

Clinical Review

Safety of Drug Therapy for Inflammatory Bowel Disease in Pregnant and Nursing Women

William R. Connell

Department of Gastroenterology, St. Vincent's Hospital, Victoria, Australia

Summary: Drug therapy is justified in pregnant patients with active inflammatory bowel disease. Selection of medical treatment depends on disease severity and the potential for fetal toxicity. Preferably, pregnancy should be planned to coincide with periods of disease quiescence, so that drug requirements can be minimized. Sulfasalazine and prednisolone are clearly safe in pregnancy and lactation. Preliminary studies suggest that low-to-moderate-dose mesalazine is well tolerated in pregnant and nursing mothers. Immunosuppressive therapy during pregnancy in transplant and nontransplant recipients may be associated with an increased risk of fetal growth retar-

ation and prematurity. The risk of congenital malformations from azathioprine and cyclosporin is not markedly increased, although exposure to methotrexate during the first trimester may cause fetal loss and characteristic anomalies. Short-term therapy with metronidazole in the first trimester is not associated with an increased risk of teratogenicity, although the safety of this drug in pregnancy as primary therapy for Crohn's disease using higher doses for prolonged periods has not been confirmed. **Key Words:** Pregnancy—Drug therapy—Lactation.

Inflammatory bowel disease commonly affects young adults, many of whom wish to have children themselves. Fertility is normal in women with ulcerative colitis, but is possibly reduced with active Crohn's disease (1,2). The main factor determining the outcome of pregnancy in inflammatory bowel disease is the activity of the condition. Provided inflammation is well controlled during pregnancy, especially at the time of conception, the risk of fetal complications is not increased. In contrast, pregnant women with active disease are at greater risk of spontaneous or therapeutic abortion and of delivering premature or low-birth-weight infants (1,3-5). Moreover, emergency surgery for severe colitis during pregnancy is particularly hazardous for mother and fetus (6).

The need to maintain disease control, preferably

before conception, is an important issue for couples contemplating pregnancy. Although there is a general reluctance to use any medication during pregnancy, drug therapy is indicated in patients with active inflammatory bowel disease. The choice of appropriate therapy during pregnancy depends on the severity of the underlying condition and the potential risk of drug toxicity to the fetus. Although clinical experience has provided valuable information regarding the safety of established treatments for inflammatory bowel disease in pregnancy and lactation, the effects of newer and more potent drugs are largely theoretical, because clinical studies are rare and results from animal experiments may not apply to humans. Controlled studies have not been undertaken in which the fetal effects of drug therapy for inflammatory bowel disease, independent of disease activity, are compared with the expected incidence of congenital malformations and other fetal complications in the nontreated, healthy population. At present, management decisions regarding the suitability of these drugs in the pregnant

Address correspondence and reprint requests to Dr. W.R. Connell at Department of Gastroenterology, St. Vincent's Hospital, 41 Victoria Parade, Fitzroy 3065, Victoria, Australia.

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or nursing mother with inflammatory bowel disease depend on preliminary data or the reported experience with these agents in other illnesses.

AMINOSALICYLATES

Sulphasalazine

Sulphasalazine is deconjugated by colonic bacteria into its active component, 5-aminosalicylic acid, and the inactive carrier, sulphapyridine. Oral sulphasalazine is superior to placebo for the induction and maintenance of remission in mild to moderately active ulcerative colitis (7-9), and is beneficial for the treatment of mild to moderately active Crohn's colitis and ileocolitis. Because it is effective, cheap, and generally well tolerated, sulphasalazine is widely used in women of reproductive age with inflammatory bowel disease.

Fertility

Sulphasalazine causes reversible infertility in the male, due to oligospermia, reduced sperm motility and an increased proportion of abnormal forms. These effects are probably related to the sulphapyridine moiety (10). Fertility is neither impaired nor improved in women receiving sulphasalazine for inflammatory bowel disease.

Teratogenicity

There is no evidence of teratogenicity due to sulphasalazine from animal studies. Sulphonamide exposure to pregnant rats has resulted in skeletal anomalies and cleft palate in their offspring (11), but neither sulphapyridine nor salicylate ingestion are known to be teratogenic in humans (12). Anecdotal reports of congenital anomalies have been described in children of women treated with sulphasalazine during pregnancy (13-16). There is no characteristic pattern to these malformations, and a direct effect of the drug has not been proven. In contrast, considerable clinical experience has shown sulphasalazine to be quite safe during pregnancy (1,3,4,17-24). According to the results of a national survey that reviewed the outcome of 531 pregnancies in women with inflammatory bowel disease, the frequency of developmental defects in babies of mothers treated with sulphasalazine was no greater than that reported in the general population (3). In a separate study, a slight excess of fetal

malformations occurred among mothers taking sulphasalazine for active ulcerative colitis at conception, a finding that was thought to be due to disease activity rather than drug therapy (1). Sulphasalazine is associated with antifolate activity, and it is noteworthy that neural tube defects do not appear to be increased in babies of pregnant women treated with this agent, given the recent evidence that such defects can be prevented by folic acid supplementation during pregnancy (25).

