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Review article: reproduction in the patient with inflammatory bowel disease

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SUMMARY

Background
Inflammatory bowel disease (IBD) affects mainly the young population. The effect of IBD and its treatment on fertility and pregnancy is therefore an important clinical consideration.

Aim
To review the best management of IBD in the reproductive and pregnant population.

Methods
A MEDLINE and an EMBASE search were performed using mainly the search phrases 'pregnancy AND IBD,' 'sulphasalazine AND male fertility,' 'abdominal surgery AND female fertility,' 'AZA AND placenta' and 'infliximab AND pregnancy.' No language or date restrictions were placed. References of review articles were examined.

Results
Overall male and female fertility are not affected by IBD. Sulphasalzine reduces male fertility. No other drugs used in IBD affect significantly fertility in humans. The risk of pregnancy-related complications and the disease behaviour during pregnancy depends mainly on disease activity at time of conception. Proactive treatment for maintenance of disease remission during gestation is recommended. Except for methotrexate, drugs used in IBD appear safe in pregnancy. Breast feeding should be encouraged.

Conclusion
The management of IBD in the young and pregnant population remains controversial because the literature comes mostly from retrospective studies. Further studies particularly large prospective trials are needed to guide clinicians in decision making.

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INTRODUCTION

Ulcerative Colitis (UC) and Crohn's Disease (CD) are two chronic idiopathic gastrointestinal conditions, commonly referred to as inflammatory bowel disease (IBD). Their incidence shows a bimodal distribution curve with the higher peak in the younger population. Fifty percent of patients are less than 35-years old at the time of diagnosis[1] and a quarter of them conceive for the first time after the diagnosis.[2] The impact of IBD and its treatment on fertility and pregnancy is therefore an important clinical consideration. The management of IBD in the fertile or pregnant patient is controversial because most of the evidence relating to fertility and pregnancy in IBD comes from opinions of experts and a few case-control trials rather than randomized control trials.[3] The aim of this review article is to summarize the current literature on fertility and pregnancy in the presence of IBD and provide a critical review as to best management of IBD in the reproductive and pregnant population.

METHODS

A MEDLINE and an EMBASE search were performed using the Boolean search phrases 'pregnancy AND IBD,' 'sulphasalazine AND male fertility,' 'corticosteroids AND male fertility,' 'meta-analysis on male fertility in IPAA,' 'abdominal surgery AND female fertility,' 'smoking AND IBD,' 'pouch function AND pregnancy,' 'elemental diet AND C.D.,' 'sulphasalzine AND placenta,' 'folic acid AND congenital malformations,' 'corticosteroids AND placenta,' 'budesonide AND pregnancy,' 'AZA AND placenta,' 'methotrexate AND congenital malformations,' 'cyclosporine AND IBD,' 'co-amoxiclav AND pregnancy,' 'loperamide AND pregnancy,' 'lomotil AND pregnancy,' 'infliximab AND pregnancy,' 'adalimumab AND pregnancy,' 'corticosteroids AND breast feeding,' 'propofol AND pregnancy,' 'inheritance AND IBD' and 'genetic anticipation in IBD.' No language or date restrictions were placed on the search criteria. The references of review articles were examined for potentially eligible studies. Date of last search was 17 February 2007.

FINDINGS

A total of 196 articles were found and reviewed. These included three editorials, 11 animal and *in vitro* studies, 28 case reports, 13 epidemiological studies, 54 retrospective studies, 18 case-control studies, 16 prospective studies, 41 review articles, four meta-analyses and eight randomized trials. Articles were analysed by both physicians and surgeons experienced in the management of IBD.

RESULTS

Male fertility

Infertility is defined as the failure to conceive after 1 year of regular sexual intercourse without the use of contraception. Infertility and subfertility are used interchangeably. Overall IBD itself does not seem to affect fertility in males. Concerns about reproductive potential of men with CD arose when a case-control study of 1400 patients showed that the mean number of children born to men with CD is significantly lower compared to men with UC and the general population.[4] There was no significant difference between the mean number of children born to males with UC and the general population. The fecundability (probability of pregnancy within one menstrual cycle) of the three population groups is not significantly different from each other.[5] This suggests that the reduced family size in patients with CD may not be due to a physical effect of the disease. The confidence and self-image of young adults can easily be hampered by the course of IBD and its treatment. This may lead to difficulties in forming intimate relationships.[6] Overall frequency of sexual intercourse has however not been shown to differ significantly amongst patients with IBD compared with the matched controls.[7] The smaller family size may be due to fear of disease transmission to offspring or a decision to limit family size rather than an innate inability to conceive.

Sulphasalazine and 5-aminosalicylates are frequently used for maintenance of disease remission. Levi *et al.*[8] in 1979 initially reported four cases of infertility in males exposed to sulphasalazine. All four men were able to conceive following discontinuation of therapy. Subsequent research showed that the drug causes oligospermia and has an adverse effect on both sperm morphology and motility. These effects are secondary to the non-therapeutic sulphapyridine moiety of sulphasalazine and are fully reversible upon drug cessation.[9–12] Restoration of semen quality has also been demonstrated after replacing sulphasalazine with 5-aminosalicylic acid (5-ASA).[13] There appears to be an increased risk of congenital malformations in

infants born to males exposed to sulphasalazine.[4] Prospective fathers should be advised to discontinue the drug or be switched to 5-ASA compounds lacking the sulphapyridine moiety.

Corticosteroids are used for induction of disease remission. They are highly efficacious but their long-term use is limited by side effects. There are few data on the effect of corticosteroids on male fertility. Studies on rats show that exogenous corticosteroids cause a reduction in serum testosterone but have no effect on the level of gonadotropins.[14] In the Lerman *et al.*[15] study although there were no changes in sperm count and motility, fertility was reduced in rats exposed to corticosteroids. These changes were fully reversible upon cessation of steroid administration. In humans Roberts *et al.*[16] showed that an increase in endogenous steroids may be linked with a subsequent decrease in sperm concentration. Steroids should therefore be used only for short periods of time to control active disease.

