AP&T Alimentary Pharmacology and Therapeutics

Review article: a decision-making algorithm for the management of pregnancy in the inflammatory bowel disease patient

F. M. Habal & V. W. Huang

Department of Medicine, University Health Network, University of Toronto, Toronto, ON, Canada.

Correspondence to:
Dr F. M. Habal, Toronto General Hospital, 200 University Street, Toronto, ON M5G 2C4, 416-340-5023, Canada.
E-mail: flavio.habal@uhn.on.ca

Publication data
Submitted 18 November 2011
First decision 7 December 2011
Resubmitted 8 December 2011
Accepted 9 December 2011
EV Pub Online 5 January 2012

This uncommissioned review article was subject to full peer-review.

ABSTRACT

Background
Inflammatory bowel disease affects patients who are in their reproductive years. There are many questions regarding the management of IBD patients who are considering or who are already pregnant. These include the effect of the disease and the medications on fertility and on the pregnancy outcome.

Aim
To create an evidence-based decision-making algorithm to help guide physicians through the management of pregnancy in the IBD patient.

Methods
A literature review using phrases that include: 'inflammatory bowel disease', 'Crohn's disease', 'ulcerative colitis', 'pregnancy', 'fertility', 'breast feeding', 'delivery', 'surgery', 'immunomodulators', 'azathioprine', 'mercaptopurine', 'biologics', 'infliximab', 'adalimumab', 'certolizumab'.

Conclusions
The four decision-making nodes in the algorithm for the management of pregnancy in the IBD patient, and the key points for each one are as follows: (i) preconception counselling – pregnancy outcome is better if patients remain in remission during pregnancy, (ii) contemplating pregnancy or is already pregnant – drugs used to treat IBD appear to be safe during pregnancy, with the exception of methotrexate and thalidomide, (iii) delivery and (iv) breast feeding – drugs used to treat IBD appear to be safe during lactation, except for ciclosporin. Another key point is that biological agents may be continued up to 30 weeks gestation. The management of pregnancy in the IBD patient should be multi-disciplinary involving the patient and her partner, the family physician, the gastroenterologist and the obstetrician.

Aliment Pharmacol Ther 2012; **35:** 501–515

doi:10.1111/j.1365-2036.2011.04967.x

INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), affects the population in a bimodal distribution. Many patients are diagnosed in their reproductive years,[1] often after conception has occurred. Some studies have shown that women with IBD may have increased incidence of prematurity, low birth weight, caesarean section and congenital anomalies.[2] Most women with IBD are able to conceive, and have a normal pregnancy. Most of the drugs used to treat IBD are safe to use during pregnancy. Traces of drugs have been reported in breast milk in women on drug therapy, but no major foetal or neonatal complications have been reported. With the increasing early use of immunosuppressant and biological therapy to treat active IBD, more studies are focusing on these issues. However, ethical concerns have limited the types of studies that can be performed to answer the multitude of questions related to IBD and pregnancy.

Patients and their partners are concerned about the effects of disease activity, disease complications and medications used to treat IBD, on fertility and pregnancy. They may discontinue medications or choose voluntary infertility because of their concerns. However, studies have shown that the benefits of maintaining remission prior to conception and during pregnancy outweighs the risks of disease flares and associated adverse effect on the pregnancy outcome.[3] They will present to clinic with many questions about the various decisions that need to be made regarding pregnancy and IBD.

Inflammatory bowel disease patients who are contemplating conception or who are already pregnant should be cared for by a multidisciplinary team that considers the individual patient wishes and concerns, and that manages them accordingly. In this review article, we propose a decision-making algorithm that will aid in discussing common questions IBD patients will have regarding pregnancy and IBD. We will discuss the current understanding of the relationship between IBD, medications used to treat IBD, and pregnancy outcome and present the available data to support our suggestions. We bring up some issues that should be discussed with the patient and her partner, so that they can make educated decisions regarding treatment plans.

PROPOSED DECISION-MAKING ALGORITHM

When managing female IBD patients of reproductive age, fertility, conception and pregnancy must be considered when making decisions regarding treatment. Figure 1 shows our proposed decision-making algorithm that illustrates the decision-making nodes which are encountered depending on where the patient is. The first decision-making node is at the preconception stage. The usual preconception advice given to any female patient is also given to IBD patients. However, there are IBD specific decisions that need to be made regarding medications, surgery, conception and planning pregnancies. It is at this step that issues relating to heredity, fertility, conception, IBD effect on pregnancy outcome are discussed. The second decision-making node arises once the patient has decided that she would like to become pregnant, or if the patient is already pregnant, and questions arise about the medications that can be used safely. The third decision-making node is the method of delivery, which can be an issue especially in CD patients with perianal disease. The fourth decision-making node pertains to breast feeding.

DECISION-MAKING NODE #1: PRECONCEPTION

Question 1: Is it safe for the IBD patient to become pregnant? What is the risk to the foetus?

Preconception counselling is a cornerstone of IBD consultation for young IBD patients of reproductive age. The concept of 'voluntary childlessness' may explain some of the increased infertility rates in IBD patients. A recent study showed that patient-reported reasons for voluntary infertility included fear of IBD-related congenital abnormalities, concern about genetic risk of IBD in the child, concern about medication teratogenicity, medical advice that conception is not possible or is inadvisable with IBD, and IBD-related fatigue.[4] Patients want to know about their risks of passing on the disease to their child, their chances of becoming pregnant and the likelihood of having a successful pregnancy and healthy infant. At this step, regular preconception care should be followed as well.

Heredity. Twin studies show that genetic factors play a role in the development of CD or UC; however, environmental factors (such as smoking status) are also important.[5, 6] Children of parents with IBD are 2–13 times more likely to develop IBD compared with the general population. If one parent has IBD, the risk of developing IBD is 8–11%, and if both parents have the disease, it is 20–35%. Some data suggest that breastfed infants may be at decreased risk.[7]

Many studies that report prematurity and small for gestational age infants in pregnancies of IBD patients did not report maternal smoking, alcohol consumption,