Fetal Growth and Prematurity

In the national survey, the frequency of fetal complications among 181 women treated with sulphasalazine for inflammatory bowel disease during pregnancy was less than that reported in the general population and no different than that recorded in 244 women with inflammatory bowel disease who were untreated during pregnancy (3).

Chromosomal Effects

In vitro testing of human lymphocytes indicates that sulphasalazine may induce sister-chromatid exchange and micronuclei (26). The significance of this finding in individuals exposed to the drug antenatally has not been specifically studied. Although there is no evidence showing sulphasalazine to be associated with the future development of malignancy, recent studies suggest that vigorous medical therapy with agents such as sulphasalazine may actually reduce the risk of colorectal carcinoma in ulcerative colitis (27).

Placental and Breast Transfer

Sulphasalazine and sulphapyridine cross the placenta, resulting in cord concentrations similar to those in the maternal serum (28). Elimination of the drug by neonates is slower than by adults. Theoretically, neonatal kernicterus may develop due to displacement by sulphapyridine of bilirubin from albumin in the baby's blood. In practice, however, no cases of kernicterus have been reported, and the concentrations of sulphasalazine or sulphapyridine transferred to the fetus appear insufficient to cause this complication (29). Moreover, the intact sulphasalazine molecule preferentially binds to albumin at sites other than the high-affinity site for bilirubin (30). Concentrations of sulphasalazine or sulphapyridine transferred via breast milk are

negligible, and this agent does not appear to present any hazard to the breastfed, healthy term infant (24,31).

Summary

Pregnant or nursing mothers with mild to moderately active ulcerative colitis or Crohn's disease can be safely treated with oral sulphasalazine. Clinical experience does not indicate this agent to be teratogenic or associated with an increased risk of fetal complications. When the drug is required to maintain a quiescent state of disease, there is no indication to discontinue sulphasalazine. Folate supplementation is advisable in women treated with this agent who are planning pregnancy and in those who conceive while taking this drug.

Other 5-Aminosalicylic Acid Compounds

Newer preparations of 5-aminosalicylic acid that lack the sulphapyridine moiety of sulphasalazine have been developed to deliver 5-aminosalicylic acid to the distal intestine either by using a slow or delayed release system (mesalazine/mesalamine) or an alternative carrier to sulphapyridine (olsalazine). Pharmacologically, these agents differ in terms of site of release and systemic absorption of 5-aminosalicylic acid, although clinical trials have not yet clarified the unique benefits of individual formulations. Oral olsalazine and mesalazine are as effective as sulphasalazine in inducing and maintaining remission in moderately active ulcerative colitis. Oral mesalazine is efficacious in mild to moderate Crohn's disease at doses 3.2–4.0 g per day (32,33), and appears to be superior to placebo in maintaining remission in Crohn's disease, especially Crohn's ileitis (34,35). Topical mesalazine is effective therapy for distal colitis. 5-aminosalicylic acid drugs are well tolerated and have increasing application in the management of mild to moderate inflammatory bowel disease.

Fertility

Unlike sulphasalazine, 5-aminosalicylic acid agents do not impair male fertility.

Teratogenicity, Fetal Growth, and Prematurity

There is no convincing evidence from animal studies that mesalazine or olsalazine are teratogen-

ic. Clinical data in humans regarding the safety of 5-aminosalicylic acid in pregnancy and lactation are scarce, although the results of a recently published study are encouraging. In that report, 17 women with inflammatory bowel disease were treated with oral mesalazine (Asacol) at a mean dose of 1.7 g per day throughout their pregnancy. None of the neonates had evidence of any clinical or biochemical abnormalities. One woman miscarried, although she later had a successful pregnancy with 5-aminosalicylic acid (36).

Renal Effects

According to one case report, maternal use of mesalazine was attributed to causing renal insufficiency in a newborn baby, on the basis of chronological linkage between exposure to mesalazine and discovery of renal hyperechogenicity, and on the absence of other causes of congenital renal disease. Mesalazine (Pentasa) was given for Crohn's disease between the 3rd and 5th month of pregnancy, initially at a dose of 4 g per day and tapered to 2 g per day, 6 weeks later. Ultrasound at 17 weeks was normal, but 4 weeks later revealed bilateral renal hyperechogenicity. At birth, the infant had a raised creatinine level, and a renal biopsy showed focal tubulointerstitial lesions (37). A subsequent letter from the manufacturers reported the absence of nephrotoxicity in 60 women treated with Pentasa during pregnancy (38).

Chromosomal Effects

There are no reports associating 5-aminosalicylic acid with chromosomal anomalies. In contrast to sulphasalazine, *in vitro* testing of human lymphocytes found that 5-aminosalicylic acid did not induce sister-chromatid exchange or micronuclei (26).

