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• REVIEW •

Fertility and pregnancy in inflammatory bowel disease

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disorder affecting young adults in the reproductive years. It is common for both female and male patients with IBD to ask questions about IBD's effect on their relationships, sexual and reproductive function, in particular fertility, the outcome of pregnancy and its possible effects on the disease. An open discussion of the social situation and education targeted at these issues therefore forms an essential part of the management of any young person with IBD. The questions that are most commonly asked are summarised in Table 1. In order to answer these questions we need evidence. There are few large prospective case controlled studies to provide the information which is required but the available data, some of it from small observational studies, will be summarised in this chapter.

Table 1 Questions commonly asked by IBD patients

Sexual health	Will I be able to have normal relationships and a family?
Inheritance	Will my children inherit IBD?
Fertility	Will my fertility be impaired by IBD or its treatment?
Outcome of pregnancy	Will I have a normal, healthy baby?
Disease activity in pregnancy	Will my IBD flare up in pregnancy?
Drug and other treatments	I don't want to take any drugs during pregnancy?
Breast feeding	Is breast feeding advisable and safe

SEXUAL HEALTH

It is well established that general measures of quality of life are impaired in patients with IBD[1]. Sexual health is an important aspect of quality of life which is often overlooked in a routine gastroenterological consultation. Sexual problems in IBD often seem to be focused around three major factors: body image problems, difficulties with social relationships and impaired sexual function[2]. Crohn's disease (CD), in particular has been shown to have an impact on self-image, social relationships and sexual function[1]. Body image concerns are frequently found in IBD patients relating either to the direct physical effects of their disease such as weight loss, growth retardation as a result of chronically active disease in childhood, fistulae or perianal disease. The effect of surgery especially when a stoma is involved is associated with low self-esteem and poor body image. The side effects of steroids and other medications may lead to weight gain, hirsutism, skin changes and other features which promote feelings of unattractiveness. There is some evidence that psycho-social effects of stoma surgery performed in childhood, before puberty may be less severe than if such surgery is performed during the teenage and early adult years[3]. Partners of IBD patients with stomas have been found to be more likely to be able to accept the stoma than the patient themselves[4]. Psychological fears of loss of control of bodily functions and the fear of rejection by new or established partners in an intimate relationship all contribute to difficulties in social and sexual relationships. Counselling and practical advice and support is frequently helpful, but the need for it is not always identified in general gastroenterological practice.

Some studies have reported an increase in sexual difficulties including dyspareunia in women who have had surgery for IBD and there is some evidence that patients with IBD may delay or even defer pregnancy because of their disease[4,5]. Most of the reports of sexual dysfunction are in women with Crohn's disease. There are no specific reports of sexual dysfunction in women with ulcerative colitis (UC) who have not had previous surgery.

In men with IBD the risk of impotence after proctocolectomy is the main concern[4]. Advances in surgical technique have decreased although not eliminated post-operative sexual dysfunction, and this seems to apply to both conventional proctocolectomy and pouch surgery with a reported incidence of impotence of around 4%-8%[6]. It is important to remember that patients are often quite reluctant to discuss such delicate matters and tactful prompting and adequate time during the consultation is the key to their detection.

CONTRACEPTION

As there is clear evidence that the outcome of pregnancy is better in women with IBD who have quiescent disease at the time of conception, advice about contraception is keenly sought and opinions have differed over the years. In women who do not smoke and who have quiescent or mildly active Crohn's disease (CD), the use of a low dose combined oral contraceptive is not associated with increased disease activity compared with non-users[9,10]. There are no data about the thrombo-embolic complications of the oral contraceptive pill in IBD but this should be considered especially in patients with active UC.

INHERITANCE OF IBD

Individuals with IBD are often concerned that their children may inherit the illness. There is a familial increased risk in IBD which is stronger if the parent has CD. This risk also appears to be greater in Jewish families. The life-time risk factor for a child of a parent with CD is around 7%-9% of developing CD and about 10% for the development of IBD[11]. If both parents are affected the risk for any children may be up to 35%.

FERTILITY

Women with UC generally appear to have normal fertility, although one retrospective study from Scotland reported that women who had had surgery for IBD had increased infertility compared to the general population (25% *vs* 7%)[12]. Voluntary childlessness in people with IBD is still probably greater than in the general population however, possibly relating to fear of pregnancy or even inappropriate professional advice suggesting that pregnancy might be dangerous. In CD, fertility is probably normal in individuals with inactive disease[13,14]; however, fertility is impaired in women with active Crohn's disease. This relates directly to disease activity and fertility appears to revert to normal with the induction of remission. Women whose IBD develops before their first pregnancy have been shown to have fewer pregnancies than population controls. In women who had had a pregnancy prior to the onset of IBD, however, they seem to have a similar reproductive history to a control population[13].

