuppressive drugs. Am J Obstet Gynecol 1977; 128 (6): 668-76
33. Warrell DW, Taylor R. Outcomes for the fetus of mothers receiving prednisolone during pregnancy. Lancet 1968; I: 117-8
34. Bongiovanni AM, McPadden AJ. Steroids during pregnancy and possible fetal consequences. Fertil Steril 1960; 11: 181-6
35. Bulmash JM. Systemic lupus erythematosus and pregnancy. Obstet Gynecol Annu 1978; 7: 153-94
36. Turner ES, Greenberger PA, Patterson R. Management of the pregnant asthmatic patient. Ann Int Med 1980; 93: 905-18
37. Katz FH, Duncan BR. Entry of prednisolone into breast milk [letter]. N Engl J Med 1975; 293: 1154
38. Ost L, Wettrell G, Bjorkhem I, et al. Prednisolone excretion into breast milk. J Pediatr 1985; 106 (6): 1008-11
39. Greenberger PA, Odeh YK, Frederiksen MC, et al. Pharmacokinetics of prednisolone transfer to breast milk. Clin Pharmacol Ther 1993; 53 (3): 324-8
40. Klotz U, Maier K, Fischer C, et al. Therapeutic efficacy of sulfasalazine and its metabolites in patients with ulcerative colitis and Crohn's disease. N Engl J Med 1980; 303: 1499-502
41. Peppercorn MA. Sulfasalazine. Pharmacology, clinical use, toxicity, and related drug developments. Ann Intern Med 1984; 101: 377-86
42. O'Morain C, Smethurst P, Dore CJ, et al. Reversible male infertility due to sulphasalazine: studies in man and rat. Gut 1984; 25: 1078-84
43. Craxi A, Pagliarello F. Possible embryotoxicity of sulfasalazine. Arch Intern Med 1980; 140 (12): 1674
44. Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. Med J Aust 1983; 1 (11): 528-9
45. Hoo JJ, Hadro TA, Von Behren P. Possible teratogenicity of sulfasalazine [letter]. N Engl J Med 1988; 318: 1128
46. Levi S, Liberman M, Levi AJ, et al. Reversible congenital neutropenia associated with maternal sulphasalazine therapy. Eur J Pediatr 1988; 148 (2): 174-5

47. Moody AG, Probert C, Jayanthi 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 Colorectal Dis 1997; 12: 220-4
48. Willoughby CP. Fertility, pregnancy and inflammatory bowel disease. In: Allan RN, Keighley MRB, Hawkins CF, et al., editors. Inflammatory bowel disease, 2nd ed. Edinburgh: Churchill Livingstone, 1990: 547-58
49. Nielsen OH, Andreasson B, Bondesen S, et al. Pregnancy in ulcerative colitis. Scand J Gastroenterol 1983; 18: 735-42
50. Hensleigh PA, Kauffman RE. Maternal absorption and placental transfer of sulphasalazine. Am J Obstet Gynecol 1977; 127 (4): 443-4
51. Esbjorner E, Jarnerot G, Wranne L. Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. Acta Paediatr Scand 1987; 76 (1): 137-42
52. Jarnerot G, Into-Malmberg MB, Esbjorner E. Placental transfer of sulphasalazine, sulphapyridine and some of its metabolites. Scand J Gastroenterol 1981; 16: 693-7
53. Azad Khan AK, Truelove SC. Placental and mammary transfer of sulphasalazine. BMJ 1979; 2: 1553
54. Czeizel AE, Dundas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992; 327 (26): 1832-5
55. Connell WR. Safety of drug therapy for inflammatory bowel disease in pregnant and nursing women. Inflamm Bowel Dis 1996; 2: 33-47
56. Jarnerot G, Into-Malmberg MB. Sulphasalazine treatment during breast feeding. Scand J Gastroenterol 1979; 14: 869-71
57. Branski D, Kerem E, Gross-Kieselstein E, et al. Bloody diarrhea possible complication of sulfasalazine transferred through human breast milk. J Pediatr Gastroenterol Nutr 1986; 5 (2): 316-7
58. Committee on Drugs, American Academy of Paediatrics. The transfer of drugs and other chemicals into human milk. Paediatrics 1994 93 (1): 137-50
59. Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: a meta-analysis of 5 amino salicylic acid in the treatment of ulcerative colitis. Ann Intern Med 1993; 118: 540-9
60. Mulder CJJ, Tytgat GNJ, Wetermen T, et al. Double-blind comparison of slow release 5-aminosalicylate and sulfasalazine in remission maintenance in ulcerative colitis. Gastroenterology 1988; 95: 1449-53
61. Singleton JW, Hanauer SB, Gitnick GL, et al. Mesalazine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Gastroenterology 1993; 104: 1293-301
62. Messori A, Brignola C, Trallori G, et al. Effectiveness of 5-aminosalicylic acid for maintaining remission in patients with Crohn's disease: a meta-analysis. Am J Gastroenterol 1994; 89: 692-8
63. Marteau P, Nelet F, Le Lu M, et al. Adverse events in patients treated with 5-aminosalicylic acid: 1993-1994 pharmacovigilance report for Pentasa in France. Aliment Pharmacol Ther 1996; 10: 949-56
64. Meyers S, Sachar DB, Present DH, et al. Olsalazine in the treatment of ulcerative colitis among patients intolerant to sulfasalazine: a prospective, randomised, placebo-controlled. double-blind, dose-ranging clinical trial. Scand J Gastroenterol 1988; 23: 29-37
65. Diav-Citrin O, Park YH, Veerasuntharam G, et al. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. Gastroenterology 1998; 114: 23-8
66. Lundberg C, Asberg I, Smedegard G, et al. 5-aminosalicylic acid (5-ASA)-induced nephrotoxicity is dose dependent in rats [abstract]. Gastroenterology 1996; 112: A952
67. Marteau P, Devaux CB. Mesalazine during pregnancy. Lancet 1994; 344: 1708-9
68. Segars LW, Gales BJ. Mesalamine and olsalazine: 5-aminosalicylic acid agents for the treatment of inflammatory bowel disease. Clin Pharm 1992; 11 (6): 514-28
69. Christensen LA, Rasmussen SN, Hansen SH. Disposition of 5-aminosalicylic acid and N-acetyl-5-aminosalicylic acid in fetal and maternal body fluids during treatment with different 5-aminosalicylic acid preparations. Acta Obstet Gynecol Scand 1994; 74 (5): 399-402
70. Colombel J, Brabant G, Gubler M, et al. Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? Lancet 1994; 344: 620-1
71. Habal FM, Hui G, Greenberg GR. Oral 5-aminosalicylic acid for inflammatory bowel disease in pregnancy: safety and clinical course. Gastroenterology 1993; 105 (4): 1057-60
72. Trallori G, d'Albasio G, Bardazzi G, et al. 5-Aminosalicylic acid in pregnancy: clinical report. Ital J Gastroenterol 1994; 26: 75-8
73. Bell CM, Habal FM. Safety of topical 5-aminosalicylic acid in pregnancy. Am J Gastroenterol 1997; 92 (12): 2201-2
74. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. Lancet 1993; 342: 618-9
75. Nelis GF. Diarrhoea due to 5-aminosalicylic acid in breast milk [letter]. Lancet 1989; I: 383
76. Ito S, Blajchman A, Stephenson M, et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol 1993; 168: 1393-9
77. Ginsberg AL, Davis ND, Nochomovitz LE. Placebo-controlled trial of ulcerative colitis with oral 4-aminosalicylic acid Gastroenterology 1992; 102 (2): 448-52
78. Schreiber S, Howaldt S, Raedler A. Oral 4-aminosalicylic acid versus 5-aminosalicylic acid slow release tablets: double blind, controlled pilot study in the maintenance treatment of Crohn's ileocolitis. Gut 1994; 35 (8): 1081-5
79. Present DH, Meltzer SJ, Krumholz MP, et al. 6-mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. Ann Intern Med 1989; 111: 641-9
80. O'Donoghue DP, Dawson AM, Powell-Tuck J, et al. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. Lancet 1978; II: 955-7