Placental and Breast Transfer

After oral or rectal administration, 5-aminosalicylic acid crosses the placenta and enters breast milk at low concentrations (39). Maternal and fetal plasma levels of 5-aminosalicylic acid and the metabolite, *N*-acetyl-5-aminosalicylic acid, were measured at delivery in women who had inflammatory bowel disease and who were treated with various 5-aminosalicylic acid preparations (Asacol, Pentasa, Dipentum, Mesasal). In nine women, concentrations of 5-aminosalicylic acid were lower in the

fetus than in the mother, and concentrations of *N*-acetyl-5-aminosalicylic acid were similar in the fetal and maternal circulations (40). In this study, small amounts of 5-aminosalicylic acid and *N*-acetyl-5-aminosalicylic acid were excreted in the breast milk of 13 women (40). This finding supports the results of two other reports that showed only small amounts of 5-aminosalicylic acid are excreted into breast milk, even with oral doses up to 3 g per day (39,41).

Although 5-aminosalicylic acid therapy appears to be safe during breastfeeding, the induction of watery diarrhea in infants may represent a rare allergic reaction. A breastfed baby whose mother was treated with mesalazine rectally (500 mg twice daily) developed watery diarrhea within 12 h of the first dose. The diarrhea improved after cessation of mesalazine, but recurred within 10 h each time the agent was reintroduced on four separate occasions (42). In eight mothers who used mesalazine during lactation, one reported diarrhea in her infant (43).

Summary

Oral mesalazine (Asacol) at low to moderate doses appears to be safe in pregnancy. A single case report has raised concerns about possible renal insufficiency occurring in an infant exposed to a high dose of oral mesalazine (Pentasa, 4 g per day) in the mid trimester. Until this possible association is clarified, high-dose formulations of mesalazine with high systemic concentrations should be used cautiously, and only when alternative treatment is unsuitable or ineffective. Published clinical information concerning the safety of olsalazine in pregnancy is limited. Although the concentration of 5-aminosalicylic acid excreted into breast milk is small, nursing mothers receiving oral or topical 5-aminosalicylic acid compounds should be aware that these agents may cause an allergic reaction in breastfed infants consisting of acute watery diarrhea, which subsides after the drug is discontinued.

CORTICOSTEROIDS

Corticosteroids remain the mainstay of therapy for inducing remission in moderately severe inflammatory bowel disease. These agents may be administered orally, rectally, or intravenously. Corticosteroids cross the placenta but are converted by the fetus to relatively inactive metabolites, resulting in

only 10–12% of blood concentrations seen in the maternal circulation (44).

Teratogenicity

Animal studies have demonstrated a dose-related effect on fetal growth in mice and rats (45–47) and a dose-dependent increased frequency of cleft palate in the offspring of pregnant mice, rabbits, and hamsters given prednisone or prednisolone during pregnancy (48–51). Other reports show a dose-dependent increased frequency of congenital abnormalities and behavioral alterations among offspring of mice treated with corticosteroids during pregnancy (46–49,52). In contrast to these animal studies, there is no evidence of teratogenicity from corticosteroids in humans.

Fetal Growth and Prematurity

An increased frequency of stillbirths (53), and reduction in fetal birth weight (45) have been reported among pregnant women receiving prednisolone for asthma and connective tissue disorders. However, the general experience with corticosteroids in pregnancy for inflammatory bowel disease (3,17–23), rheumatoid arthritis, systemic lupus erythematosus, and asthma (54–59) show considerable evidence of its safety when used judiciously and is justified by the severity of the underlying illness in the mother. In the national survey that reviewed the outcome of pregnancies in inflammatory bowel disease, fetal morbidity and mortality were no greater among 185 women receiving steroids alone or in combination with sulphasalazine than that reported in the general population (3). In comparison to untreated pregnant women with inflammatory bowel disease, the frequency of fetal complications was higher among patients who received corticosteroids for Crohn's disease but not ulcerative colitis. This effect was thought to be due to the underlying disease rather than corticosteroid therapy (3).

Other Effects

Theoretically, suppression of the fetal hypothalamic–pituitary–adrenal axis may arise from maternal corticosteroid use during pregnancy. However, a suppressive fetal blood concentration usually is not achieved with normal therapeutic doses. Measurement of cortisol secretion in eight neonates exposed to corticosteroids during pregnancy revealed

no evidence of adrenal suppression (60). Isolated cases of adrenal insufficiency (61), thymic hypoplasia (62), and premature rupture of membranes (63) have been described in transplant recipients receiving corticosteroids during pregnancy.

Lactation

Prednisolone crosses breast milk at concentrations ranging from 5 to 25% of maternal serum levels (64). Although the milk:plasma ratio varies with increasing serum concentrations, the amounts measured even at high therapeutic doses do not appear to be clinically significant (64). The American Academy of Pediatrics considers prednisolone to be compatible with breast feeding (65).