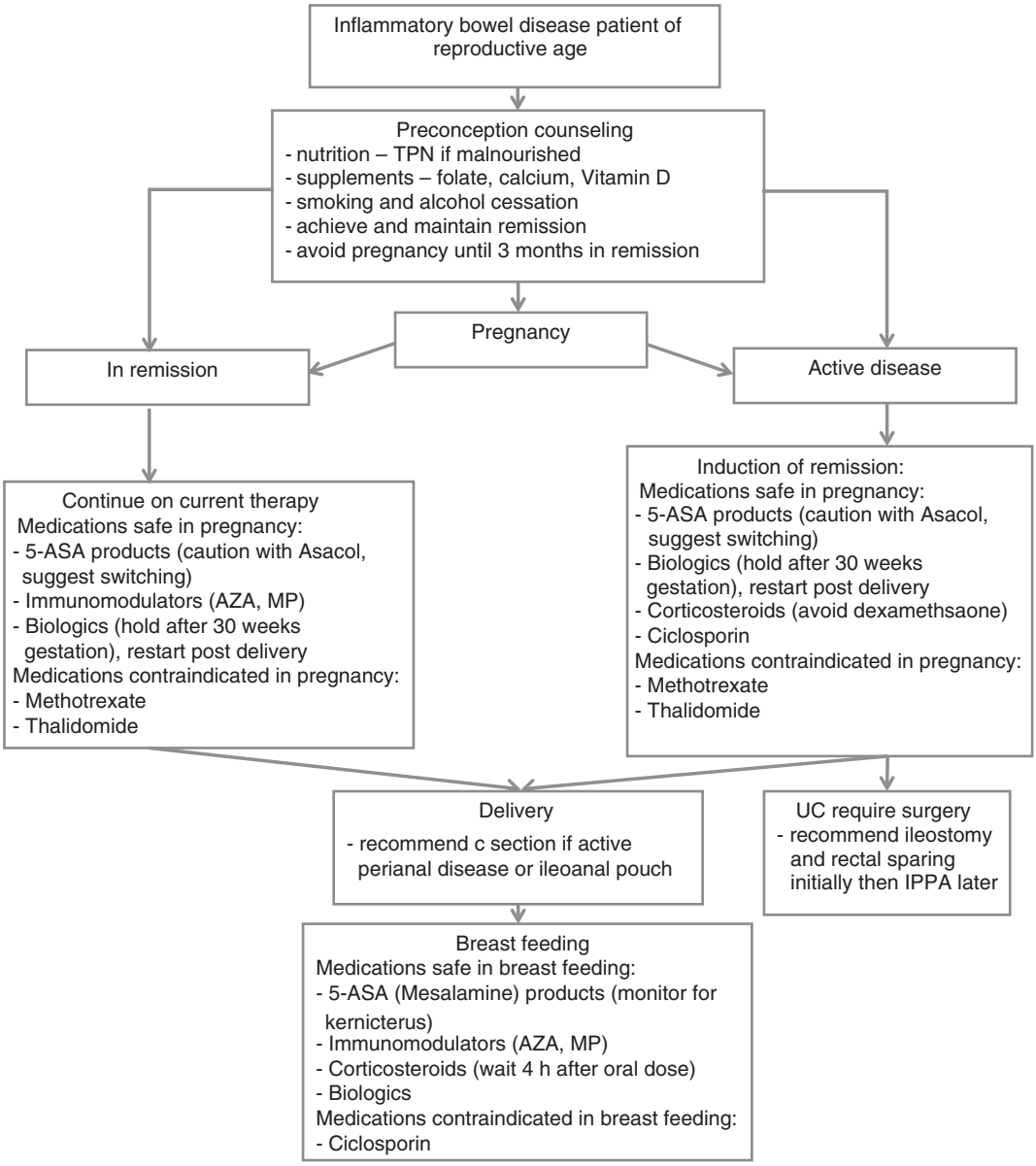

Figure 1 | Proposed decision-making algorithm for the management of pregnancy in IBD patients.

disease status and medication use, all factors that could affect pregnancy outcome. The incidence of congenital abnormalities in IBD patients reported in most studies is similar to the incidence in the general population of approximately 4%.

Fertility. Disease activity, surgical history, inflammation of reproductive organs and psychological factors may affect fertility. Women with inactive CD or UC appear to have normal fertility when compared with the general population; infertility rates in women with inactive CD are similar to those of the general population (8–10%).[8, 9] Women with CD may have slightly decreased fertility, especially when having active disease.[10, 11] This may partly be explained by the formation of adhesions resulting in tubal infertility.[12] Fertility may normalise during remission,[8] especially in patients with CD,[13] and so it is recommended that females wait until their disease is controlled before considering pregnancy.

Women with UC have been shown to have normal fertility until they have had surgical treatment.[14, 15] Recent systematic reviews showed that restorative proctocolectomy

(RPC) for UC results in decreased fertility (40% of females conceiving before RPC and only 29 per cent conceiving after RPC)[16] or increased infertility (15–48% in women post-ileal pouch-anal anastomosis for UC).[17] The resultant scarring, adhesions and tubal involvement of the surgery may contribute towards infertility.[12, 18]

However, the reviews also showed that IVF is a successful fertility treatment after RPC, and that RPC does not pose increased risk to the foetus.[16, 19, 20] More females who have had RPC have caesarean sections than vaginal deliveries, as it has the potential benefit of decreased risk of faecal incontinence or damage to the anal sphincters and pelvic pouch.[16, 19] A small study showed that ileorectal anastomosis preserves female fertility and may be a surgical option when considering effect on fertility.[21]

Although there is no firm data to support the following approach,[22] it is recommended that female patients who are planning to conceive and who require colectomy for acute UC undergo ileostomy and rectal sparing initially and then ileal pouch-anal anastomosis could then be performed after conception, pregnancy, and delivery.

Effect of IBD on pregnancy outcome. Outcomes from studies on pregnancy outcome in patients with IBD have been variable. Some studies found that pregnancies in women with IBD were associated with poor outcome such as increased risk of preterm birth, low birth weight,[11, 23, 24] small for gestational age (SGA) infants and increased caesarean section delivery.[24] However, some studies found there was no increased risk of low birth weight or IUGR in children of women with UC,[25] and that IBD is not associated with adverse perinatal outcomes.[26]

In a 1998 review, Subahani *et al.* reported that CD, especially active disease, was associated with decreased birth weights, preterm delivery and caesarean section.[27] A cohort study from a Northern Californian Kaiser population found that pregnant women with IBD were more likely to have a spontaneous abortion (OR: 1.65; 95% CI: 1.09–2.48); an adverse pregnancy outcome (stillbirth, preterm birth, or SGA infant; OR:1.65; 95% CI: 1.00–2.38) or a complication of labour (OR: 1.78; 95% CI: 1.13–2.91). However, the study did not find any difference in the rate of congenital malformations, regardless of IBD type.[28] Analysis of an Asian population database from Taiwan showed that there was an increase of preterm births (11.73 vs. 6.25%; $P = 0.004$) and LBW (12.76 vs. 5.55%; $P < 0.001$) controlling for maternal age, parity and education level.[29]

A case–control study in 2004 comparing 116 pregnancies in patients with IBD with 56 398 controls, found that the incidence of neonatal complications (low birth weight LBW, very LBW, intrauterine growth restriction, Apgar scores and congenital anomalies) were similar in both groups.[30] There were no differences in antepartum complications (chronic hypertension, hyperemesis gravidarum, preterm labour or pre-eclampsia). However, there was a higher incidence of induction of labour (32 vs. 24%; $P = 0.002$), chorioamnionitis (7 vs. 3%; $P = 0.04$) and caesarean section (32 vs. 22%; $P = 0.007$) in patients with IBD.

In 2007, a meta-analysis that included 1952 women with CD, 1113 with UC and 320,531 controls[2] reported that women with IBD had a 1.87-fold increase in premature births (<37 weeks; $P < 0.001$); more than two-fold increase in the incidence of low birth weight (LBW) (<2500 g; $P < 0.001$); a 1.5-fold increase in caesarian section ($P < 0.001$); and a 2.37-fold increase in congenital abnormalities ($P < 0.001$). However, on sub group analysis according to IBD type, they found some significant differences. The increase in low birth weight was significant only in CD patients (OR 2.82, $P = 0.003$) and not in UC patients (OR 1.66, $P = 0.42$). The increase in caesarean section was higher in CD patients (OR 1.65, $P = 0.003$) and not in UC patients (OR 1.30, $P = 0.21$). The increased risk of congenital abnormalities was significant only in UC patients (OR 3.88, $P = 0.009$), but not in CD patients (OR 2.14, $P = 0.06$). This meta-analysis found no significant increase in small for gestational age or still births in either UC or CD patients. Limitations of this meta-analysis include the observational nature of the studies that make them vulnerable to bias; the low incidence of adverse outcomes that makes statistical precision difficult; and the fact that disease activity was not reported in relation to outcomes. Increased risks of congenital abnormalities associated with 5-ASA, azathioprine and anti-TNF-alpha medications seen in a pooled analysis may be associated with the disease itself and not the medications.[2]

A recent large population based prevalence study on 2637 primiparous women with UC and 868 942 primiparous women with no UC in Denmark and Sweden reported that maternal UC was associated with increased risk of preterm birth (prevalence OR 1.77), caesarean section (POR 2.01) and neonatal death (POR 1.93), as well as SGA (POR 2.78). There was no association between UC and risk of congenital abnormalities. These adverse birth outcomes appeared to be correlated with UC disease severity.[31]

Activity of disease may have affected pregnancy outcome and if not accounted for, the results of many studies. Dejaco *et al.* conducted a prospective study to assess risk factors for poor pregnancy outcome in 58 patients with IBD, and found that active disease during pregnancy represents a significant risk factor for unfavourable birth outcomes.[32] Therefore, the current treatment guidelines state that the maintenance of remission during pregnancy is essential[33] and pregnant women should be treated as aggressively as women who are not pregnant.