81. Voogd CE. Azathioprine, a genotoxic agent to be considered non-genotoxic in man. Mutat Res 1989; 221 (2): 133-52
82. Githens JH, Rosenkrantz JG, Tunnock SM. Teratogenic effects of azathioprine (Imuran). J Pediatr 1965; 66: 962-3
83. Rosenkrantz JG, Githens JH, Cox SM, et al. Azathioprine (Imuran) and pregnancy. Am J Obstet Gynecol 1967; 97: 387-94
84. Tuchmann-Duplessis H, Mercier-Parot L. Production in rabbits of malformations of the limbs by administration of azathioprine and 6-mercaptopurine. C R Seances Soc Biol Fil 1966; 166 (3): 501-6
85. Bermas BL, Hill JA. Effects of immunosuppressive drugs during pregnancy. Arthritis Rheum 1995; 38 (12): 1722-32
86. Reimers TJ, Sluss PM. 6-mercaptopurine treatment of pregnant mice: effects on second and third generations. Science 1978; 201: 65-7
87. 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

88. Ramsey-Goldman R, Schilling E. Immunosuppressive drug use during pregnancy. Rheum Dis Clin North Am 1997; 23 (1): 149-67
89. Alstead EM, Ritchie JK, Lennard-Jones JE, et al. Safety of azathioprine in pregnancy in inflammatory bowel disease. Gastroenterology 1990; 99 (2): 443-6
90. Davison JM. Pregnancy in renal allograft recipients: prognosis and management. Ballieres Clin Obstet Gynaecol 1987; 1 (4): 1027-45
91. Baxi LV, Rho RB. Pregnancy after cardiac transplantation. Am J Obstet Gynecol 1993; 169 (1): 33-4
92. Haagsma EB, Visser GHA, Klompmaker IJ, et al. Successful pregnancy after orthotopic liver transplantation. Obstet Gynecol 1989; 74: 442-3
93. Ramsey-Goldman R, Mientus JM, Kutzer JE, et al. Pregnancy outcome in women with systemic lupus erythematosus treated with immunosuppressive drugs. J Rheum 1993; 20 (7): 1152-7
94. Penn I, Makowski EL, Harris P. Parenthood following renal transplantation. Kidney Int 1980; 18: 221-33
95. Roubenoff R, Hoyt J, Petri M, et al. Effects of antiinflammatory immunosuppressive drugs on pregnancy and fertility. Semin Arthritis Rheum 1988; 18: 88-110
96. Whetham JCG, Cardella C, Harding M. Effect of pregnancy on graft function and graft survival in renal cadevar transplant patients. Am J Obstet Gynecol 1983; 145: 193-7
97. Wagoner LE, Taylor DO, Olsen SL, et al. Immunosuppressive therapy, management, and outcome of heart transplant recipients during pregnancy. J Heart Lung Transplant 1994; 13: 993-1000
98. Brown JH, Maxwell AP, McGeown MG. Outcome of pregnancy following renal transplantation. Ir J Med Sci 1991; 160: 255-6
99. Marushak A, Weber T, Bock J, et al. Pregnancy following kidney transplantation. Acta Obstet Gynaecol Scand 1986; 65: 557-9
100. O'Donnell D, Sevitz H, Seggie JL. Pregnancy after renal transplantation. Aust N Z J Med 1985; 15: 320-5
101. The Consultative Council on Obstetrics and Paediatric Mortality and Morbidity. Annual report for the year 1997: incorporating the 36th Survey of Perinatal Deaths in Victoria. Melbourne, 1998: 39
102. Pirson Y, van Lierde M, Ghysen J, et al. Retardation of fetal growth in patients receiving immunosuppressive therapy [letter]. N Engl J Med 1985; 313 (5): 328
103. Little BB. Immunosuppressant therapy during gestation. Semin Perinatol 1997; 21 (2): 143-8
104. Briggs GG, Freeman RK, Yaffe SJ, editors. Drugs in pregnancy and lactation. 4th ed. Baltimore (MA): Williams and Wilkins, 1994: 80
105. DeWitte DB, Buick MK, Cyran SE, et al. Neonatal pancytopenia and severe combined immunodeficiency associated with antenatal administration of azathioprine and prednisone. J Pediatr 1984; 105: 625-8