Summary

When clinically required to induce remission of disease, corticosteroids administered orally, topically, or intravenously can be given safely to pregnant or nursing mothers with active ulcerative colitis or Crohn's disease. The risk of congenital anomalies is not increased in humans, and fetal complications are no higher than that seen in the general population. There is no reason to withdraw cortisone during pregnancy or breastfeeding if this drug is required to control disease activity. Neonates should be observed for evidence of adrenal insufficiency, and supplemental steroids should be given during labor to mothers receiving glucocorticoid therapy.

IMMUNOSUPPRESSIVES

Azathioprine, 6-Mercaptopurine

Azathioprine is used in the management of chronic active inflammatory bowel disease as a steroid-sparing agent and to prevent disease recurrence (66–69). Little data are available regarding the safety of azathioprine for inflammatory bowel disease in pregnancy, and most experience emanates from organ transplant recipients. The reported effects of azathioprine on the fetus include congenital malformations, chromosomal aberrations, immunosuppression, hemopoietic disturbances, prematurity, and growth retardation.

Teratogenicity

Azathioprine is teratogenic to animals, thought to be due to inhibition of protein synthesis. When given to mice in high doses shortly after conception, embryonic resorption has been observed to be 40–100% (70). An increased incidence of limb malformations, ocular anomalies, and cleft palate have been reported in the offspring of experimental rabbits and mice treated with high doses of azathioprine (71–73). In pregnant rats treated with azathioprine at doses within the therapeutic human range, the rate of malformations in offspring was not increased, although a greater frequency of fetal loss and growth retardation was observed (72,74,75).

In humans, physical malformations have been reported in up to 9% of babies whose mothers were treated with azathioprine during pregnancy for renal transplantation (61,76,77). However, no consistent representation of any particular congenital defect is evident in these series, and the effects of renal disease, hypertension and other drug therapy could possibly have contributed to some of the anomalies. Many studies show the frequency of congenital malformations among transplant and non-transplant recipients treated with azathioprine during pregnancy to be no different from that reported in the general population (78–83). In a comprehensive review of published reports, the estimated prevalence of congenital malformations among a total of 487 women treated with azathioprine during pregnancy was 4.3% (95% confidence interval, 2.7–6.6%) (78). For comparison, the rate of congenital anomalies in the Australian community is reportedly 3.9% (84).

Fetal Growth and Prematurity

Although exposure to azathioprine does not seem to markedly increase the frequency of congenital anomalies or fetal death in humans, its use in pregnancy is commonly associated with fetal growth retardation and prematurity. Approximately 20–40% of infants of transplant recipients are small for gestational age (82,85). Although reduced renal function and hypertension may have been a contributing factor in these patients, immunosuppressive agents have been directly associated with growth retardation in rats (74) and implicated in humans (85). In women who received azathioprine for systemic lupus erythematosus before or during pregnancy, adverse fetal outcomes occurred in 8 of 15 pregnan-

cies, including 1 neonatal complication, 2 miscarriages, 2 cases of growth retardation, and 3 preterm infants, 1 of whom died. No congenital malformations were reported. These results are similar to a fetal complication rate of 57% and fetal or neonatal death rate of 27% that occurred in pregnancies in which lupus was not treated with immunosuppressive therapy (86).

Fertility

The effects of azathioprine on fertility in humans have not been directly studied, although current evidence suggests it probably does not cause infertility (78).

Chromosomal Effects

Chromosomal aberrations including sister-chromatid exchanges, chromatin gaps, and chromosome deletions and fragments have been reported in nonpregnant renal transplant recipients treated with azathioprine (62,70,87). The relationship of the drug to these findings is not clear. One child was born with two separate *de novo* constitutional chromosomal anomalies after the use of azathioprine during pregnancy in a mother with systemic lupus erythematosus (88). Transient chromosomal aberrations have been detected in the lymphocytes of infants born to renal transplant mothers, although these disturbances disappeared within 5–32 months (61, 62,89). It is unknown whether these abnormalities persist in other tissues not studied, such as germ cells, and if this was the case, abnormalities may not become apparent until the next generation (89). No studies have specifically assessed the risk of long-term complications from possible chromosomal aberrations, such as neoplasia, among individuals exposed to immunosuppressive agents antenatally, although clinical experience to date is reassuring (61,77,85).

Immunosuppression

Azathioprine and 6-mercaptopurine readily crosses the placenta, but can only be detected in trace amounts in fetal blood (90). The major circulating metabolite in the fetus, 6-thioguanine, is inactive (90). During organogenesis, the fetal liver lacks the enzyme inosinate pyrophosphorylase, which converts azathioprine to its active metabolite, thioinosinic acid (91). Nevertheless, isolated

cases of neonatal immunosuppression have been reported. One newborn whose mother received 150 mg of azathioprine and 30 mg prednisolone daily throughout her pregnancy developed lymphopenia, diminished thymic radiographic shadowing, and low serum concentrations of immunoglobulins M and G. Although the immune status normalized by 15 weeks of age, its impairment at birth may have contributed to persistent cytomegalovirus infection in the neonate (92). Defective coupling of surface receptors to signal-transducing proteins in T lymphocytes resulting in a failure of lymphocyte activation was implicated in the development of immune deficiency in a 9-year-old boy exposed to azathioprine antenatally (93). Follow-up studies of children exposed to azathioprine antenatally revealed accelerated T-cell development but no clinical evidence of immunodeficiency or autoimmunity (94).