Immunosuppressants have a well-defined role in refractory IBD. The use of mercaptopurine (MP) and azathioprine (AZA) in men of child-bearing age is controversial. The use of MP in male mice has been associated with a significant reduction in fertility.[17] Rajapakse *et al.*[18] showed an increased incidence of congenital malformations, particularly congenital limb abnormalities and gestational complications in offsprings of men exposed to MP within 3 months of conception. However, it was a small study (only 13 men were exposed to MP within 3 months of conception) and several statistical flaws have been outlined.[19] Furthermore, MP has not been shown to have any deleterious effect on sperm quality nor quantity.[20] More importantly, Francella *et al.*[21] in a large case-control study with 76 males failed to corroborate the above findings. Data from the transplant literature would also support the safe use of MP in prospective fathers.[22] As MP is an inhibitor of *de novo* purine synthesis, some authors have mentioned the possibility of occult sperm damage.[17, 18] However DNA damage due to MP at doses used in IBD has not been demonstrated. It is therefore inappropriate to stop immunosuppressive therapy in males desiring feritility.[23]

Methotrexate (MTX) is used in cases of failure of or intolerance to AZA/MP. It is classified as a Pregnancy Category X by the American's Food and Drug Administration (FDA) (Appendix 1). MTX causes reversible sterility in males.[24, 25] There are currently no reports of MTX-induced congenital abnormalities in infants born to males exposed to the drug. It should nevertheless be discontinued prior to a planned conception. A delay of at least 3 months is recommended due to the prolonged tissue-binding characteristics of MTX.[26]

Biological agents – infliximab (INF) and adalimumab – have recently been introduced in the armamentarium against IBD. INF is a chimeric monoclonal antibody against tumour necrosis factor-alpha (TNF-α). It is indicated in CD resistant to standard therapy and fistulating CD.[27] Evidence of its beneficial effect in UC is accumulating.[28, 29] INF does not cross-react with TNF-α in species other than humans and chimpanzees. Animal reproduction studies with INF have therefore not been conducted. Animal studies using analogous anti-TNF-α agents have not demonstrated an adverse effect on male fertility.[30] There are currently no human data on effect of INF on male fertility. Adalimumab is a recombinant human monoclonal antibody. It is effective and safe in the treatment of CD.[31] There is growing evidence of its effectiveness in patients who have lost response to INF. Its effect on male fertility is equally poorly documented. The use of biological agents in prospective fathers is controversial.

Surgery is required in cases failure of medical therapy, intestinal obstruction or perforation, toxic megacolon and localized complications such as abscesses and fistulae. There is currently no data on the effect of small or large bowel resection on male fertility. An ileal pouch anal anastomosis is the surgery of choice in patients with UC who have failed medical therapy. Rectal excision and pouch formation carries a small risk of male subfertility.[12] One retrospective study involving 111 patients showed that the incidence of sexual dysfunction after an ileal pouch anal anastomosis was nearly 20%.[32] Berndtsson *et al.*[33] in a prospective study with 18 patients demonstrated a small incidence of loss of ejaculation (less than 5%) in males after the surgery. In both studies, however, patients reported a good overall satisfaction with their sexual life albeit some minor complications after surgery.

Female fertility

Overall, the rate of infertility in women with IBD varies between 7% and 12%[34, 35] which does not differ significantly from that of the general population. Earlier studies demonstrated higher rates of infertility up to 66% in CD patients[36] and 49% in patients with UC,[37] possibly reflecting less efficacious treatment available previously. Elbaz *et al.*[38] in a case-control study demonstrated that women with IBD had

increased needs for fertility treatment; however, this association was no longer significant after controlling for maternal age. It is well known that increasing maternal age is associated with subfertility and an increased need for fertility treatment.[39] Rates of dyspareunia and overall frequency of sexual intercourse amongst women with IBD does not differ significantly compared with matched controls.[7] Baird *et al.*[40] in a case-control study involving 216 patients demonstrated a reduction in mean number of children born to women with IBD. This was, however, an effect of the patient's own choice rather than an inability to conceive. It is therefore important to differentiate between voluntary and involuntary childlessness.[12, 41]

Fertility seems to be reduced in patients with CD. In a case-control study involving 275 patients, Mayberry *et al.*[42] showed that the mean number of children born to women with CD is significantly lower compared with the general population. Subfertility in this population can be due to ovarian and tubal disruption, which results from severe active CD and surgery.[12, 41, 43]

There are no reports of an adverse effect on female fertility with the use of sulphasalazine. Corticosteroids have not been associated with impaired fertility in females despite its widespread use in different diseases. AZA use in transplant patients and in patients with autoimmune diseases has not been associated with subfertility in females.[44, 45] MTX should be avoided in women of child-bearing age because it is clearly teratogenic and mutagenic (discussed later). There is currently no data on the effect of the newer biological agents on female fertility in humans; animal studies have not demonstrated an adverse effect on female reproductive potential.[30]

The impact of surgical treatment of IBD on fertility is an important consideration in the young female. The effect of small or large bowel resection on female fertility is poorly documented. Data from the gynaecological literature suggests that bowel resection for other reasons, e.g. endometriosis, is not associated with an adverse effect on fertility.[47, 48] The available literature on the effect of ileal pouch anal anastomosis on fertility is conflicting. Ording *et al.*[49] and Olsen *et al.*[50] demonstrated a significant reduction in fertility after an ileal pouch anal anastomosis. Johnson *et al.*[51] showed in a cohort of 153 females that the mean age for an ileal pouch anal anastomosis is 31 years and the majority of females (57%) do not seek to become pregnant after the procedure. It is currently not clear whether it is an effect of increased maternal age or pouch formation that is responsible for the reduced fertility in this population.

Table 1 summarizes the information regarding male and female fertility.

Effect of inflammatory bowel disease on pregnancy and its outcome

The effect of IBD on pregnancy and its outcome is primarily dependent on disease activity at conception and during gestation. Most studies suggest that women with quiescent disease throughout pregnancy are not at an increased risk of spontaneous abortion, pregnancy-related complications, adverse perinatal outcomes or having a child with congenital abnormalities.[12, 38, 52–58] However, one large Swedish population-based cohort study involving 756 patients with IBD showed that irrespective of disease activity and medical treatment, IBD was an independent risk factor for preterm delivery, low birth weight (LBW) and small for gestational age babies.[59] This study did not differentiate between UC and CD. In a large nationwide Danish cohort study performed by Norgard *et al.*[60]

Table 1. Effect of disease activity and treatment of disease on fertility in males and females

Inflammatory Bowel Disease/Treatment Type	Effect on Fertility		
	Male	Female	References
Active disease	No effect	Reduces	5, 7, 41–43
Sulphasalazine	Significantly reduces	No effect	8–11
5-Aminosalicylic acid	No effect	No effect	13
Corticosteroids	Reduces	No effect	14–16
Mercaptopurine/azathioprine	No effect	No effect	21–23, 44, 45
Biological agents	Unlikely	Unlikely	30
Small/large bowel resection	Unlikely	Unlikely	46–48
Ileal pouch anal anastomosis	Reduces	Reduces	32, 33, 49–51

Table 2. Effect of ulcerative colitis and Crohn's disease on rates of preterm delivery and low birth weight compared to the general population

Outcome	Study	Number of patients	UC adjusted odds ratio	CD adjusted odds ratio*
Preterm delivery (<37 weeks)	Norgard *et al.*[60]	10 565	1.2 (0.9–1.5)	
	Dominitz *et al.*[62]	1570	1.01 (0.40–2.52)	2.31 (1.41–3.77)
	Fonager *et al.*[65]	3528		2.4 (1.6–3.7)
Low Birth Weight (<2500 g)	Norgard *et al.*[60]	10 598	0.8 (0.6–1.2)	
	Dominitz *et al.*[62]	1570	1.13 (0.38–3.35)	3.62 (2.22–5.88)
	Fonager *et al.*[65]	3528		1.6 (1.1–2.3)

CD, Crohn's disease; UC, ulcerative colitis.
* in cases where the adjusted odds ratio was not available, the crude odds ratio is presented.

involving 1531 offsprings born to mothers with UC, there was no significant difference in the rates of preterm delivery, LBW and small for gestational age babies in the patient population compared with controls (Table 2). A compilation of more than 1000 pregnancies carried out by Lamah *et al.*[61] showed that patients with UC are not at an increased risk of spontaneous abortions, perinatal mortality or congenital malformations. Baird *et al.*[33] showed an increased risk of preterm labour in patients with UC before the diagnosis of IBD. These findings were not reproduced in the larger Norgard *et al.*[60] study.