There has also been interest in pregnancy outcome according to whether the mother was diagnosed before or during pregnancy. In a case–control study of pregnancy outcome in patients before and after diagnosis of IBD, Molnar *et al.* found that IBD itself, independent of disease activity, drug therapy or types of drugs used, increased the risk of preterm birth.[34] Raatikainen conducted a retrospective analysis of a clinical birth database of 135 women diagnosed with IBD before pregnancy and 77 after pregnancy. They did not find an increased risk of preterm births in mothers with IBD. However, there was an increased incidence of SGA in the UC and IBD groups than in the control group (17% vs. 9%, $P = 0.014$; 16% vs. 9%, $P = 0.015$). There was a similar trend in CD patients, but it was not statistically significant. There were no statistically significant differences in maternal or pregnancy outcomes between women diagnosed with IBD before or after pregnancy.[35]

Until recently, studies regarding pregnancy outcome in IBD were retrospective and often of small sample size. In 2011, Bortoli *et al.* from the ECCO-Epicom study published a prospective case-controlled study of 145 women with CD and 187 with UC to evaluate the pregnancy outcome in patients with IBD. They showed that there were no statistically significant differences in frequency of abortions, preterm deliveries, caesarean sections, congenital abnormalities or birth weight, when compared with a population of non-IBD pregnant women. Maternal age >35 years was the only risk factor associated with congenital anomaly and preterm delivery. Smoking was also found to increase the risk of preterm delivery. However, the majority of patients were in remission on maintenance therapy (86% of CD and 88% of UC), and they had a low number of patients on immunomodulators (22% of CD and 10% of UC were on AZA/MP, and only eight CD were on anti-TNF-alpha).[36]

Patients with active disease had higher risks of adverse outcome than those in remission, but only 19% of women were concerned about the effect of the disease activity itself on pregnancy.[3] Many patients (84%) are concerned that IBD medications would harm their pregnancy, as reflected by medication taking behaviour (stopping or decreasing medication). They and their partners should be educated about the possibility of disease exacerbation during pregnancy if treatment is stopped. However, treatment choices during pregnancy vary according to individual patient preference, disease activity and concern for potential drug toxicity. The risks and benefits of continuing vs. discontinuing maintenance therapies during pregnancy should be discussed and the best evidence presented to the patients and their partners. More than 50% of pregnancies are unplanned; therefore, it is important that even at diagnosis or when medications are initially started, practitioners discuss pregnancy related issues with their patients.

Based on the available outcomes studies and literature, patients should be informed that there is a small risk for small for gestational age infants and preterm delivery; however, this risk mainly seems to be associated with poor disease control, rather than the diagnosis itself.

Question 2: What preconception medical care does the IBD patient need?

Nutritional therapy. Pregnant women with active IBD who are not gaining weight appropriately (average weight gain during pregnancy is 11–16 kg) may require nutritional intervention. Total parenteral nutrition may be required in very sick IBD patients, as it is lifesaving in malnourished pregnant women, and it has been shown to promote foetal growth.[37]

Folic acid, calcium, vitamin D. Folic acid is important as neural tube defect can occur as soon as conception is discovered; it is recommended for all women of reproductive age. In a recent study, only 65% of women knew the benefit of taking folic acid preconception and during the first trimester of pregnancy.[38] Women with IBD are at higher risk of folic acid deficiency, especially those with CD on low residue diets and those on medications such as sulphasalazine, which interfere with folic acid metabolism.[39] Therefore, they should be encouraged to take 5 mg of folic acid daily which is more than the 1 mg/day recommended for healthy patients. Pregnant women on steroid therapy should be encouraged to take calcium and vitamin D supplementation to prevent bone loss.

Smoking cessation. Smoking has been shown to increase the risk of developing CD and to worsen disease activity, whereas smoking cessation has been shown to improve CD and aggravate UC.[40] However, smoking during

pregnancy can result in placenta previa, placental abruption and premature rupture of membranes.[41, 42] It can also lead to small foetal size at 10–19 weeks, premature birth, low birth weight and poor foetal outcome. Therefore, all female patients of reproductive age who are considering conception or who are pregnant should be encouraged to stop smoking.

Abstinence from alcohol. Similarly, patients considering pregnancy or who are already pregnant should be counselled to avoid alcohol. Maternal alcohol consumption during pregnancy can result in Fetal Alcohol Syndrome (FAS) – a syndrome of growth deficiency, central nervous system damage and dysfunction, and unique facial abnormalities, as well as Fetal Alcohol Spectrum Disorders (FASDs) – a syndrome of less prominent mental, learning and behaviour disabilities.[43]

DECISION-MAKING NODE #2: CONTEMPLATING PREGNANCY OR IS PREGNANT

Question 1: What investigations are safe for the mother and foetus?

Endoscopy during pregnancy. Endoscopy may be required for significant or continued gastrointestinal bleeding, dysphagia, severe or refractory nausea and vomiting or abdominal pain, or strong suspicion of a colonic mass.[44] To avoid vena caval or aortic compression by the gravid uterus, which may lead to decreased uterine blood flow and foetal hypoxaemia,[45] the patient should be placed in the lateral decubitus position.

Endoscopy should be done with minimal sedation and obstetrical support and monitoring should be available prior, during and after the procedure. Drugs that should be avoided in the first trimester include Meperidine (FDA class B) and midazolam (FDA class C), and Benzodiazepines (FDA class D), as they have been associated with congenital cleft palate.[44] They should also be avoided in late pregnancy as they have been associated with neurobehaviour disorders.[46, 47] Propofol (FDA class B) should be administered by an anaesthetist, but its safety in first trimester has not been studied.[48] If possible, endoscopy should be postponed until the second trimester.

Radiological investigations during pregnancy. Radiological investigations may be needed to rule out obstruction, perforation or toxic megacolon. It is preferred to use tests such as plain abdominal films or ultrasound as they use less radiation than CT or barium studies, and ultrasound can be used to assess for abscesses or for bowel wall thickness. MRI is also safe, and can be used to diagnosis terminal ileal CD during pregnancy. The CDC has published a thorough guideline on pregnancy and radiation, which can be referred to for more information (Radiation and Pregnancy: A Fact Sheet for Clinicians http://emergency.cdc.gov/radiation/prenatalphysician.asp).

Question 2: What medications are safe to use for maintenance of remission, or for induction of remission?

Most of the medications used to treat IBD are safe during gestation, except for Methotrexate and Thalidomide. The US FDA classification of drugs should be used to guide the use of medications during pregnancy. The FDA categories are listed in Table 1.

The medications used to treat IBD include aminosalicylates (e.g. mesalamine), immunomodulators (azathioprine and methotrexate), corticosteroids and biologics (infliximab, adalimumab). In an attempt to determine the effect of medications on pregnancy in IBD, Moskovitz *et al.* (2004) assessed the effect of 5-ASA drugs, metronidazole, ciprofloxacin, prednisone, mercaptopurine (MP), azathioprine and ciclosporin (CsA) on pregnancy outcomes in 113 IBD patients with 207 documented conceptions. They looked at spontaneous abortion, therapeutic abortion, maternal or foetal illness resulting in abortion, premature birth, healthy full-term birth, multiple births, ectopic pregnancy and congenital defects. They analysed the effect of medication use during the first trimester and at any time during pregnancy on the pregnancy outcome, and found no significant differences among groups.[49]

5-Aminosalicylates: sulfasalazine/mesalamine (FDA B)/olsalazine (FDA C). Sulfasalazine was one of the earliest therapeutics used in IBD, and has been assigned to pregnancy category B by the FDA. It is metabolized by intestinal bacterial flora to sulfapyridine and 5-ASA. Sulfapyridine crosses the placenta to reach the foetus. It may lead to deficiency of dihydrofolate and tetrahydrofolate by acting as a competitive inhibitor of the enzyme dihydropteroate synthase in the folate metabolism. Patients receiving sulfasalazine should receive folic acid supplementations to prevent the development of foetal neural tube defect.[50, 51] In men, sulfasalzine can cause oligospermia and infertility, which are reversible when sulfasalzine has been discontinued.

In a review of studies including 1155 pregnancies in women with UC being treated with sulfasalazine during pregnancy, the pregnancy outcome was similar to that

Table 1 | Food and drug administration (FDA) classes in pregnancy

Class	Definition
A	Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of risk in later trimesters) and the possibility of foetal harm appears remote
B	Either animal reproduction studies have not demonstrated a foetal risk, but there are NO controlled studies in pregnant women OR animal reproduction studies have shown an adverse effect (other than decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters)
C	Either studies in animals have repeated adverse effects on the foetus (teratogenic, embryonic or other) and there are NO controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus
D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)
X	Studies in animals or human beings have demonstrated foetal abnormalities OR there is evidence of foetal risk based on human experience OR both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

expected in the general population with no significant increase in prevalence of selected congenital abnormalities.[52]

At the 2006 Digestive Disease Week in Los Angeles, USA, Mahadevan and Corley reported that the use of 5-ASA and sulfasalazine during pregnancy was associated with an increased risk of congenital malformations when sulfasalazine was used during conception and the first trimester, but not with 5-ASA use. The use of 5-ASA was not associated with an increase in adverse outcomes[53]; an increased risk of adverse outcomes was seen in women not taking 5-ASA during the second and third trimesters, suggesting a protective effect of the medication.