Myelotoxicity

Maternal immunosuppression by azathioprine during pregnancy can depress fetal hemopoiesis and result in neonatal thrombocytopenia and leukopenia with potentially serious sequelae. A transplant recipient treated with 125 mg of azathioprine and 12.5 mg prednisolone daily delivered a baby who eventually died at 28 days from complications of pancytopenia and severe combined immune deficiency (95). Nonfatal cases of neonatal lymphopenia and thrombocytopenia have also been reported (61,62, 76,96,97). To reduce the risk of fetal myelotoxicity, an adjustment in the dose of azathioprine has been recommended in the third trimester (97). In a study of 10 infants born to mothers receiving azathioprine for renal transplantation, neonatal bone marrow suppression was less common when the dose of azathioprine was reduced for maternal white blood cell counts $<10,000/\text{cm}^3$ at 32 weeks gestation (97).

Paternal Use of Azathioprine

The risk to infants born to fathers using azathioprine at the time of conception is less clear. In one study, 58 of 60 babies born to fathers treated with azathioprine at the time of conception were normal. One infant with a family history of spina bifida had a large myelomeningocele. The remaining infant died from multiple congenital abnormalities including microcephaly and polycystic kidneys (61). A child whose father was taking azathioprine for in-

inflammatory bowel disease at the time of conception developed a Wilm's tumor of the kidney at the age of 4 years (98).

Experience in Inflammatory Bowel Disease

Until recently, women using azathioprine or 6-mercaptopurine for inflammatory bowel disease were advised to avoid pregnancy or undergo termination if conception occurred while taking the drug (20,22,23,98). A preliminary study was reported by Alstead et al. in which 12 patients with Crohn's disease and 2 with extensive ulcerative colitis conceived during azathioprine therapy at a daily dose of 2 mg/kg. Two patients elected to have their pregnancy terminated, and five others discontinued the drug within 16 weeks of conception. The remaining seven mothers decided to continue azathioprine during the entire pregnancy. One baby was born prematurely at 32 weeks, and healthy twins were delivered at 35 weeks. Apart from one neonate born with hepatitis B virus to a hepatitis B carrier, no perinatal complications or congenital anomalies occurred. Follow-up of these children for 6 months–16 years revealed no abnormality of growth or development, and no malignancies (99).

In another study, no congenital abnormalities were detected in three neonates born to women who conceived while taking 6-mercaptopurine for inflammatory bowel disease. All three mothers discontinued the drug within 4 weeks of conception (98). In a separate account reported by the same authors, no difference was observed in the outcome of children born to mothers who were treated with 6-mercaptopurine before or at the time of conception for inflammatory bowel disease in comparison to a control group of patients who required 6-mercaptopurine after pregnancy (100).

Lactation

Azathioprine is excreted into breast milk in small amounts. Three infants breastfed by mothers receiving azathioprine after renal transplantation did not have disturbances in blood analyses or growth rates (101,102). Until further information is available regarding the effect of azathioprine on nursing infants, however, breastfeeding is not recommended in mothers treated with this drug (63,103).

Summary

Azathioprine use during pregnancy may be associated with fetal growth retardation and prematu-

rity, as well as a small risk of congenital malformations, immunosuppression, and myelotoxicity to the fetus. The significance of incidental, transient chromosomal aberrations in infants of transplant recipients treated with azathioprine is unknown. Clinical studies indicate that the fetal risk is not sufficient to warrant mandatory termination of pregnancy when women inadvertently conceive while receiving the drug. The elective use of azathioprine for inflammatory bowel disease during pregnancy may be indicated if it is the most effective agent to control disease activity, provided the potential risks to the fetus are clearly explained to the patient. Theoretical concerns about paternal use of azathioprine at the time of conception do not appear to have been substantiated from clinical experience. Breastfeeding is not recommended in mothers receiving azathioprine.

Cyclosporin

Cyclosporin is a fungal peptide that suppresses interleukin-2 production by T-helper lymphocytes, resulting in reversible impairment of cell-mediated immunity and T-cell-dependent humoral immunity. Although cyclosporin is effective in the short-term treatment of severe ulcerative colitis, its overall place in the management of inflammatory bowel disease has not been clarified (104). With a single exception (105), there are no reported data regarding the use of this drug in pregnant women with inflammatory bowel disease. However, the experience with cyclosporin in other conditions such as organ transplantation provides valuable information about its effects on pregnant women.

Cyclosporin crosses the placenta, producing blood levels in the fetus 30–64% of that in the maternal circulation (106–109). High concentrations of cyclosporin metabolites have been detected in the placenta, indicating the presence of metabolizing enzymes in this tissue (110). Cyclosporin requirements seem to increase during the third trimester, although not invariably (111).