Population-based case-control studies from the American and Danish population showed an increased risk of preterm delivery, LBW and small for gestational age in infants born to mothers with CD[62, 63] (Table 2). Furthermore, Riis *et al.*[64] in a recent European-based cohort study demonstrated a significant increase in rates of spontaneous abortions after the diagnosis of IBD. This increase occurred mainly in patients with CD. The risk of preterm delivery and LBW also seems to be increased after the diagnosis of CD.[65] The rates of congenital malformation are not affected by IBD.[64]

Active disease at time of conception or during gestation is associated with a worse pregnancy outcome. Khosla *et al.*[35] in a cohort of 54 women showed that patients with active CD at conception display rates of miscarriage as high as 35%. Moreover, the incidence of LBW, premature labour and adverse perinatal outcomes are significantly increased.[2, 12, 34, 35, 56, 58, 63, 66] The risk appears to be greater in CD than in UC.[2] The presence of ileal disease in CD patients is also a strong predictor for LBW babies.[67] Women with their first acute episode of IBD during pregnancy are at an increased risk of delivering preterm or low-birth weight babies as documented in a series of 76 cases reported by Beniada *et al.*[53] First hospitalization for UC during pregnancy has also been associated with an increased risk of preterm birth.[60] Most preterm deliveries occur after 35 weeks of gestation and therefore perinatal outcomes are favourable.[38, 62] There has been no consistent reports of increased rates of congenital malformations or perinatal mortality due to active disease. IBD is not associated with complications of pregnancy such as hypertension and proteinuria.[52]

The prevalence of smoking amongst patients with CD is significantly higher compared with the general population.[68] Smoking is an independent risk factor for LBW babies[69] and for disease activity in patients with CD, especially women.[70, 71] Pregnant patients with CD who smoke are at a substantially increased risk of LBW babies and preterm labour.[34, 61] This population should be actively encouraged to give up smoking. Prevalence of smoking in patients with UC is lower compared with the general population.[70] Smoking in patients with UC does not place them at an increased risk of preterm delivery[38] probably due to the beneficial effects of smoking on the course of UC.

Nielsen *et al.*[72] demonstrated in a cohort of 173 pregnancies that resectional surgery during pregnancy carries an increased risk of preterm delivery. The evidence as to whether previous surgery might be a predictor for LBW babies is conflicting.[57, 67]

Effect of gestation on disease activity

Effect of pregnancy on activity of UC

The effect of pregnancy on disease activity is dependent on the disease status at the time of conception. When conception occurs during a period of quiescence, 70–80% of patients will remain in remission throughout the gestational period.[34, 72, 73] The rate of relapse in pregnant patients is therefore similar to non-pregnant patients. If the colitis recurs, it is likely to be mild and responsive to medical treatment. Contrary to previous reports, the first trimester has not been shown to be the time of predilection for disease relapse.[34, 72] The risk of flare-up in the postpartum period seems to be related to disease activity at term. Modagam *et al.*[73] with 324 patients showed that only 13% of patients with quiescent to mild disease at term experienced a flare in the puerperal period in contrast to 53% of patients with active disease at delivery. Disease relapse during pregnancy is often due to discontinuation of maintenance regimen[53] and relapse during the puerperium can be associated with resumption of at-risk behaviours such as smoking.[71]

The presence of active disease at time of conception is associated with a worse prognosis. In 50–70% of patients, the disease will either become chronically active (24% of patients) or worsen and in only one third of women will the disease settle.[6, 73, 74] Willoughby *et al.*[34] in their series noted that active disease under these circumstances is more resistant to medical treatment. This study also documented that 7% of patients will experience their first attack of UC during pregnancy and the puerperium. Previous studies had suggested a poor prognosis for these patients[75] but current experience shows that these attacks are generally mild and respond favourably to medical treatment[34] (Table 3).

In patients with an ileal pouch anal anastomosis, pregnancy is generally well tolerated. A total of 20–30% of patients can be expected to develop disturbances of pouch function, most commonly in the third trimester.[76, 77] These are mainly increased bowel frequency and mild decrease in continence. The majority of these changes are temporary and resolve completely during the puerperium.

The rate of caesarean section is higher in patients with UC compared with the general population.[78] Riis *et al.*[64] in a cohort of 580 pregnancies demonstrated a significant increase in rates of caesarean section in gestations occurring after the diagnosis of IBD compared with prediagnosis pregnancies. The reasons for this trend are unknown. The risk of occult sphincter damage following vaginal delivery especially with forceps is well documented and the presence of sphincter defects is associated with bowel symptoms such as urgency and incontinence.[79] This is particularly important in patients with a chronic diarrhoeal illness. The higher rate of caesarean section may therefore reflect fear of postpartum faecal incontinence. However UC is not an indication for caesarean section. Women with UC should be allowed to have a normal vaginal delivery and caesarean section only be performed for obstetrical reasons. The recommended mode of delivery in a patient with an ileal pouch anal anastomosis remains disputed. Caesarean section is more commonly performed in this population compared with patients with an ileostomy and less that 50% of those are for obstetrical reasons.[77] Pouch function, including continence and quality of life are not affected by uncomplicated vaginal delivery on the short term.[80–82] There is however no long-term data (i.e. 30–40 years) on pouch function after vaginal delivery. Most colorectal surgeons would advise for an elective caesarean section due to the potential risk of faecal incontinence on long term.

Table 3. Summary of effect of gestation on course of IBD

	% of patients in remission during pregnancy		% of patients with worsening/ chronically active disease during pregnancy	
	UC	CD	UC	CD
Disease in remission at conception	70–80%[34, 72, 73]	70%[35, 55, 83]	20–30%[34, 72, 73]	30%[35, 55, 83]
Active disease at conception	30%[6, 73, 74]	33%[6, 52, 61, 85]	50–70%[6, 73, 74]	67%[6, 52, 61, 85]

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease.