However, a meta-analysis of seven studies prior to 2007, with a total of 2200 pregnant women with IBD, 642 on 5-ASA drugs and 1158 on no medication, reported an 1.16-fold increase in congenital malformations, an 2.38-fold increase in stillbirth, an 1.14-fold increase in spontaneous abortion, an 1.35-fold increase in preterm delivery and an 0.93-fold increase in low birth weight in infants of the pregnant women exposed to 5-ASA drugs.[54]

Asacol is a mesalamine covered with a special enteric coating that prevents the medication from degrading before it reaches the small intestine. This coating, dibutyl phthalate (DBP), was associated with external and skeletal malformations and adverse effects on the male reproductive rodents system. Patients who are using Asacol have 50 times higher mean urinary concentration of the main DBP metabolite, monobutyl phthalate, than nonusers (2257 μg/L vs. 46 μg/L; $P < 0.0001$).[55] These results raise concern about potential human health risks for pregnant women and children. Although this has not been shown in any human study, Asacol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. At the present time, physicians should caution their patients regarding this effect and consider switching patients to non-DBP containing meslamine.[56]

Immunomodulators: azathioprine/mercaptopurine (FDA D). Mercaptopurine and its prodrug azathioprine (AZA) are purine analogues that interfere with the synthesis of adenine and guanine ribonucleosides, precursors of DNA and RNA. They are classified as pregnancy FDA category D drugs. When taken orally, 47% of AZA is available to the systemic circulation, whereas only 16% of MP is available.[57] These have been proven to be effective in the treatment of steroid-dependent or resistant IBD.[58] These drugs are also used as immunosuppressive therapies in autoimmune diseases, transplant patients and in leukaemia.

The safety of azathioprine in pregnancy has been shown in studies in transplantation and rheumatology patients. The foetus lacks the enzyme inosinate phosphorylase that is necessary to convert AZA and MP to active metabolites, and therefore is protected from potential teratogenic effects of AZA and MP. Small doses of these medications do not appear to have adverse effects on human reproduction.[59, 60] In a retrospective study of patients who had received MP for IBD before or during conception compared with controls, there was no statistical difference in conception failure, abortion due to birth defect, major congenital malformations, neoplasia or increased infections (RR = 0.85 (0.47–1.55), $P = 0.59$).[61]

In a recent prospective, controlled, multicenter study conducted by the Tel Aviv University (Israel), there was

no increase in congenital malformation, but there was more prematurity (21% vs. 5%, $P < 0.001$) and low birth weight (23% vs. 6%, $P < 0.001$) in the AZA treated women.[62]

A large Danish nationwide cohort study on women who were exposed to azathioprine or MP during pregnancy reported an overall increased risk of preterm birth, low birth weight at term babies and congenital anomalies among newborns of AZA or MP exposed women, but when the comparison was limited to women with same types of underlying disease, only the risk of induced preterm birth remained elevated (RR 4.0, 95% CI: 1.5–10.8). The conclusion of the authors was that the adverse effects may have been caused by the underlying disease rather than being drug induced.[63]

However, in a study on 900 children born to women with CD between 1996 and 2004, the risk of preterm birth and congenital abnormalities in thiopurine exposed women were 4.2 (95% CI 1.4–12.5) and 2.9 (95% CI 0.9–8.9) respectively; these risks remained elevated even after adjusting for confounders.[64] However, some challenged the findings of this study based on issues with confidence interval difference, lack of primary endpoint and bias of confounding by indication of drug therapy for disease activity.[65]

A retrospective Swedish registry study that reviewed patients receiving azathioprine (AZA) during pregnancy (for IBD, autoimmune disorders, malignancy, organ transplantation) reported the rate of congenital malformations was 6.2% in the AZA group and 4.7% among all infants born (adjusted OR: 1.41, 95% CI: 0.98–2.04). Infants exposed to AZA were more likely to be preterm, weight <2500 gm, small for gestational age and had increased risk of congenital malformations (adjusted OR: 1.42; 95% CI: 0.93–2.18). Early pregnancy AZA exposure was associated with ventricular/atrial septal defects (adjusted OR: 3.18; 95% CI: 1.45–6.04). The authors make note that there may be an association between severity of disease and drug use which may influence the results.[66]

Recently, in a study of 19 births exposed to AZA/MP and 74 controls, the use of AZA/MP was not associated with an increased risk of preterm birth, LBW at term, neonatal adverse outcomes or congenital anomalies.[67] Also reporting similar findings, the results from 215 pregnancies in 204 women who were a cohort of the CESAME study in France was published. Three groups of women were compared – women exposed to thiopurines, women receiving other drugs and women not receiving any medication. The study showed that thiopurine use during pregnancy was not associated with increased risks of adverse outcomes (prematurity, birth weight, congenital abnormalities, death).[68]

Based on most of the literature and all-observational studies, it appears that thiopurines are safe during pregnancy and should not be discontinued. The most recent ECCO consensus guidelines consider AZA to be safe and well tolerated in pregnant women.[69] Although there are some cases of negative outcomes reported with the use of these medications, the majority of case series or cohort studies have not reported an increase in congenital anomalies. The American Gastroenterology Association recommends the continuation of AZA treatment during pregnancy. Stopping medication use during pregnancy may precipitate a flare resulting in adverse neonatal outcome.[70] However, the risks and benefits of treatment must be carefully balanced by the patient in consultation with her doctor and partner.

Corticosteroids (FDA C). Corticosteroids, including prednisone, prednisolone, dexamethasone and budesonide, are FDA class C drugs. They are often used to induce remission in CD and UC patients. They are given as oral or topical formulations and in severe cases via parenteral solution. Corticosteroids are not effective in maintenance therapy and are associated with side effects in almost 100% of patients who use them long term.[71] The placenta contains the enzyme 11 beta hydroxysteroid dehydrogenase type 2 (11 beta – HSD2), which metabolizes cortisol and corticosterone to inert 11-keto forms (cortisone, 11-dehydrocorticosterone). This inactivates the maternal cortisol, so that the majority of cortisol in the foetal circulation is foetal adrenal cortisol.[72–75] However, dexamethasone is not inactivated by this placental enzyme, and as it passes the placenta freely, it should be avoided during conception and pregnancy. In a prospective study of 287 IBD pregnancies using corticosteroids and/or sulfasalazine vs. 244 pregnant IBD patients on no treatment, there were no increased incidences of prematurity, spontaneous abortion, stillbirth or developmental defects in pregnancies with corticosteroid use.[76] Corticosteroids have been associated with oral cleft palate when used in the first trimester.[30, 77, 78] Recently, in a systematic review covering 17 studies in which pregnant women were treated with dexamethasone or betamethasone, nine of the 17 studies reported a reduction in birth weight (range 12–332 g), five of nine, a reduction of head circumference (range 0.31–1.02 cm) and two of four, a reduction in birth length (0.8 cm). The authors concluded that there is an association between in utero exposure to synthetic glucocorticoids and

reduced birth size.[79] A large Danish health registry data study did not find this association.[80]

Budesonide: Budesonide has a pH and time-dependent coating that times its release into the ileum and ascending colon. It has extensive first-pass hepatic metabolism, and therefore acts locally with minimal systemic side effects. It has been shown to be effective for induction of remission and treatment of mild to moderate CD. A small study of eight patients with CD using 6–9 mg budesonide daily did not find any evidence of foetal abnormality.[81]

Ciclosporin (FDA C). Ciclosporin is a selective immunosuppressant that inhibits the activation of T cells, thus preventing formation of IL-2. It is often used in solid organ transplant (liver, kidney, heart). In IBD, it is sometimes used to induce remission in acute UC that is nonresponsive to conventional therapy and intravenous corticosteroids,[82, 83] and to delay surgery as well.

A meta-analysis of 15 studies of pregnancy in 410 transplant patients receiving CsA reported that the incidence of congenital malformations was 4.1%, which was similar to the general population.[84] Pregnant transplant patients who are clinically stable on CsA have good pregnancy and foetal outcome.[84]

Biologics: infliximab, adalimumab, etanercept, certolizumab (FDA B). TNF-alpha is important in embryonic implantation, foetal development and labour.