Fertility

Although ovarian toxicity was observed in female rabbits treated with 15 mg/kg of cyclosporin (112), this has not been demonstrated in humans (113). Prepubertal male rats exposed to cyclosporin had reduced testosterone production, spermatogenesis

and fertility (114). Cyclosporin is not known to interfere with testicular function in humans.

Teratogenicity

According to animal studies, cyclosporin is neither myelotoxic, mutagenic, carcinogenic, nor teratogenic (115). The frequency of congenital malformations is not increased in rats, mice, or rabbits administered cyclosporin (115–117). Although congenital anomalies have been reported in humans exposed to cyclosporin in utero, there is no definite pattern to these defects, and most children born to women treated with cyclosporin appear to be free of malformations (118–125).

Fetal Growth and Prematurity

Embryonic resorption and growth retardation occurred when pregnant rats were administered high-dose cyclosporin (116,126). In one of these reports, proximal tubular damage occurred in the kidneys of fetal rats and their mothers receiving high-dose cyclosporin, suggesting that embryotoxicity was more likely due to the effects of nephrotoxicity than teratogenesis (116). A review compiled by the manufacturers of cyclosporin reported 51 pregnancies in 48 transplant recipients. There were 43 live births, of which 15 were premature (45% delivered between 28 and 33 weeks), 3 had congenital anomalies (1 occurring in an aborted fetus), and 4 were growth retarded. In addition, there was one spontaneous abortion, one missed abortion, and six induced abortions (121). A recent report reviewed the outcome of 115 transplant recipients treated with cyclosporin during pregnancy, in which there were 68.6% live births. Fifty-six percent were premature (earlier than 37 weeks) and 49.5% were of low birth weight (<2,500 g) (127). In the general population, 5.9% of babies are born at a gestational age <37 weeks, and 6.0% have a birth weight <2,500 g (84). An increased frequency of fetal growth retardation in pregnant women treated with cyclosporin for organ transplantation has been observed elsewhere (120,123,124,128,129). Suggested causes of intrauterine growth retardation associated with cyclosporin exposure include a direct toxic effect of the drug on the fetus (129), and placental vascular changes resembling those that occur in the kidney after prolonged treatment with cyclosporin (130). Heart and liver transplant recipients who require higher doses of cyclosporin may be at greater risk of

delivering smaller neonates. To minimize the risk of intrauterine growth retardation, a reduction in the total daily dose of cyclosporin to the lowest possible level has been recommended during pregnancy (103).

Immunosuppression

Transient neonatal thrombocytopenia and neutropenia were reported in one twin born to a mother receiving cyclosporin for deteriorating chronic graft rejection after liver transplantation. The severity of the mother's condition was reflected by the need to replace the graft 8 days after delivery (131). Lymphopenia was detected in an infant exposed to cyclosporin in utero, and further studies revealed an increased CD4/CD8 ratio in this infant (132). In another study, antenatal exposure to cyclosporin exerted a minimal effect on fetal immune development, and had less impact on T lymphocytes than azathioprine did (94).

Renal Toxicity

Of 26 infants born to mothers treated with cyclosporin during pregnancy for renal transplantation, none had evidence of disturbed renal function for up to 39 months of follow-up (133).

Chromosomal Effects

Although cyclosporin induces sister-chromatid exchange on in vitro testing with human cells, and chromosomal aberrations have been detected in peripheral lymphocytes of patients treated with this agent, there have been no cases of chromosomal anomalies reported in children born to mothers receiving cyclosporin during pregnancy (134).

Paternal Use of Cyclosporin

Among 39 children whose fathers were treated with cyclosporin, azathioprine, and prednisolone at the time of conception for cardiac or heart-lung transplantation, 33 were healthy, 3 were premature, 1 had a cleft lip and palate, 1 died of interruption of umbilical cord circulation, and 1 with a positive family history of cardiomyopathy was born with this condition (80).

Experience in Inflammatory Bowel Disease

To date, there is only one reported case of a pregnant woman who had inflammatory bowel disease and who received cyclosporin therapy. Intravenous cyclosporin (4 mg/kg/day) was given to a woman with fulminant ulcerative colitis at 29 weeks gestation for 10 days. Thereafter, oral cyclosporin was administered in two daily doses to produce blood levels ranging between 400 and 600 µg/L. The patient's condition improved and the need for surgery was averted. At 34 weeks of gestation, a healthy 2,070 g baby was delivered. Cyclosporin was discontinued 6 weeks after delivery (105).

Lactation

Significant passage of cyclosporin into breast milk has been documented (108,109), and its use in nursing mothers is not advised (65,128).