Effect of pregnancy on the activity of CD

The behaviour of CD during pregnancy is very similar of that of UC. If conception occurs during a period of remission, the disease is likely to remain quiescent in 70% of patients throughout the pregnancy comparable with non-pregnant women with CD.[12, 35, 54, 83, 84] Some studies have suggested that symptoms may actually improve during gestation.[35, 83] Relapse, if it occurs is more common in the first trimester and during the puerperium.[35, 38] If active disease is present at time of conception, one-third of patients will achieve remission, one-third will experience an exacerbation of disease status and for one-third of patients, the disease will become chronically active.[6, 12, 52, 61, 85] There is little data on patients who suffer their first attack of CD during pregnancy and thus no definite conclusions can be drawn about disease activity under these circumstances (Table 3).

There is no general consensus as to the recommended mode of delivery in patients with CD. Caesarean sections are carried out more frequently among these patients compared with the general population.[78] The rate of caesarean section increases after the diagnosis of CD and there is no significant difference in rates of caesarean section in patients with UC and CD.[64] The low frequency of vaginal delivery may relate to uncertainty of how these patients would fare after child-birth and also concerns on the part of clinicians to avoid the development or reactivation of perianal CD. Ilnyckyji *et al.*[78] in a retrospective study of 64 pregnancies demonstrated that patients with active perianal disease at delivery were at high risk of developing worsening of perianal symptoms. Patients with inactive perianal disease at delivery were symptom free in a 1 year follow-up. Brandt *et al.*[86] showed a high risk of developing perianal CD after vaginal delivery with episiotomy. This study however had several methological flaws (selection bias and no verification of clinical data obtained from patients). Rogers *et al.*[87] in a small study of 17 patients showed that the mode of delivery did not influence the development or worsening of perianal CD. In the absence of clear evidence of how perianal disease behaves after vaginal delivery, a caesarean section is recommended in patients with active perianal disease.[12] Patients with uncomplicated CD can deliver vaginally and episiotomy should be avoided if possible. The presence of an ileal pouch anal anastomosis in a CD patient is an indication for caesarean section, whereas in patients with colostomy or ileostomy caesarean section should only be carried out for obstetrical reasons.[12]

Effect of pregnancy on the long-term course of inflammatory bowel disease

Pregnancy has no deleterious long-term effect on the course of IBD and there is no place for therapeutic abortion.[88, 89] Pregnancy has not been shown to alter the disease phenotype.[64] There is emerging evidence as to a beneficial effect of pregnancy on the course of the disease. Riis *el al.*[64] in a cohort of 40 patients and Castiglione *et al.*[90] in a cohort of 37 patients demonstrated that parous women with IBD experienced a significant reduction in relapse rates in the 3 years following pregnancy when compared with the three preceding years. This effect was seen in both CD and UC patients. Moreover, Nwokolo *et al.*[91] in a cohort of 58 patients with terminal ileal CD and colonic CD demonstrated a negative correlation between increasing parity and number of surgical resections. These findings were not reproduced by the Riis *et al.*[64] study with a cohort of 46 patients. More data is thus required to clarify this issue.

Disease diagnosis and assessment

Disease assessment during pregnancy should rely more on clinical features rather than on haematological and biochemical parameters. During gestation, haemoglobin and albumin levels fall as a result of haemodilution and the erythrocyte sedimentation rate rises.[52, 54] The C-reactive protein can however still be used to monitor disease activity.[92] Patients should be asked in particular about stool frequency, including nocturnal diarrhoea and the presence of blood and mucus in stools. The pulse rate and temperature should be recorded. Stool cultures should be obtained in the presence of diarrhoea.

Imaging is often required in disease assessment. Abdominal X-ray can be used to assess distribution of disease, mucosal oedema and extent of bowel dilatation. It is particularly useful if toxic megacolon or intestinal obstruction is suspected. The risk to the foetus is minimal and women should be counselled likewise.[6] Daily abdominal X-ray should however be avoided. Abdominal ultrasound is safe. It can be used to demonstrate abscess formation and to determine bowel wall thickness as an indicator of inflammation.[92] Magnetic resonance imaging (MRI)–abdomen is also considered safe but it rarely used for this purpose.

Sigmoidoscopy can be performed safely in pregnancy. Its use has not been associated with preterm labour or congenital malformations.[93] In most patients, this sole invasive investigation may suffice. Colonoscopy should only be performed in carefully selected patients because of the need for sedation. It is best delayed until after delivery. Foetal monitoring is only indicated in high-risk and third trimester pregnancies.[94] Midazolam is recommended over diazepam for sedation (potential association between diazepam and oral cleft).[95] Both are classed as Pregnancy Category D drugs by the FDA. The aim should be to achieve calmness and relaxation but not somnolence. Another interesting sedative for endoscopic procedures is propofol. It is a Pregnancy Category B drug. Data regarding its safety in pregnancy comes from its use in induction and maintenance of general anaesthesia for caesarean section. Celleno *et al.*[96] noted a transient depression of the nervous system of the newborn with the use of propofol during gestation, while Yau *et al.*[97] noted this effect only with prolonged propofol infusion times. However, larger studies have failed to demonstrate any adverse effect on neonates following the use of propofol during pregnancy.[98–100] Also propofol offers greater haemodynamic stability compared with other types of anaesthesia.[98, 101] Propofol should preferably be avoided in the first trimester because of lack of data regarding its use during this period. Antispasmotics such as hyoscine butylbromide should be used with caution in pregnancy and are best avoided.

Treatment of inflammatory bowel disease in pregnancy

The majority of drugs used in IBD are safe in pregnancy. Proactive treatment for maintenance of disease remission is advised.[12] However many women are apprehensive about taking medications during pregnancy and often discontinue treatment despite medical advice.[95] The continuation of maintenance regimen should be discussed in full with the patient and possibly her partner before conception. A key principle is that active disease and not therapy, poses the greatest risk to the pregnancy.[12, 56] All drugs should be used at the smallest effective dose and for the minimum amount of time.

Elemental diet

Elemental diet has been shown to be as effective as steroids in inducing remission in an acute flare-up of CD.[102, 103] Its current role in the management of CD is less certain.[104] There are however no contraindications to its use in pregnancy although it is relatively unpalatable. Teahon *et al.*[105] in one small study with four patients demonstrated that use of elemental diet in pregnant patients with active CD is associated with a favourable pregnancy outcome (Table 4).