TNF-alpha induces cyclo-oxygenase-2 gene expression in first trimester trophoblasts, thus increasing the synthesis of prostaglandins (PGE2 and PGF2alpha), which promotes blastocyst implantation, endometrial vascular permeability and uterine deciduation.[85] TNF-alpha may promote blastocyst implantation in early pregnancy, but it may also mediate recurrent spontaneous abortion at a later stage of gestation. Levels of TNF-alpha and TNFR-1 were found to be higher in women who had spontaneous early abortions.[86] TNF-alpha production is low in the first trimester, and increases to reach a peak at the onset of labour.[87] TNF-alpha appears to have a dual role in embryogenesis. Researchers have hypothesised that it may prevent the birth of offspring with structural anomalies by boosting death signalling if the foetus has been exposed to detrimental damages that will lead to structural anomalies, but trigger protective mechanisms if these damages can be repaired to prevent anomalies.[88]

Crohn's disease and UC appear to be mediated by different aspects of the immune system. CD seems to be related to the over expression of T cell helper (Th) 1 cytokines, such as TNF-alpha, which stimulate cell-mediated immunity and result in transmural inflammation of the gut.[89] On the other hand, UC is thought to be a result of dysregulation of intestinal immunity involving the Th2 cytokine response, although increased expression of TNF-alpha has been observed in patients with UC.

Anti-TNF agents have improved the management of IBD refractory to conventional treatment. It can be used for steroid-sparing therapy, in perianal disease, and maintenance of remission. In addition, it has been shown to result in mucosal healing, an important foundation of IBD treatment. Anti-TNF agents are classified as FDA B drugs because although animal studies have not shown risk to the foetus, there are no adequate and well-controlled studies of pregnant women.

Anti-TNF agents include infliximab, a chimeric monoclonal immunoglobulin G1 (IgG1) anti-TNF antibody, adalimumab, a human monoclonal IgG1 anti-TNF antibody and etanercept, a soluble TNF receptor fusion protein linked to the Fc portion of a human IgG1 antibody. These agents cross the placenta by the late second trimester and the third trimester.[90] Certolizumab another anti-TNFα antibody, is a PEGylated Fab' fragment of humanized anti-TNF-alpha monoclonal antibody rather than a whole human IgG1 antibody.[91] A recent abstract on Certolizumab found low levels of the antibody in cord blood confirming placental transfer.[91, 92]

Although there are few studies regarding anti-TNF agents in pregnant IBD patients, these medications are used in autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis. Many studies on anti-TNF-alpha agents in pregnancy are on rheumatoid arthritis patients. These studies are retrospective, registry studies or case reports. In 2007, Roux *et al.* presented their experience with three rheumatoid arthritis patients who became pregnant while using anti-TNF-alpha therapy. One patient terminated her pregnancy although there was no known pregnancy or foetal complications, and the other two delivered healthy infants.[93] Recently, the British Society for Rheumatology Biologics Register (BSRBR) reported a higher rate of spontaneous abortion among patients exposed to anti-TNF agents at the time of conception (with methotrexate/leflunamide 33% and without 24%) compared with 17% spontaneous abortions in those with prior exposure to anti-TNF agents, and 10% spontaneous abortions in the control group. They suggested that these drugs be avoided at the time on conception although no firm conclusions can be drawn about the safety of anti-TNF agents during pregnancy.[94]

In the first large series of infliximab (IFX) use in 96 women with RA and CD, Katz *et al.* queried the infliximab safety database and found that results of pregnancy outcomes in women exposed directly to infliximab were similar to the general US population in terms of live births, miscarriages and therapeutic termination.[95] In a series of intentional infliximab use during pregnancy in 10 CD patients, Mahadevan *et al.* showed good outcomes, with no congenital malformations, intrauterine growth retardation or small for gestational age infants. However, three infants were premature, and one had low birth weight.[96] Other smaller case reports and case series of IFX use in pregnancy in IBD patients have also reported no congenital malformations, although infants were preterm or small for gestational age.[97–101]

A recent observational study assessed pregnancy outcomes in 212 women with IBD treated with anti-TNF treatments- 42 pregnancies in women who received anti-TNF (35 IFX, 7 ADA), 23 pregnancies prior to IBD diagnosis, 78 pregnancies before start of IFX, 53 pregnancies with indirect exposure to IFX and 56 matched pregnancies in healthy women. They found that pregnancy outcomes after exposure to anti-TNF treatments were no different than before anti-TNF treatment, but were worse than before IBD diagnosis.[99]

Both the recent review by the mother risk programme in Canada[102] and the London position statement at the World Congress of Gastroenterology consensus guideline[102, 103] consider infliximab to have a low foetal risk and to be compatible with the use during conception in at least first and second trimester. Studies have not shown an increased risk of embryo toxicity, teratogenicity or adverse pregnancy outcome in patients treated with anti-TNF therapy.[104]

However, the use of IFX up to week 30 of gestation results in foetal intra-uterine exposure to high IFX levels (up to three fold higher than in the maternal peripheral blood), which raises concern regarding long-term effects of IFX on the children of women with IBD on IFX.[105] The authors recommended that such therapy be avoided after 30 weeks gestation when possible.

Particularly, caution should be taken when considering vaccination for the infants who were exposed to IFX. There is a case report of an infant who was exposed to IFX during gestation and then vaccinated with BCG vaccine at 3 months. This infant died of disseminated BCG.[106]

Bisphosphonates (FDA C). Bisphosphonates are used to treat and prevent osteoporosis due to corticosteroid use. Almost 50% of the bisphosphate binds to the skeleton and the remainder is excreted by the kidneys.[107] The half-life of alendronate, one of the commonly used bisphosphonates, is >10 years, and the long-term effects on human bone development remain unknown. The drug may be slowly released from the maternal bone, and may cross the placenta, incorporating itself into the foetal bone during gestation. In animal studies, bisphosphonates cross the placenta, accumulate in the foetal skeleton, decrease foetal weight, decrease bone growth and resulted in protracted deliveries and neonatal deaths.[108] In 2006, Ornoy *et al.* published a short report of the pregnancy outcome of 24 women on alendronate, 1–6 months before pregnancy (eight women) or before and during the first 3–8 weeks of pregnancy (15 women). They found significantly lower weight and gestational age at birth in these pregnancies compared with a control group. They also found a higher rate of spontaneous abortions (20.8%), but they reported no major anomalies in the children of the treated women, whereas 2.8% of the control children had major anomalies.[109]

There have been multiple other small studies and case reports on the effect of bisphosphonate use prior to conception, and the literature shows that preconceptional bisphosphonate therapy does not seem to induce substantial foetal or maternal risks or serious adverse effects.[110]

A recent multi-centre, prospective cohort study of 21 women exposed to Bisphosphonate (alendronate, etidronate, risedronate, pamidronate) during or <3 months before pregnancy and 21 matched-comparison group women without exposure to known teratogens, also did not find any statistically significant difference in spontaneous or therapeutic abortion, mean gestational age, mean birth weight or congenital anomalies.[111] The risks and benefits of using bisphosphonates in women of childbearing age must be considered, and discussed with the patient and her partner.

DECISION-MAKING NODE #3: DELIVERY

Question: Should the patient have caesarean section or vaginal delivery?

Pregnant women with IBD may be up to 1.5–2 times more likely to undergo a cesaerean section.[2, 35] This may be an attempt to avoid risk of anal sphincter damage or to avoid the risk of development or worsening of perianal CD.[112] Indications for caesarean section are active perianal disease and the presence of an ileoanal pouch, but there is no absolute contraindication to vaginal delivery in pregnant patients with inactive IBD.[113] The

Aliment Pharmacol Ther 2012; 35: 501-515

decision to have a caesarean section should be based on a discussion with the patient, the obstetrician, and the gastroenterologist.

DECISION-MAKING NODE #4: BREAST FEEDING

Question: What medications are safe to use during breast feeding?

5-ASA compounds sulfasalazine/mesalamine/olsalazine. Caution should be exercised when Sulfasalazine is administered to a nursing woman as sulphonamides are excreted in the milk (reportedly about 40% of maternal serum concentration.[52] In the newborn, they compete with bilirubin for binding sites of the plasma proteins and may cause kernicterus.