Summary

At present, the role of cyclosporin in inflammatory bowel disease appears restricted to short-term use in severe ulcerative colitis. Generally, such patients are too ill to conceive. If patients do become pregnant while taking oral cyclosporin, the risk of teratogenesis does not appear to be increased, and elective termination of the pregnancy is not necessary. Use of the drug during pregnancy may be indicated for acute severe inflammation that does not respond to intravenous corticosteroids, thereby avoiding the need for emergency surgery. Under these exceptional circumstances, cyclosporin may be indicated, although growth retarded or premature neonates may be delivered. Children exposed to cyclosporin in utero are thought to be at low risk of immunodeficiency. Breastfeeding is not advisable during cyclosporin use.

Methotrexate

According to a double-blind, placebo-controlled Canadian study, methotrexate was beneficial in improving symptoms, inducing remission, and reducing steroid requirements in patients with chronic Crohn's disease (135). Its efficacy in ulcerative colitis is not proven. There are no data regarding the safety of methotrexate during pregnancy in inflammatory bowel disease, although its use in pregnant women with other disorders such as neoplasia, con-

nective tissue diseases, and dermatological conditions allows some generalizations to be made.

Teratogenicity

Methotrexate is a folic acid antagonist that crosses the placenta. Folic acid is important in the replication of nucleic acids and folic acid antagonism or deficiency may result in abnormal development (136). Fetal wastage is increased in pregnant mice, rats, cats, and rabbits treated with methotrexate (137-140). Furthermore, dose-dependent increases in malformations occur in the offspring of rats and rabbits exposed to methotrexate, including cleft palate, limb malformations, and facial clefts (137,140-142).

In humans, methotrexate exposure during the first trimester is associated with a characteristic pattern of congenital abnormalities, including abnormal head shape, large fontanelles, craniosynostosis, ocular hypertelorism, and skeletal deformities (143,144). Despite this, there are many reports of normal infants born to mothers who required the drug during the first trimester (145-148). The critical period in which malformations may occur is 6-8 weeks after conception (149), and the frequency of anomalies in infants exposed to methotrexate during pregnancy is probably dose related (147,149). Exposure to low-dose methotrexate in early gestation seems to pose a relatively low risk to the fetus (149).

Fetal Growth and Prematurity

In addition to the possible teratogenic effects of methotrexate, ~40% of infants exposed to this drug are growth retarded, regardless of the timing of its exposure (145). It is possible that the fetal effects of methotrexate may persist for a time after its discontinuation (150), even though normal infants have been born to women who stopped the drug 3-12 months before conception (151,152).

Chromosomal Effects

A higher than expected frequency of acquired chromosomal aberrations have been described in adult somatic cells, in cultured cells, and in mouse embryonic oogonia exposed to methotrexate (153-156). Various acquired cytogenetic abnormalities were observed in lymphocytes of an infant exposed to methotrexate during the latter half of pregnancy

(157). The long-term risk of carcinogenesis and genetic damage in the next generation from possible chromosomal aberrations have not been studied.

Myelotoxicity

There are two reports of severe neonatal bone marrow suppression, one of which occurred after exposure to methotrexate in the third trimester (158), the other after single exposure during the 12th week of gestation (159).

Fertility

Reversible impairment of fertility is recognized in men and women treated with methotrexate (160,161). Previous treatment with methotrexate does not preclude future parenthood (161).

Lactation

Methotrexate is excreted in breast milk in small amounts (162), and its use in nursing mothers is not recommended because of possible immunosuppression, neutropenia, adverse effects on growth, and risk of carcinogenesis in the newborn (65).

Summary

The elective use of methotrexate during the first trimester of pregnancy is contraindicated because of its known abortifacient and teratogenic effects. If a patient does conceive while taking methotrexate, the critical time of exposure in regard to congenital malformations is between 6 and 8 weeks after conception, and the risk of these anomalies is dose related. Because the effect of methotrexate may persist for an ill-defined period after its discontinuation, patients should be advised to defer pregnancy for several months after the drug is withdrawn. Breastfeeding is not recommended in women receiving methotrexate.

ANTIBIOTICS

Uncontrolled studies have suggested antibiotic therapy to be useful in certain circumstances for patients with inflammatory bowel disease. The two most commonly used antibiotics in patients with Crohn's disease are metronidazole and ciprofloxacin. A recent controlled study has shown possible benefits of metronidazole for 3 months at a dose of

20 mg/kg daily in the prevention of postoperative ileal recurrence in Crohn's disease (163).

Metronidazole

Teratogenicity

Metronidazole passes freely across the placenta (164). Offspring of pregnant animals treated with metronidazole were originally thought to be at increased risk of birth defects, stillbirths, and prematurity, although this has not been substantiated (165). Three cases of midline facial defects have been reported in human infants exposed to metronidazole between 5 and 7 weeks after gestation (166).

In a recent metaanalysis concerning the safety in pregnancy of metronidazole therapy for 7–10 days in patients with *Trichomonas vaginalis*, seven studies were considered suitable for review. Six of these were prospective studies in which a total of 283 women were exposed to metronidazole in the first trimester. The other report was a retrospective study of 1,083 exposed pregnant women. The overall weighted odds ratio of exposure versus no exposure during the first trimester was 0.93 (95% confidence interval 0.73–1.18), suggesting that there is no increased risk of teratogenicity during first trimester exposure to metronidazole (166).