106. Cote CJ, Meuwissen HJ, Pickering RJ. Effects on the neonate of prednisolone and azathioprine administered to the mother during pregnancy. J Pediatr 1974; 85 (3): 324-8
107. Davison JM, Dellagrammatikas H, Parkin JM. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. Br J Obstet Gynaecol 1985; 92: 233-9
108. Huynh LA, Min DI. Outcomes of pregnancy and the management of immunosuppressive agents to minimise fetal risks in organ transplant patients. Ann Pharmacotherapy 1994; 28: 1355-7
109. Ostrer H, Stamberg J, Perinchief P. Two chromosome aberrations in the child of a woman with systemic lupus erythematosus treated with azathioprine and prednisone. Am J Med Genet 1984; 17: 627-32
110. Leb DE, Weisskopf B, Kanovitz BS. Chromosome aberrations in the child of a kidney transplant recipient. Arch Int Med 1971; 128 (3): 441-4
111. Francella A, Dayan A, Rubin P, et al. 6-mercaptopurine is safe therapy for child bearing patients with inflammatory bowel disease (IBD): a case controlled study [abstract]. Gastroenterology 1996; 112 (4): A909
112. Marion JF. Toxicity of 6-mercaptopurine/ azathioprine in patients with inflammatory bowel disease. Inflamm Bowel Dis 1998; 2: 116-7
113. Rajapakse RO, Korelitz BI, Zlatanic J, et al. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease [abstract]. Gastroenterology 1998; 114: A1066
114. Grekas DM, Vasiliou SS, Lazarides AN. Immunosuppressive therapy and breast-feeding after renal transplantation [letter]. Nephron 1984; 37: 68
115. Lichtiger S, Present D, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994; 330: 1841-5
116. Sandborn WJ. A review of immune modifier therapy for inflammatory bowel disease: azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. Am J Gastroenterol 1996; 91 (3): 423-33
117. Ryffel B, Donatsch P, Madorin M, et al. Toxicological evaluation of cyclosporin A. Arch Toxicol 1983; 53: 107-41
118. Brown PAJ, Gray ES, Whiting PH, et al. Effects of cyclosporin A on fetal development in the rat. Biol Neonate 1985; 48: 172-80
119. Mason RJ, Thomson AW, Whiting PH, et al. Cyclosporine-induced fetotoxicity in the rat. Transplantation 1985; 39: 9-12
120. Al-Chalabai HA. Effect of cyclosporin A on the morphology and function of the ovary and fertility in the rabbit. Int J Fertil 1984; 29: 218-23
121. Seethalakashmi L, Flores C, Carboni AA, et al. Cyclosporine: its effects on testicular function and fertility in the prepubertal rat. J Androl 1990; 11: 17-24
122. Lamarque V, Leleu MF, Monka C, et al. Analysis of 629 outcomes in transplant recipients treated with Sandimmun. Transplant Proc 1997; 29: 2480
123. Armenti VT, Ahlswede KM, Ahlswede BA, et al. National transplantation pregnancy registry: outcomes of 154 pregnancies in cyclosporin-treated female kidney transplant recipients. Transplantation 1994; 57 (4): 502-6
124. Haugen G, Fauchald P, Sodal G, et al. Pregnancy outcome in renal allograft recipients: influence of ciclosporin A. Eur J Obstet Gynecol Reprod Biol 1991; 39: 25-9
125. Ostensen M. Treatment with immunosuppressive and disease modifying drugs during pregnancy and lactation. Am J Reprod Immunol 1992; 28: 148-52
126. Shaheen FAM, Al-Sulaiman MH, Al-Khader AA. Long-term nephrotoxicity after exposure to cyclosporine in utero. Transplantation 1993; 56 (1): 224-5
127. Roll C, Luboldt HJ, Winter A, et al. Hepatoblastoma in a 2-year-old child of a liver-transplanted mother. Lancet 1997; 349: 103