Immunomodulators: azathioprine/mercaptopurine. Women who are receiving thiopurine derivatives are often discouraged from nursing with the concern that the drug is excreted in the mother's milk. There are potential risks of bone marrow suppression, susceptibility to infection and pancreatitis in the neonate. The majority of the metabolites is excreted within the first 4 h after drug intake.[114] In a prospective study of 10 women on AZA while breast feeding, only one woman had a low measurable level of MP in two breast milk samples. The concentration of MP was 1.2 and 7.6 ng/mL, compared with the therapeutic immunosuppressant level of 50 ng/mL in serum.[115] In a study of 11 mothers taking AZA during pregnancy and lactation compared with 12 patients without any immunosuppressive therapy, there was no increased risk of infections in babies exposed to AZA in utero and via breastfeeding.[116] The ECCO consensus supports that breastfeeding under maintenance AZA therapy could be advised for women who wish to nurse their infants. The risks and benefits of continuing treatment with thiopurines should be discussed with the mother [114, 117] and the infants should receive continued monitoring and long-term assessment.[115, 118]

Corticosteroids. Corticosteroids are secreted into breast milk, and foetal levels are 10–12% of the maternal levels, depending on the steroid preparation. Infants of mothers who are taking more than a daily dose of 40 mg prednisolone or equivalent are unlikely to have systemic effects,[119, 120] but it is suggested that they should be monitored for adrenal suppression. Mothers should be encouraged to wait 4 hrs after taking oral steroids before breastfeeding to decrease neonatal exposure. There are few studies on oral budesonide and breast feeding, but a study on nursing mothers with asthma on maintenance treatment of inhaled budesonide (200 or 400 μg BID) showed minimal systemic exposure in the breast fed infants.[121]

Ciclosporin. Ciclosporin has been measured in breast milk in varying levels, with reported high concentrations in the infant.[122] Current recommendations by the American Paediatric Association are to avoid breast feeding while taking CsA because of the potential toxic side effects and immunosuppressive action on the newborn.[20]

Biologics. Vasiliauskas[123] measured infliximab levels in a 32-year-old pregnant patient who continued on standard-dose infliximab therapy during her pregnancy and lactation. The measurement of serum infliximab in the breast-fed infant was 39.5 μg/mL or less and the drug was not detected in the breast milk. Despite continued breast feeding and adherence to therapy, the levels declined in the infant over the subsequent 6 months. They concluded that infliximab levels were more likely due to placental transfer and less likely the result of breastfeeding.

Recently, Stengel *et al.*[124] published a case report in which serial sampling over a 1-month time period failed to detect infliximab in breast milk, and no developmental abnormalities were noted in the child up to 2 years. Ostensen *et al.*[125] showed that etanercept, a soluble TNF-alpha receptor fusion protein, was detected in breast milk with maximal doses noted the day after the injection. The European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT), an international multidisciplinary panel emphasises the need for further large, randomized controlled trials on the safety of biologics.[126]

The risks and benefits of continuing biologics during pregnancy should be discussed with the patient. It is suggested that pregnant women who are receiving biologics and are in remission should continue therapy, but Infliximab and Adalumimab should be held at 30 weeks and restarted after delivery. There is no data to contradict breast feeding in these patients.

SUMMARY: TYING IT ALL TOGETHER FOR THE PATIENT

A better understanding of the issues surrounding IBD and pregnancy and frank discussion with the patient and her partner may help them to address their fears and make educated decisions regarding family planning. Management of a pregnant woman with IBD should include the family physician, the gastroenterologist and the obstetrician. Most women with IBD who are in

remission will be able to conceive and have a normal pregnancy. Women with UC who have undergone ileal pouch-anal anastomosis may have a lower chance of conception. Therefore, women with active UC who require colectomy and who plan to have a family may consider having an ileostomy first, and then a pouch surgery after conceiving. Most drugs used to treat IBD are safe to use in pregnancy and breast feeding, with the exception of methotrexate and thalidomide. The biological agents do cross the placenta, mainly in the third trimester, and should be held after 30 weeks of gestation and restarted after delivery. Pregnant IBD patients should be encouraged to continue their medications during the pregnancy and while breast feeding, with the understanding of the current evidence of the risks and benefits of doing so. Most importantly, the mother's decision on disease management and drug therapy should be respected and they should be supported throughout this life-changing event.

Important concepts in management of the IBD patient considering conception and pregnancy:

(i) Preconception counselling on the following issues: nutrition, cessation of smoking and alcohol use, controlling disease activity, continuation of medications to ensure maintenance of remission.

(ii) Pregnancy outcome is better if patients remain in remission during pregnancy.

(iii) Drugs used to treat IBD appear to be safe during pregnancy, with the exception of methotrexate and thalidomide.

(iv) Drugs used to treat IBD appear to be safe during lactation, except for CsA.

(v) Biological agents may be continued up to 30 weeks gestation.

(vi) Management of the pregnant patient should be multi-disciplinary involving the patient and her partner, the family physician, the gastroenterologist and the obstetrician.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

1. Andres PG, Friedman LS. Epidemiology and the natural course of inflammatory bowel disease. *Gastroenterol Clin North Am* 1999; **28**: 255–81, vii.
2. Cornish J, Tan E, Teare J, *et al.* A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007; **56**: 830–7.
3. Mountifield RE, Prosser R, Bampton P, Muller K, Andrews JM. Pregnancy and IBD treatment: this challenging interplay from a patients' perspective. *J Crohns Colitis* 2010; **4**: 176–82.
4. Mountifield R, Bampton P, Prosser R, Muller K, Andrews JM. Fear and fertility in inflammatory bowel disease: a mismatch of perception and reality affects family planning decisions. *Inflamm Bowel Dis* 2009; **15**: 720–5.
5. Orholm M, Binder V, Sorensen TI, Rasmussen LP, Kyvik KO. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. *Scand J Gastroenterol* 2000; **35**: 1075–81.
6. Tysk C, Lindberg E, Jarnerot G, Floderus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. *Gut* 1988; **29**: 990–6.
7. Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut* 1993; **34**: 517–24.
8. Khosla R, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. *Gut* 1984; **25**: 52–6.
9. Hudson M, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997; **58**: 229–37.
10. 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**: 821–5.
11. Baird DD, Narendranathan M, Sandler RS. Increased risk of preterm birth for women with inflammatory bowel disease. *Gastroenterology* 1990; **99**: 987–94.
12. Arkuran C, McComb P. Crohn's disease and tubal infertility: the effect of adhesion formation. *Clin Exp Obstet Gynecol* 2000; **27**: 12–3.
13. Baiocco PJ, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. *J Clin Gastroenterol* 1984; **6**: 211–6.
14. Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. *Int J Colorectal Dis* 2011; **26**: 1365–74.
15. Olsen KO, Joelsson M, Laurberg S, Oresland T. Fertility after ileal pouch-anal anastomosis in women with ulcerative colitis. *Br J Surg* 1999; **86**: 493–5.
16. Cornish JA, Tan E, Teare J, *et al.* The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. *Dis Colon Rectum* 2007; **50**: 1128–38.
17. Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006; **55**: 1575–80.
18. Oresland T, Palmblad S, Ellstrom M, Berndtsson I, Crona N, Hulten L. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. *Int J Colorectal Dis* 1994; **9**: 77–81.