Fetal Growth and Prematurity

In a recent comprehensive review of the genotoxicity and carcinogenicity of metronidazole, Dobias et al. refer to studies in which >900 pregnant patients were treated with metronidazole in conventional doses for 7–10 days. No difference in the incidence of stillbirths, small for gestational age infants, prematurity, or congenital anomalies were observed (165).

Carcinogenicity

Metronidazole is mutagenic to bacteria, and carcinogenic in mice after prolonged treatment. There is no evidence associating metronidazole with the development of malignancy in humans (167).

Lactation

Metronidazole is expressed in breast milk (168), and should only be used in exceptional circum-

stances by nursing women with inflammatory bowel disease (22).

Ciprofloxacin

Teratogenicity

Quinolones impair DNA metabolism by inhibiting DNA gyrase, and may have theoretical mutagenic and teratogenic potential (169). According to studies on experimental animals, growing cartilage is a target of quinolone toxicity, and the drug has formerly been considered to be contraindicated during pregnancy and growth (170). In a study of cynomolgus monkeys, ciprofloxacin administration did not influence fetal development and there was no increase in abortion rate (171).

In a review of 38 women treated with norfloxacin or ciprofloxacin during the first trimester mostly for urinary tract infections, no neonatal malformations nor developmental abnormalities occurred. However, the number of caesarian sections for fetal distress was greater than expected for reasons which were not clear. In this study, no joint problems or delay in walking were reported, although the authors believe longer follow-up is required to exclude subtle joint changes (169).

Summary

Concerns about the use of antibiotics for inflammatory bowel disease in pregnancy result from the lack of convincing data showing these agents to be effective, the mutagenicity of metronidazole in bacteria, a possible teratogenic effect of metronidazole in animal studies, and the accumulation of ciprofloxacin in developing cartilage in animals. According to clinical studies in which metronidazole and ciprofloxacin have been used for other purposes in the first trimester of pregnancy, the risk of teratogenicity associated with these antibiotics appears to be low. These results are reassuring for patients who have inflammatory bowel disease and who inadvertently become pregnant receiving this treatment, or for those who require short-term, low-dose therapy for infective complications. However, the elective administration of these agents as primary therapy for Crohn's disease during pregnancy should be used cautiously, because their safety has not been verified using the higher doses during a prolonged duration that are required for clinical benefits in this condition. Breastfeeding is not ad-

visable during therapy with metronidazole or ciprofloxacin.

CONCLUSIONS

Many patients with inflammatory bowel disease have successful pregnancies. Disease activity is the most important factor determining the outcome of pregnancy in this condition. The choice of drug therapy during pregnancy depends on the clinical indications for treatment and the possible drug toxicity to the fetus. There are considerable advantages for individuals with inflammatory bowel disease to plan pregnancy to obtain clinical remission before conception, and to ascertain minimum drug requirements. The elective use of treatment can then be tailored according to the severity of the condition. Women with inactive inflammatory bowel disease requiring no treatment in the non-pregnant state should not be advised to commence treatment during pregnancy unless their disease worsens. Continued therapy is indicated in patients who require ongoing treatment to maintain remission, because inflammation is likely to deteriorate after withdrawal of therapy. There is an inexorable link between disease severity and the need for stronger therapy. Women with severe colitis who would otherwise require potent and potentially toxic drugs to control their condition may be advised to consider the advantages of surgical options before conception. Disease flareups that occur during pregnancy should be dealt with in the same way as for the nonpregnant state, remembering that emergency surgery may be particularly hazardous for the fetus.

In practice, however, many pregnancies are unplanned, in which case the fetus may inadvertently become exposed to medication. Clinicians managing women of reproductive age with inflammatory bowel disease should therefore detail the risks posed by these agents in the event of pregnancy, and at the same time emphasize the need for satisfactory disease control to minimize fetal and maternal complications. If patients requiring drug therapy to maintain clinical remission are unwilling to risk possible fetal toxicity, pregnancy should be avoided. Series in which considerable experience has been obtained in inflammatory bowel disease show that sulphasalazine and corticosteroids are safe during pregnancy and lactation. Available data suggest oral and rectal mesalazine to be safe in low to moderate doses during pregnancy, but caution is

required if higher doses are used. Provided their use is clinically warranted, azathioprine and cyclosporin may be used electively in pregnancy, but these drugs are not recommended during breastfeeding. Elective use of methotrexate is contraindicated in the first trimester of pregnancy and during breastfeeding. Termination of pregnancy is not mandatory if patients inadvertently conceive while taking immunosuppressive therapy for inflammatory bowel disease, although this option ultimately remains the choice of the individual patient. Metronidazole or ciprofloxacin used in small doses for brief periods do not appear to be teratogenic, although data regarding their safety in higher doses for a longer duration are unavailable.

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