Sulphasalazine

Sulphasalazine is constituted of 5-ASA and sulphapyridine. It is a Pregnancy Category B drug. Sulphasalazine readily crosses the placenta and foetal concentrations are approximately the same as maternal concentrations.[106] Its absorption is generally poor and the levels of drug in maternal plasma are less than 20% of the administered dose.[107] Multiple daily dosing regimens, however, results in higher systemic absorption. It was formerly believed that sulphapyridine and bilirubin would compete for the same binding site on albumin potentially leading to unconjugated hyperbilirubinaemia and an increased risk of kernicterus in the newborn. *In vitro* and human studies have not shown any decrease in the bilirubin-binding capacity of albumin in the presence of sulphapyridine.[108] In addition, there was no increased risk of kernicterus in infants born to women exposed to sulphasalazine during pregnancy.[108, 109] Moskovitz *et al.*[110] in a cohort of 100 pregnancies exposed to sulphasalazine or 5-ASA demonstrated no increased risk of birth defects, spontaneous abortions or premature delivery. The average dose of sulphasalazine was 2 g/day. Mogadam *et al.*[111] showed in a cohort of 102 pregnancies that the use of sulphasalazine was not associated with an increased risk of adverse pregnancy outcome compared with women with IBD on no treatment. The use of sulphasalazine in pregnancy is therefore considered safe.[12]

Folic acid supplementation has been shown to be protective against cardiovascular defects, neural tube defects and cleft palate.[112] Supplementation with 400 μg of folic acid daily is recommended in all women of child-bearing age. Sulphasalazine interacts with the cell-membrane transporter for natural folates.[113] This interferes with folate absorption and may lead to folate deficiency. More aggressive folate supplementation with up to 2 mg of folic acid daily is recommended in all female patients on sulphasalazine.[12, 95] Alternatively, sulphasalazine can be switched to mesalazine (mesalamine) but the patient

Table 4. Summary of the drugs used in IBD during pregnancy and breast feeding

Drug (References)	FDA pregnancy category	Comments on use during pregnancy	Comments on use during breast feeding
Elemental diet [103–105]	Not Applicable	No contraindications but exact role undefined	No contraindications but exact role undefined
Sulphasalazine [12, 95, 106–114, 175–178]	B	Low risk – large studies showed no adverse effects; 2 mg folate daily should be given Limited data on high-dose treatment	Probably low risk – potential diarrhoea Limited data on high-dose treatment
Mesalazine [110, 115–118, 175–178]	B	Low risk – large studies showed no adverse effects Limited data on high-dose treatment	Probably low risk – potential diarrhoea Limited data on high-dose treatment
Corticosteroids [12, 52, 54 110, 119–131, 179]	C	Low risk – small increased risk of cleft palate and cleft lip; should be used for short periods to control active disease Rectal preparations – low risk	No evidence of harm
Azathioprine/mercaptopurine [6, 12, 21, 23, 44, 45, 132–140]	D	Low risk – large studies from the IBD, transplant and autoimmune litterature demonstrated no significant adverse effects	Not recommended – limited data
Methotrexate [12, 26, 141–144, 180]	X	Absolute contraindication – high risk of teratogenicity	Contraindicated: potential association with carcinogenesis
Ciclosporin [12, 95, 145–150, 180]	C	Low risk – data from transplant litterature supports low risk to mother and foetus	Contraindicated: potential association with carcinogenesis
Tacrolimus[151–153]	C	Probably low risk – increased incidence of prematurity noted in transplant studies	Not recommended – limited data
Co-amoxiclav[95, 154, 155]	B	Low risk	No evidence of harm
Metronidazole[156–160]	B	Use with caution – limited human data on prolonged courses	Best avoided – limited human data
Ciprofloxacin[161–164]	C	Use with caution – limited human data on prolonged courses	Best avoided – limited human data
Loperamide[54, 165]	B	Low risk – avoid prolonged use	Not recommended
Lomotil[12, 54]	C	Limited human data – not recommended	Not recommended
Kaolin and pectin[166]	Not applicable	Low risk – not absorbed	Low risk – not absorbed
Bismuth subsalicylate[167]	D	Avoid – use during third trimester is associated with adverse effects for the pregnancy and its outcome	Best avoided – limited human data
Cholestyramine[12]	B	Low risk – not absorbed	Low risk – not absorbed
Infliximab[12, 29, 30, 168–172]	B	Probably low risk – but limited human data	Probably low risk – but limited human data

Table 4. (*Continued*)

Drug (References)	FDA pregnancy category	Comments on use during pregnancy	Comments on use during breast feeding
Adalimumab[12, 173]	B	Probably low risk – but limited human data	Probably low risk – but limited human data
Midazolam[95]	D	Can be used with caution	Low risk – delay feeding for 4 h

IBD, inflammatory bowel disease; FDA, Food and Drug Administration.

should still be advised to take 400 μg of folic acid daily when planning conception. A case-control study of the Hungarian population found no significant teratogenic risk associated with the use of sulphasalazine during pregnancy.[114] There were however only 17 patients exposed to sulphasalazine and therefore conclusions are limited (Table 4).

Mesalazine

Mesalazine, balsalazide and olsalazine are 5-ASA derivatives commonly used in IBD. Mesalazine and balsalazide are Pregnancy Category B drugs, while olsalazine is a Category C. Indications for their use are the same as for sulphasalazine. Mesalazine has indeed now largely replaced the latter because of its better side effect profile. Marteau *et al.*[115] in retrospective study involving 123 pregnancies exposed to mesalazine showed that the drug is not associated with an increased risk of pregnancy-related complications, congenital abnormalities or stillbirths. The average dose of mesalazine in this study was 2.1 g/day. In the Moskovitz *et al.*[110] study the average dose of mesalazine was slightly higher but the outcomes were similar. Diav-Citrin *et al.*[116] in a prospective case-control study with 165 patients exposed to mesalazine demonstrated an increased risk of preterm delivery, less mean maternal weight gain and a lower mean birth weight. Rates of spontaneous abortions, stillbirths and congenital malformations were not significantly affected. Mean daily dose was 2 g/day. Women who experienced active disease or who were on numerous anti-IBD drugs had higher rates of premature and LBW babies compared with women on mesalazine monotherapy. This again suggests that the above findings could be an effect of the disease itself and not due to the drug and stresses the need to maintain disease quiescence during pregnancy. Treatment with 2–3 g/day or less (usual maintenance therapy) of mesalazine appears safe in pregnancy (Table 4).

Safety data on higher doses of sulphasalazine or mesalazine are lacking. High dose mesalazine has been associated with one case of neonatal interstitial nephritis.[117] The patient had been taking 4 g/day of mesalazine during the period of renal morphogenesis (second trimester). In the Moskovitz *et al.*[110] study the use of 4 g/day of mesalazine during pregnancy appeared safe. In the Marteau *et al.*[115] study the six women who were exposed to 4 g/day of mesalazine at some point during gestation had a normal pregnancy outcome. Twenty percent of patients in the Diav-Citrin *et al.*[116] study were exposed to more than 3.2 g/day of mesalazine. An increased risk of LBW and prematurity was observed in the study but these findings were thought to be secondary to the disease itself. It is recommended, because of the paucity of data available, that women are not kept on high-dose mesalazine if feasible during pregnancy and/or to monitor foetal kidneys during gestation.[118]