19. Cornish JA, Tan E, Singh B, *et al.* Female infertility following restorative proctocolectomy. *Colorectal Dis* 2011; **13**: e339–44.
20. Kwan LY, Mahadevan U. Inflammatory bowel disease and pregnancy: an update. *Expert Rev Clin Immunol* 2010; **6**: 643–57.
21. Mortier PE, Gambiez L, Karoui M, *et al.* Colectomy with ileorectal anastomosis preserves female fertility in ulcerative colitis. *Gastroenterol Clin Biol* 2006; **30**: 594–7.
22. van der Woude CJ, Kolacek S, Dotan I, *et al.* European evidenced-based consensus on reproduction in inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 493–510.
23. Fonager K, Sorensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. *Am J Gastroenterol* 1998; **93**: 2426–30.
24. Kornfeld D, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease – a population-based cohort study. *Am J Obstet Gynecol* 1997; **177**: 942–6.
25. Norgard B, Fonager K, Sorensen HT, Olsen J. Birth outcomes of women with ulcerative colitis: a nationwide Danish cohort study. *Am J Gastroenterol* 2000; **95**: 3165–70.
26. Elbaz G, Fich A, Levy A, Holcberg G, Sheiner E. Inflammatory bowel disease and preterm delivery. *Int J Gynaecol Obstet* 2005; **90**: 193–7.
27. Subhani JM, Hamiliton MI. Review article: the management of inflammatory bowel disease during pregnancy. *Aliment Pharmacol Ther* 1998; **12**: 1039–53.
28. Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007; **133**: 1106–12.
29. Lin HC, Chiu CC, Chen SF, Lou HY, Chiu WT, Chen YH. Ulcerative colitis and pregnancy outcomes in an Asian population. *Am J Gastroenterol* 2010; **105**: 387–94.
30. Bush MC, Patel S, Lapinski RH, Stone JL. Perinatal outcomes in inflammatory bowel disease. *J Matern Fetal Neonatal Med* 2004; **15**: 237–41.
31. Stephansson O, Larsson H, Pedersen L, *et al.* Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. *Inflamm Bowel Dis* 2011; **17**: 795–801.
32. Dejaco C, Angelberger S, Waldhoer T, *et al.* Risk factors for pregnancy outcome in patients with inflammatory bowel disease (IBD). *Gastroenterology* 2006; **130**(Suppl. 2): A: 39.
33. Carter MJ, Lobo AJ, Travis SP, IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004; **53** (Suppl. 5): V1–16.
34. Molnar T, Farkas K, Nagy F, *et al.* Pregnancy outcome in patients with inflammatory bowel disease according to the activity of the disease and the medical treatment: a case-control study. *Scand J Gastroenterol* 2010; **45**: 1302–6.
35. Raatikainen K, Mustonen J, Pajala MO, Heikkinen M, Heinonen S. The effects of pre- and post-pregnancy inflammatory bowel disease diagnosis on birth outcomes. *Aliment Pharmacol Ther* 2011; **33**: 333–9.
36. Bortoli A, Pedersen N, Duricova D, *et al.* Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003–2006. *Aliment Pharmacol Ther* 2011; **34**: 724–34.
37. Caruso A, De Carolis S, Ferrazzani S, Trivellini C, Mastromarino C, Pittiruti M. Pregnancy outcome and total parenteral nutrition in malnourished pregnant women. *Fetal Diagn Ther* 1998; **13**: 136–40.
38. Chakrabarty G, Poullis A. Inflammatory bowel disease, drug therapy and pregnancy: awareness in female IBD patients of reproductive age. *Gut* 2011; **60**: A135.
39. Alstead E. Inflammatory bowel disease in pregnancy. *Postgrad Med J* 2002; **78**: 23–6.
40. Lakatos P, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: good, bad or ugly? *World J Gastroenterol* 2007; **13**: 6134–9.
41. Shah N, Bracken BM. A systemic review and meta-analysis of prospective studies on the association between cigarette smoking and preterm delivery. *Am J Obtstet Gynecol* 2000; **182**: 465–72.
42. Mercer BM, Merlino AA, Milluzzi CJ, Moore JJ. Small fetal size before 20 weeks' gestation: associations with maternal tobacco use, early preterm birth, and low birthweight. *Am J Obstet Gynecol* 2008; **198**: 673, e7–8.
43. Davies J, Bledsoe BJ. Prenatal alcohol and drug exposures in adoption. *Pediatr Clin* 2005; **52**: 1369–93.
44. Qureshi WA, Rajan E, Adler DG, *et al.* ASGE guideline: guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2005; **61**: 357–62.
45. Kammerer WS. Non-obstetric surgery during pregnancy. *Med Clin North Am* 1979; **63**: 1157.
46. Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998; **317**: 839–43.
47. Ornoy A, Arnon J, Shechtman S, Moerman L, Lukashova I. Is benzodiazepine use during pregnancy really teratogenic? *Reprod Toxicol* 1998; **12**: 511–5.
48. Gin T. Propofol during pregnancy. *Acta Anaesthesiol Sin* 1994; **32**: 127–32.
49. Moskovitz DN, Bodian C, Chapman ML, *et al.* The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. *Am J Gastroenterol* 2004; **99**: 656–61.
50. Czeizel AE, Dudas I, Paput L, Banhidy F. Prevention of neural-tube defects with periconceptional folic acid, methylfolate, or multivitamins? *Ann Nutr Metab* 2011; **58**: 263–71.
51. Bayless TM, Hanauer SB ed. *Advanced Therapy of Inflammatory Bowel Disease*. Hamilton: B.C. Decker Inc, 2001.
52. Jarnerot G, Into-Malmberg MB. Sulphasalazine treatment during breast feeding. *Scand J Gastroenterol* 1979; **14**: 869–71.
53. Mahadevan U, Corley DA. Aminosalicylate (ASA) use during pregnancy is not associated with increased adverse events or congenital malformations (CM) in women with inflammatory bowel disease (IBD). *Gastroenterology* 2006; **130**(Suppl. 2): A40.
54. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008; **25**): 271–5.
55. Hernández-Díaz S, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates in the U.S. population. *Environ Health Perspect* 2009; **117**: 185–9.
56. FDA U.S. Food and Drug Administration: Asacol (mesalamine) delayed release tablets. *FDA 2010 Safety Labeling Changes Approved By FDA Center for Drug Evaluation and*

Research (CDER). Silverspring, MD, 2010.
57. Zimm S, Collins JM, Riccardi R, *et al.* Variable bioavailability of oral mercaptopurine. Is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? *N Engl J Med* 1983; **308**: 1005–9.
58. Gisbert JP, Linares PM, McNicholl AG, Mate J, Gomollon F. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. *Aliment Pharmacol Ther* 2009; **30**: 126–37.
59. Golby M. Fertility after renal transplantation. *Transplantation* 1970; **10**: 201–7.
60. Penn I, Makowski E, Droegemueller W, Halgrimson CG, Starzl TE. Parenthood in renal homograft recipients. *JAMA* 1971; **216**: 1755–61.
61. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003; **124**: 9–17.
62. Goldstein LH, Dolinsky G, Greenberg R, *et al.* Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res A Clin Mol Teratol* 2007; **79**: 696–701.
63. Langagergaard V, Pederson L, Gislum M, *et al.* Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy : a Danish nationwide cohort study. *Aliment Pharmacol Ther* 2006; **25**: 73 –81.
64. Norgard B, Pedersen L, Christensen LA, Sorensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007; **102**: 1406–13.
65. Simpson PW, Melmed GY, Dubinksy M. The impact of medical therapy for inflammatory bowel disease on pregnancy outcome. *Am J Gastroenterol* 2008; **103**: 805–6.
66. Cleary BJ, Kallen B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res A Clin Mol Teratol* 2009; **85**: 647–54.
67. Shim L, Eslick GD, Simring AA, Murray H, Weltman MD. The effects of azathioprine on birth outcomes in women with inflammatory bowel disease (IBD). *J Crohns Colitis* 2011; **5**: 234–8.
68. Coelho J, Beaugerie L, Colombel JF, *et al.* Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME study. *Gut* 2011; **60**: 198–203.
69. Van Assche G, Dignass A, Reinisch W, *et al.* The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 2010; **4**: 63–101.
70. Mahadevan U, Kane S. American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 2006; **131**: 283–311.
71. Alstead EM, Nelson-Piercy C. Inflammatory bowel disease in pregnancy. *Gut* 2003; **52**: 159–61.
72. Murphy BE, Clark SJ, Donald IR, Pinsky M, Vedady D. Conversion of maternal cortisol to cortisone during placental transfer to the human fetus. *Am J Obstet Gynecol* 1974; **118**: 538–41.
73. Lopez Bernal A, Anderson AB, Parry DM, Turnbull AC. Evidence that fetal membranes are not involved in cortisol metabolism: study of dichorionic twin pregnancies. *Am J Obstet Gynecol* 1980; **138**: 1168–72.
74. Beitins IZ, Bayard F, Ances IG, Kowarski A, Migeon CJ. The metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. *Pediatr Res* 1973; **7**: 509–19.
75. Stewart PM, Rogerson FM, Mason JI. Type 2 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid and activity in human placenta and fetal membranes: its relationship to birth weight and putative role in fetal adrenal steroidogenesis. *J Clin Endocrinol Metab* 1995; **80**: 885–90.
76. Mogadam M, Dobbins WO3rd, Korelitz BI, Ahmed SW. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. *Gastroenterology* 1981; **80**: 72–6.
77. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999; **86**: 242–4.
78. Pradat P, Robert-Gnansia E, Di Tanna GL, *et al.* First trimester exposure to corticosteroids and oral clefts. *Birth Defects Res A Clin Mol Teratol* 2003; **67**: 968–70.
79. Khan AA, Rodriguez A, Kaakinen M, Pouta A, Hartikainen AL, Jarvelin MR. Does in utero exposure to synthetic glucocorticoids influence birthweight, head circumference and birth length? A systematic review of current evidence in humans. *Paediatr Perinat Epidemiol* 2011; **25**: 20–36.
80. Anders H, Molgaard-Nielsen D. Corticosteroid use during pregnancy and risk of oro facial clefts. *CMAJ* 2011; **183**: 796–804.
81. Beaulieu DB, Ananthakrishnan AN, Issa M, *et al.* Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. *Inflamm Bowel Dis* 2009; **15**: 25–8.
82. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999; **94**: 1587–92.
83. Lichtiger S. Treatment of choice for acute severe steroid-refractory ulcerative colitis is cyclosporine. *Inflamm Bowel Dis* 2009; **15**: 141–2.
84. Nagy S, Bush MC, Berkowitz R, Fishbein TM, Gomez-Lobo V. Pregnancy outcome in liver transplant recipients. *Obstet Gynecol* 2003; **102**: 121–8.
85. Imseis HM, Zimmerman PD, Samuels P, Kniss DA. Tumour necrosis factor-alpha induces cyclo-oxygenase-2 gene expression in first trimester trophoblasts: suppression by glucocorticoids and NSAIDs. *Placenta* 1997; **18**: 521–6.
86. Yu XW, Li X, Ren YH, Li XC. Tumour necrosis factor-alpha receptor 1 polymorphisms and serum soluble TNFR1 in early spontaneous miscarriage. *Cell Biol Int* 2007; **31**: 1396–9.
87. Daher S, Fonseca F, Ribeiro OG, Musatti CC, Gerbase-DeLima M. Tumor necrosis factor during pregnancy and at the onset of labor and spontaneous abortion. *Eur J Obstet Gynecol Reprod Biol* 1999; **83**: 77–9.
88. Toder V, Fein A, Carp H, Torchinsky A. TNF-alpha in pregnancy loss and embryo maldevelopment: a mediator of detrimental stimuli or a protector of the fetoplacental unit? *J Assist Reprod Genet* 2003; **20**: 73–81.
89. Niessner M, Volk BA. Altered Th1/Th2 cytokine profiles in the intestinal mucosa of patients with inflammatory bowel disease as assessed by quantitative reversed transcribed polymerase chain reaction (RT-PCR). *Clin Exp Immunol* 1995; **101**: 428–35.
90. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am J Gastroenterol* 2009; **104**: 228–33.
91. Stephens P, Nesbitt A, Foulkes R. Placental transfer of the anti-TNF antibody TN3 in rats: comparison of immunoglobulin G1 and pegylated