128. Anderson JB, Turner GM, Williamson RCN. Fulminant ulcerative colitis in late pregnancy and the puerperium. J R Soc Med 1987; 80: 492-4
129. Bertschinger P, Himmelmann A, Risti B, et al. Cyclosporine treatment of severe ulcerative colitis during pregnancy [comment]. Am J Gastroenterol 1995; 90 (2): 330

130. 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 (1): 60-3
131. Thiru Y, Bateman DN, Coulthard MG. Successful breast feeding while mother was taking cyclosporin. BMJ 1997; 315: 463
132. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. N Engl J Med 1995; 332: 292-7
133. Subhani JM, Hamilton MI. Review article: the management of inflammatory bowel disease during pregnancy. Aliment Pharmacol Ther 1998; 12: 1039-53
134. Milunsky A, Graef JW, Gaynor MF. Methotrexate-induced congenital malformations. J Pediatr 1968; 72: 790-5
135. Powell HR, Ekert H. Methotrexate-induced congenital malformations. Med J Aust 1971; 2: 1076-7
136. Feldkamp M, Carey JC. Clinical teratology counselling and consultation case report: low dose methotrexate exposure in the early weeks of pregnancy. Teratology 1993; 47 (6): 533-9
137. 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 (6): 589-92
138. 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 (5); 971-3
139. Nicholson HO. Cytotoxic drugs in pregnancy: a review of reported cases. J Obstet Gynaecol 1968; 75: 307-12
140. Pizzuto J, Aviles A, Noriega L, et al. Treatment of acute leukemia during pregnancy: presentation of nine cases. Cancer Treat Rep 1980; 64: 79-83
141. Schleuning M, Clemm C. Chromosomal aberrations in a newborn whose mother received cytotoxic treatment during pregnancy. N Engl J Med 1987; 317: 1666-7
142. Johns DG, Rutherford LD, Leighton PC, et al. Secretion of methotrexate into human milk. Am J Obstet Gynecol 1972; 112: 978-80
143. Ursing B, Alm T, Barany F, et al. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden: II: results. Gastroenterology 1982; 83 (3): 550-62
144. Rutgeerts P, Hiele M, Geboes K, et al. Controlled trial of metronidazole for the prevention of Crohn's recurrence after ileal resection. Gastroenterology 1995; 108: 1617-21
145. Dashe JS, Gilstrap LC. Antibiotic use in pregnancy. Obstet Gynecol Clin North Am 1997; 24 (3): 617-29
146. Heisterberg L. Placental transfer of metronidazole in the first trimester of pregnancy. J Perinatol Med 1984; 12: 43-5
147. Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. Am J Obstet Gynecol 1995; 172: 525-9
148. Caro-Paton T, Carvajal A, de Diego IM, et al. Is metronidazole teratogenic?: a meta-analysis. Br J Clin Pharmacol 1997; 44 (2): 179-82
149. Dobias L, Cerna M, Rossner P, et al. Genotoxicity and carcinogenicity of metronidazole. Mutat Res 1994; 317: 177-94
150. Erikson SH, Oppenheim GL, Smith GH. Metronidazole in breast milk. Obstet Gynecol 1981; 57 (1): 48-50
151. Clements CJ. Metronidazole and breast feeding. N Z Med J 1980; 92: 329
152. Berkovitch M, Pastuszak A, Gazarian M, et al. Safety of the new quinolones in pregnancy. Obstet Gynecol 1994; 84 (4): 535-8
153. Mayer DG. Overview of toxicological studies. Drugs 1987; 34 Suppl. 1: 150-3
154. Schluter G. Ciprofloxacin: toxicologic evaluation of additional safety data. Am J Med 1989; 87 Suppl. 5A: 37-9
155. Giamarellou H, Kolokythas E, Petrikkos G, et al. Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am J Med 1989; 87 (5A): 49S-51S

Correspondence and reprints: Dr *William Connell,* St Vincent's Hospital, Victoria Parade, Fitzroy, Victoria 3065, Australia.
E-mail: connelwr@svhm.org.au