Corticosteroids

Corticosteroids are indicated for moderate to severely active disease. They are classed as Pregnancy Category C drugs. Large case-control studies[119, 120] and one meta-analysis[121] have demonstrated an increased risk of cleft palate with the use of steroids during pregnancy. Reinisch *et al.*[122] documented an increased incidence of LBW and small for gestational age babies in women exposed to prednisolone during gestation. Moskovitz *et al.*[110] however in a large study with 107 pregnancies (49 of which were exposed to steroids) failed to corroborate any of the above findings. Gur *et al.*[123] in a recent prospective study of 311

women did not demonstrate an increased risk of teratogenicity with use of steroids during gestation. In the light of the available data, it appears that steroids poses a small but significant risk of cleft lip and cleft palate but does not affect the rates of LBW or small for gestational age babies. Active disease would have a greater detrimental effect on the pregnancy and use of steroids to control active disease is justified. Budesonide is generally recommended in terminal ileal CD Inhaled budesonide has been proven to be safe in pregnancy.[124, 125] There are no human studies to date relating to the effect of oral budesonide on pregnancy and its outcome. Animal studies have demonstrated an increased risk of spontaneous abortions, intra-uterine growth retardation and congenital malformations, particularly skeletal abnormalities with high doses of budesonide.[126] Its use during pregnancy is therefore controversial.

Glucocorticoids have the potential to cross the placenta. The ratio between maternal and foetal levels depends on a variety of factors.[127] Prednisolone should be used in preference to other steroids because foetal exposure is lower compared with betamethasone and dexamethasone.[128–131] This is due to the extent of placental metabolism and placental- and albumin-binding affinities of different steroids. Interestingly, in spite of reaching significant pharmacological levels, steroids cause only a transient suppression of the foetal adrenocortical system and their use is not associated with long-term organ dysfunction.[127] Furthermore, steroids have a beneficial effect on the functional activity of other organ systems. There are few data about placental transfer of topical steroids but it is likely to be low. It is generally agreed that rectal preparations can be continued until the third trimester [12, 54] (Table 4).

Immunosuppressants

Immunosuppressive treatment is used for refractory IBD. There are no large prospective studies on the use of immunosuppressants in IBD during pregnancy. The most commonly used immunosuppressive drugs are AZA, MP, MTX and ciclosporin.

Azathioprine and mercaptopurine: AZA/MP are classified as Pregnancy Category D drugs. Animal studies have clearly demonstrated an increased risk of teratogenicity with the use of AZA/MP in pregnancy.[132] Human studies are controversial. The foetal exposure to AZA/MP following oral administration is poor. The oral bioavaibility of AZA/MP is low (47% for AZA and 16% for MP)[132] and the placenta forms a relative barrier to AZA/MP.[133, 134] Furthermore, the foetal liver lacks the enzymes necessary to convert AZA/MP into their active metabolites therefore protecting the foetus.[135] Norgard *et al.*[136] in a population-based cohort study demonstrated an increased risk of congenital abnormalities, preterm delivery and stillbirths in women exposed to AZA/MP during gestation. It was however a small study – only 11 women had a history of drug exposure and it did not take into account severity of underlying disease and polypharmacy. Data from the transplant literature and treatment of autoimmune diseases found no consistent reports of prematurity or congenital defects in infants following *in utero* exposure to AZA/MP.[44, 45, 132] Francella *et al.*[21] in a large retrospective study of 325 pregnancies showed that AZA/MP use prior to, at conception or throughout pregnancy does not increase the risk of spontaneous abortions, stillbirth, prematurity or the rate of neonatal or childhood infections. Other case studies in the IBD literature documented similar findings.[137, 138] These studies used AZA at doses of 125 mg/day or less; dose of MP was 75 mg/day or less. Cases documenting neonatal myelotoxicity, immunosuppression and chromosomal abnormalities in infants exposed to AZA *in utero* come form the transplant and oncology literature where higher doses of AZA are used.[139, 140] Therefore despite being Pregnancy Category D drugs, current evidence suggests that AZA/MP are safe in pregnancy.[12] Relapse rates for patients on AZA/MP have been shown to be less than would be expected without medications.[21] Discontinuation of maintenance therapy in both males and females prior to a planned conception is inappropriate [23] (Table 4).

Methotrexate: MTX is clearly mutagenic and teratogenic and should not be used in pregnancy.[12] The offsprings of women treated with MTX have a high risk of developing craniofacial deformities, limb defects and severe central nervous system abnormalities.[141] The critical period appears to be at 8–10 weeks of pregnancy.[142] The exposure to high-dose MTX (50 mg/m^2) in early pregnancy is embryolethal in most cases.[143] The drug should be stopped at least 3 months prior to a planned conception due to the prolonged tissue-binding characteristics of MTX.[26] Women on treatment should be strongly advised as to the need for reliable contraception. If conception occurs while on treatment, MTX should be stopped and the patient placed on high-dose

folic acid.[144] Therapeutic abortion may be discussed (Table 4).

Ciclosporin: Ciclosporin is a Pregnancy Category C drug. It has the potential to cross the placenta but its absorption following enteral administration is poor – only 34%.[145] Data relating to the use of ciclosporin in pregnancy comes from the transplant literature. One meta-analysis of 15 studies demonstrated no increased risk of congenital malformations with the use of ciclosporin in pregnancy.[146] The rates of prematurity and LBW were higher in infants exposed to ciclosporin *in utero* but did not reach statistical significance. Its role in IBD is restricted to patients with fulminant colitis unresponsive to steroids in an attempt to avoid surgery, which carries a high rate of foetal demise.[95] It should be noted that the association between surgery for fulminant colitis during gestation and a high foetal mortality is weak. Anderson *et al.*[147] reported a series of four cases of fulminant colitis in pregnancy and the puerperium requiring either a colectomy or a proctocolectomy. The rate of foetal loss was 50%. However, both foetal deaths occurred before the surgery possibly indicating that the high stillbirth rate is an effect of the disease itself. It is not currently known whether treatment with ciclosporin for fulminant colitis is associated with a better prognosis compared with surgical management. The few case reports available show that the use of ciclosporin in this situation is effective and is associated with a favourable outcome both for the mother and the infant.[148, 149] The side effects of ciclosporin however mandate a cautious use during pregnancy.[150] Women should be offered a trial of medical management before considering surgery. Ciclosporin can be used in CD patients if clinically indicated although there is no evidence to support such practice [12] (Table 4).

Tacrolimus: Tacrolimus is a Pregnancy Category C drug. Data regarding its use in pregnancy comes from the transplant literature. Two prospective studies, one involving 21 pregnancies and the other 49 pregnancies, demonstrated an increased incidence of preterm delivery and LBW but not of congenital malformations, pregnancy-related complications or neonatal compli cations.[151, 152] The increased incidence of LBW was due to the high rates of preterm delivery which in turn seems to be a persistent problem in solid-organ transplant recipients regardless of immunosuppressive therapy used. Incidence of hypertension and pre-eclampsia in the two studies was lower than expected. Kainz *et al.*[153] in a retrospective study involving 100 pregnancies demonstrated similar pregnancy outcomes. Tacrolimus may therefore be continued at conception and during pregnancy if needed. More data is required to establish its use in the pregnant IBD patient (Table 4).