Fab versions. *Gut* 2006; **55**(Suppl.): A8.
92. Wolf D, Mahadevan U. Certolizumab pegol use in pregnancy: low levels detected in cord blood. *Arthritis Rheum* 2010; **62**(Suppl. 10): 718.
93. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology (Oxford)* 2007; **46**: 695–8.
94. Verstappen SM, King Y, Watson KD, Symmons DP, Hyrich KL, BSRBR Control Centre Consortium, BSR Biologics Register. Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011; **70**: 823–6.
95. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004; **99**: 2385–92.
96. Mahadevan U, Kane S, Sandborn WJ, *et al.* Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* 2005; **21**: 733–8.
97. Aratari A, Margagnoni G, Koch M, Papi C. Intentional infliximab use during pregnancy for severe steroid-refractory ulcerative colitis. *J Crohns Colitis* 2011; **5**: 262.
98. Angelucci E, Cocco A, Viscido A, Caprilli R. Safe use of infliximab for the treatment of fistulizing Crohn's disease during pregnancy within 3 months of conception. *Inflamm Bowel Dis* 2008; **14**: 435–6.
99. Schnitzler F, Fidder H, Ferrante M, *et al.* Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis* 2011; **17**: 1846–54.
100. Tursi A. Effect of intentional infliximab use throughout pregnancy in inducing and maintaining remission in Crohn's disease. *Dig Liver Dis* 2006; **38**: 439–40.
101. Burt MJ, Frizelle FA, Barbezat GO. Pregnancy and exposure to infliximab (anti-tumor necrosis factor-alpha monoclonal antibody). *J Gastroenterol Hepatol* 2003; **18**: 465–6.
102. Djokanovic N, Klieger-Grossmann C, Pupco A, Koren G. Safety of infliximab use during pregnancy. *Reprod Toxicol* 2011; **32**: 93–7.
103. Mahadevan U, Cucchiara S, Hyams JS, *et al.* The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 2011; **106**: 214–23.
104. Skomsvoll JF, Wallenius M, Koksvik HS, *et al.* Drug insight: anti-tumor necrosis factor therapy for inflammatory arthropathies during reproduction, pregnancy and lactation. *Nat Clin Pract Rheumatol* 2007; **3**: 156–64.
105. Zelinkova Z, de Haar C, de Ridder L, *et al.* High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2011; **33**: 1053–8.
106. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis* 2010; **4**: 603–5.
107. Papapoulos SE. Bisphosphonates: how do they work? *Best Pract Res Clin Endocrinol Metab* 2008; **22**: 831–47.
108. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. *Teratology* 1999; **60**: 68–73.
109. Ornoy A, Wajnberg R, Diav-Citrin O. The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. *Reprod Toxicol* 2006; **22**: 578–9.
110. Hassen-Zrour S, Korbaa W, Bejia I, Saidani Z, Bergaoui N. Maternal and fetal outcome after long-term bisphosphonate exposure before conception. *Osteoporos Int* 2010; **21**: 709–10.
111. Levy S, Fayez I, Taguchi N, *et al.* Pregnancy outcome following in utero exposure to bisphosphonates. *Bone* 2009; **44**: 428–30.
112. Brandt LJ, Estabrook SG, Reinus JF. Results of a survey to evaluate whether vaginal delivery and episiotomy lead to perineal involvement in women with Crohn's disease. *Am J Gastroenterol* 1995; **90**: 1918–22.
113. Ilnyckyji A, Blanchard JF, Rawsthorne P, Bernstein CN. Perianal Crohn's disease and pregnancy: role of the mode of delivery. *Am J Gastroenterol* 1999; **94**: 3274–8.
114. Christensen LA, Dahlerup JF, Nielsen MJ, Fallingborg JF, Schmiegelow K. Azathioprine treatment during lactation. *Aliment Pharmacol Ther* 2008; **28**: 1209–13.
115. Sau A, Clarke S, Bass J, Kaiser A, Marinaki A, Nelson-Piercy C. Azathioprine and breastfeeding: is it safe? *BJOG* 2007; **114**: 498–501.
116. Angelberger S, Reinisch W, Messerschmidt A, *et al.* Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. *J Crohns Colitis* 2011; **5**: 95–100.
117. Gardiner SJ, Gearry RB, Roberts RL, Zhang M, Barclay ML, Begg EJ. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006; **62**: 453–6.
118. Moretti ME, Verjee Z, Ito S, Koren G. Breast-feeding during maternal use of azathioprine. *Ann Pharmacother* 2006; **40**: 2269–72.
119. Ferguson CB, Mahsud-Dornan S, Patterson RN. Inflammatory bowel disease in pregnancy. *BMJ* 2008; **337**: a427.
120. Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. *Am J Obstet Gynecol* 1977; **127**: 264–7.
121. Falt A, Bengtsson T, Kennedy BM, *et al.* Exposure of infants to budesonide through breast milk of asthmatic mothers. *J Allergy Clin Immunol* 2007; **120**: 798–802.
122. Moretti ME, Sgro M, Johnson DW, *et al.* Cyclosporine excretion into breast milk. *Transplantation* 2003; **75**: 2144–6.
123. Vasiliauskas EA, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. *Clin Gastroenterol Hepatol* 2006; **4**: 1255–8.
124. Stengel JZ, Arnold HL. Is infliximab safe to use while breastfeeding? *World J Gastroenterol* 2008; **14**: 3085–7.
125. Ostensen M, Eigenmann GO. Etanercept in breast milk. *J Rheumatol* 2004; **31**: 1017–8.
126. Mottet C, Vader JP, Felley C, *et al.* Appropriate management of special situations in Crohn's disease (upper gastro-intestinal; extra-intestinal manifestations; drug safety during pregnancy and breastfeeding): results of a multidisciplinary international expert panel-EPACT II. *J Crohns Colitis* 2009; **3**: 257–63.