Antibiotics

These are mainly used in patients with perianal CD and in cases of pouchitis. Co-amoxiclav is a Pregnancy Category B drug. One large population-based case-control study with 6935 patients[154] and one prospective study with 191 patients[155] demonstrated no significant increase in the incidence of congenital abnormalities in offsprings of women treated with co-amoxiclav during pregnancy.

Metronidazole is a Pregnancy Category B drug. Its use even during the first trimester of pregnancy has not been associated with an increased risk of congenital malformations.[156–158] Sorensen *et al.*[159] in a retrospective study with a cohort 124 patients demonstrated no increased risk of preterm delivery following metronidazole treatment during pregnancy. In a prospective study done by Diav-Citrin *et al.*[160] involving 228 women exposed to metronidazole during gestation, there was no significant difference between the rates of congenital abnormalities and preterm delivery between cases and controls. The mean birth weight was however significantly lower in the treated group. The mean duration of therapy was 7.9 days. Ciprofloxacin and other quinolones are classified as Pregnancy Category C drugs. Animal studies showed an increased risk of arthropathy following *in utero* exposure to quinolones.[161] Loebstein *et al.*[162] in a prospective case-control study with 200 patients treated with a fluoroquinolone during pregnancy failed to demonstrate the above findings. There was furthermore no significant difference in rates of spontaneous abortions, prematurity and birth weight between the two population groups. Other population based and retrospective studies also supported the safe use of quinolones during pregnancy.[163, 164] Metronidazole and quinolones are used for longer periods of time in IBD and there is limited data regarding the effect of such regimens on pregnancy and its outcome. They should be used with caution under those physiological conditions (Table 4). Tetracyclines and sulphonamides are contraindicated in pregnancy.[12]

Antidiarrhoeals

Antidiarrhoeals are used for symptom relief in IBD. Loperamide is a Pregnancy Category B drug. It has not

been shown to be teratogenic in animals. Einarson *et al.*[165] in a prospective case-control study with 105 women found that intermittent use of loperamide during pregnancy is not associated with an increased risk of miscarriage, preterm labour or congenital abnormalities. Women who were treated with loperamide throughout pregnancy had infants with a lower mean birth weight compared with controls. Lomotil (diphenoxylate hydrochloride/atropine) is a Pregnancy Category C drug. It is not known whether the drug crosses the placenta and human studies are limited. It should be used with caution during pregnancy.[12] Kaolin and pectin do not have the potential to cross the placenta. They are not absorbed from the gut and are arguably the antidiarrhoeals of choice.[166] They are classed as Pregnancy Category B drugs. Bismuth subsalicylate should be avoided in pregnancy. It is a Pregnancy Category C drug during the first and second trimesters and a Category D drug during the third trimester. Its use during the last trimester is associated with prolongation of gestation and labour, greater blood loss at delivery and increased perinatal mortality.[167] Cholestyramine is a Pregnancy Category B drug. It can be used in pregnancy and is particularly useful in patients with diarrhoea secondary to terminal ilealitis or ileal resection [12] (Table 4).

Biological agents

Infliximab: INF is a Pregnancy Category B drug. It has been used in IBD for only 7 years. Limited available data suggests that INF is not associated with an increased risk of teratogenicity, spontaneous abortions or adverse perinatal outcomes including stillbirth.[168] INF contains the human immunoglobulin G1 constant region which can potentially cross the placenta during the second and third trimester.[169] However the effects of INF on the immune system of the foetus and the long-term effects on the developing infant are not known. Animal studies using analogous anti-TNF-α agents have not shown any evidence of teratogenicity and adverse pregnancy or maternal outcome.[30] The maximum dose of monoclonal antibody used was 40 mg/kg (usual dose of INF is 5 mg/kg).

Katz *et al.*[170] collected data from the INF Safety Database and reported pregnancy outcome for 96 women with history of direct exposure to INF and 10 women with an indirect exposure, i.e. their partner was being treated with INF. INF was given mostly at conception and during the first trimester and was not associated with an increased risk of miscarriage, neonatal complications or congenital malformations. Most of the database is maintained by spontaneous reporting which can be open to selection bias and incomplete or inaccurate information. Thirty-six pregnant CD patients with exposure to INF have been recorded in the TREAT Registry.[171] The TREAT Registry is a prospective record of all patients with CD with currently a total of 1007 patients enrolled. The rates of spontaneous abortions and perinatal complications were not significantly different from women with CD not treated with INF. There were no documented cases of congenital malformations. Mahadevan *et al.*[172] reported 10 cases of intentional use of INF throughout pregnancy for control of CD. There were three preterm deliveries and one LBW baby, which are not unexpected in women with CD severe enough to require INF therapy. There were no stillbirths or any congenital malformations (Table 4). Compilation of case reports and case series from the literature would also support the safe use of INF in pregnancy.[172] Rutgeerts *et al.*[29] in a review article on INF argued to continue INF therapy up to 20 weeks of pregnancy. Current level of evidence does not allow the routine use of INF in pregnancy but each case should be determined on an individual basis with emphasis to the (unknown) risks and benefits of therapy. If a woman chooses to delay pregnancy to avoid foetal exposure, a 6 months delay between last INF infusion and conception is required because of the pharmacokinetics of the drug.

Adalimumab: Adalimumab is a Pregnancy Category B drug. There is one case of adalimumab use throughout pregnancy in the literature, which ended in delivery by elective caesarean section at 38.5 weeks of a normal healthy infant.[173] More data should be collected in regards to the use of INF and adalimumab in pregnancy to guide physicians in their clinical decision making (Table 4).

Surgery

Indications for surgery during gestation are the same as in the non-pregnant IBD patient and include failure of medical therapy, intestinal obstruction or perforation, toxic megacolon and localized complications such as abscesses and fistulae. The effects of surgery on the pregnancy are poorly documented. Resectional surgery has been associated with an increased risk of preterm delivery[72] but this could also be an effect of the underlying disease. It is generally agreed that the effects of continued illness is a greater risk to the foetus than surgery.[92]

Breast feeding

The advantages of breast feeding to the infant are well recognized including a decreased risk of developing IBD in later life.[174] There are no data on the risk of IBD in infants who are breastfed by IBD patients. Kane *et al.*[71] in a retrospective study with 122 patients demonstrated that breast feeding does not seem to influence the pattern of disease activity in the postpartum period. Only a very small percentage of CD patients breastfed their child because of fear of medication interaction. Clinicians should bear this in mind when counselling women on the benefits of breast feeding. Risks and benefits of therapy should be weighed on an individual basis prior to prescribing in pregnancy.

Sulphasalazine and other aminosalicylates

Bloody diarrhoea in an exclusively breastfed infant whose mother was on oral sulphasalazine has been reported[175] as well as watery diarrhoea in an infant whose mother was on sulphasalazine suppositories.[176] Less than 10% of the maternal dose of mesalazine is excreted into breast milk and it is the inactive acetylated from that predominates therefore protecting the baby from the side effects of mesalazine.[177, 178] Except for the above two case reports there have been no other studies documenting an adverse effect on the breastfed infant if the mother was taking an aminosalicylate. Breast feeding should therefore not be discouraged in this population.[12] Rectal preparations can be continued during the breast-feeding period. Olsalazine should be avoided if feasible because of limited clinical data. There is limited experience on the safety of sulphasalazine and mesalazine at doses higher than standard therapeutic doses (Table 4).

Corticosteroids

There are no reports of an unfavourable outcome in infants who are breastfed by mothers being treated with corticosteroids. Only 5–25% of the maternal plasma steroid concentration is present in breast milk.[54] The infant exposure is therefore low. The serum levels of corticosteroids fall by 50% 3 h after administration.[179] It may be recommended to delay feeding 4 h after the last dose to decrease infant exposure even further,[12] but this may not be necessary in women on less than 20 mg/day of corticosteroids[52] (Table 4).

Immunosuppressants

Immunosuppressants are secreted into breast milk and can potentially interfere with infant's immune system. It is currently not recommended to breastfeed, while the patient is on AZA/MP although there seems to be some clinical experience of its safe use in nursing mothers.[6] Ciclosporin and MTX should be avoided because of the potential risk of immune suppression, an undesirable effect on growth and a possible association with carcinogenesis[180] (Table 4).

Antibiotics and antidiarrhoeals

Co-amoxiclav can be used in breast-feeding females.[95] There is limited data on the use of metronidazole and ciprofloxacin in nursing mothers. They are best avoided. Loperamide and diphenoxylate hydrochloride are both excreted into breast milk and atropine may interfere with lactation.[54] Their routine use is not recommended. Kaolin and pectin can be continued. Bismuth subsalicylate should be avoided because of limited data.

Biological agent

It is not currently known whether INF or adalimumab are excreted into breast milk. Their effects on the infant's immune system after oral administration have also not been documented. It may be preferable to avoid breast feeding in patients on biological agents[12] (Table 4).

Midazolam

Matheson *et al.*[181] in a randomized study with 22 women demonstrated that the levels of midazolam and its metabolite are undetectable 4 h after the administration of 15 mg of midazolam orally. Women who are given midazolam for endoscopic investigations should be advised to delay nursing their child until 4 h after taking the drug.

Inheritance

Inflammatory bowel disease displays a multifactorial inheritance. IBD clearly has a genetic component due to the increased risk of developing the disease among first-degree relatives[182] and higher concordance among monozygotic twins compared with dizygotic

twins.[183] Having an affected parent increases the risk, particularly for CD but the absolute risk is still low – 7.5% for CD and 10.5% for all forms of IBD. The risk increases to 35% if both parents are affected.[184] Interestingly, one study found a negative correlation between increasing maternal age and risk of developing CD.[185] The disease is more common among the Jewish population.[186] This may reflect both a genetic predisposition and a similar antigenic exposure in life. Maternal smoking during pregnancy and perinatal period is associated with an increased risk of developing childhood IBD[187] and both active and passive smoking during childhood and later life increases risk of adult-onset CD but not of UC.[188, 189] Seventy five percent of children are diagnosed with IBD at an earlier age than their parents[190] which might suggest genetic anticipation. Large population-based studies have however failed to demonstrate any evidence for same.[191–193] Earlier age of diagnosis may relate to confounders such as length of follow-up, temporal changes in risk of IBD and parental age.[191, 192] There is furthermore no concordance in phenotype, disease course and prognosis in families.[183, 192] Of interest Van Ranst *et al.*[194] showed that infants born in the month of June were at a reduced risk of developing IBD compared with infants born in other months. There is no evidence of an increased risk of IBD following *in utero* exposure to the measles virus.[195]

CONCLUSIONS

Inflammatory bowel disease affects mainly the young population and therefore fertility and pregnancy-related issues are important clinical considerations. IBD does not affect fertility in males. Sulphasalazine and possibly corticosteroids reduce the reproductive potential in males. The treatment with MP and AZA in males does not seem to have any deleterious effect on fertility and pregnancy-related complications. Active CD seems to reduce fertility in females. Treatment of IBD does not impair the reproductive potential of females. MTX should be avoided in both sexes. An ileal pouch anal anastomosis may reduce fertility in humans but overall the effect of abdominal surgery on fertility is not clearly documented. Disease behaviour during gestation and the outcome of pregnancy are dependent mostly on activity of disease at time of conception. Active disease at the beginning of pregnancy carries an increased risk of flare-up during gestation and a higher risk of spontaneous abortion, prematurity and LBW babies. Quiescent disease at conception does not influence the risk of flare-up during pregnancy. Irrespective of disease activity and medical treatment CD but not UC is associated with a small increased risk of pregnancy-related complications. Rates of congenital malformations and perinatal mortality are not affected by IBD. Pregnancy may have a beneficial effect on the long-term course of IBD. The recommended mode of delivery is disputed. Disease diagnosis and assessment should take into account the physiological changes of pregnancy. The need for imaging and invasive procedures should be carefully assessed. Proactive treatment for maintenance of disease remission is recommended. Most drugs used in the treatment of IBD do not pose a significant risk of pregnancy-related complications including spontaneous abortions, prematurity, LBW babies, congenital defects and stillbirths. Corticosteroids carry a small increased risk of cleft palate but benefits in controlling active disease outweigh risks. MTX should clearly be avoided. There is limited data on high-dose aminosalicylates and long courses of antibiotics. These may preferably be avoided if feasible. From all the data available within the literature use of INF during pregnancy appears safe. Surgery should be delayed if possible although pregnancy is not a contraindication for surgical procedures. Breast feeding may not be recommended in women on immunosuppressive therapy but should otherwise be actively encouraged.

Overall data available from the literature is derived mainly from retrospective and case-control studies. The absence of large prospective studies and randomized control trials limits the conclusions that can be drawn and maintains the controversy on this issue. The setup of robust clinical trials should therefore be actively encouraged. Prospective studies like the European Crohn's Colitis' Organization (ECCO), which is currently underway and seeking to recruit 500 patients and 1000 controls should shed more light on this clinical dilemma.

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APPENDIX 1. FDA PREGNANCY CATEGORIES[196]

FDA Pregnancy Category	Interpretation
A	Controlled studies in animals and women have shown no risk in the first trimester, and possible foetal harm is remote
B	Either animal studies have not demonstrated a foetal risk but there are no controlled studies in pregnancy women, or animal studies have shown an adverse effect that was not confirmed in women in the first trimester
C	No controlled studies in humans have been performed and animal studies have shown adverse events, or studies in humans and animals are not available; give if potential benefit outweighs the risk
D	Positive evidence of foetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease
X	Studies in animals or humans show foetal abnormalities; drug contraindicated