Increasingly, men are concerned about fertility and other issues of reproductive health. Sulphasalazine has been known for many years to cause reversible semen abnormalities with impairment of fertility in up to 60% of men on the drug. This effect is reversed two months after withdrawing sulphasalazine. Men express concerns about the safety of immunosuppressive agents in terms of fertility and the risk of congenital abnormality, but there are no reliable data at all for guidance in this area[15].

PREGNANCY OUTCOME IN IBD

In recent years there has been an increased interest in the outcome of pregnancy in IBD and a number of epidemiological surveys and case controlled studies have been published. In UC, there is a large body of evidence suggesting that the frequency of spontaneous abortion, still birth and congenital abnormality are no different to that in the general population[16-19]. In quiescent Crohn's disease, pregnancy outcome, in terms of spontaneous abortion, still birth and congenital abnormality, is also no different from the general population[14,17]. Active Crohn's disease at the time of conception or during pregnancy significantly increases foetal loss and pre-term delivery and it appears that disease activity rather than medical treatment accounts for the adverse outcomes[20,21].

A large prospective population-based study looked at adverse pregnancy outcomes in 239773 single pregnancies in Sweden over a two year period. This included 756 pregnancies in women with IBD. This is the expected number of IBD pregnancies for this population[22]. No significant increase in the most serious adverse outcomes of still birth or infant death in the first year of life was found in the IBD mothers. There was also no significant increase in babies which were small for gestational age. There was however, a significantly increased risk of pre-term birth (odds ratio 1.81, 95% confidence intervals 1.06-3.07) at less than 33 weeks and for 33-36 weeks (odds ratio 1.48, confidence intervals 1.0-1.19), and of low birth weight (less than 1500g, odds ratio 2.15 confidence intervals 1.11-4.15). IBD patients also had an increased caesarean section rate (15% *vs* 10%). These estimates were not affected by adjustments for maternal age, parity and smoking. There was, however, not any information about whether the mothers experiencing pre-term delivery and low-birth weight babies had UC or CD, or whether these were women with active disease during their pregnancies. More recent studies from France and Denmark have confirmed this small increase in pre-term birth and low birth weight, particularly in CD[23,24].

INFLUENCE OF PREGNANCY ON IBD ACTIVITY

In any woman with quiescent IBD at the time of conception, the likelihood of a flare-up of IBD during pregnancy or the puerperium is no greater than in any other year of her life. Active UC at the time of conception is associated with continuing disease activity in about two thirds of pregnant women. Chronic activity will continue throughout pregnancy in about a quarter of these patients and in about 45% the activity may actually worsen[14]. This therefore constitutes a strong indication for aggressive medical treatment, since if remission can be induced by medical therapy, the course of pregnancy is similar to that in patients with quiescent disease at conception. About two thirds of women with active Crohn's disease at the time of conception will continue to have disease activity throughout the pregnancy and in about half of these there will be a deterioration during the pregnancy (Table 2). Therefore it is inadvisable to conceive when CD is active, but if conception occurs, an aggressive therapeutic strategy is indicated as there is clear evidence in Crohn's disease that disease activity is associated with pre-term birth and low-birth weight and some suggestion that early miscarriage may be increased.

MANAGEMENT OF IBD IN PREGNANCY

All the evidence suggests that maintenance treatment, certainly with aminosalicylates, should be continued throughout pregnancy and flare-ups of disease activity should be investigated and treated appropriately as in a non-pregnant patient. All pregnant women are very concerned about taking medication during gestation and it is essential if at all possible that these issues are broached and discussed well in advance of a planned pregnancy enabling informed discussion with the patient and her partner once she becomes pregnant.

Nutrition is extremely important in pregnancy, the average weight gain during a normal pregnancy being between 11 and 16kg. Folic acid supplementation is recommended for all pregnant women but in IBD, patients who may have folic acid deficiency or be taking drugs which interfere with folic acid metabolism, a dose of 5mg daily should be recommended rather than the usually advised dose of 400μg daily. It is extremely important to remember that early nutritional intervention is indicated in a woman with active disease who may not be gaining weight. Women with active CD in pregnancy have received an elemental diet as primary therapy with rapid resolution of symptoms[25] and supplemental feeding may be required in sick IBD patients who are failing to achieve the expected weight gain during pregnancy.

Proper investigation of gastrointestinal symptoms is not contraindicated during pregnancy and indeed it is important in order to ensure that appropriate treatment is advised. Blood

investigations are often difficult to interpret in pregnancy due to haemodilution, and therefore sigmoidoscopy and indeed colonoscopy may be indicated in some circumstances. Both these investigations have been shown to be safe in a small study[26]. Monitoring foetal heart rate during endoscopy has not shown any adverse effects and there has been no evidence of increased premature labour or foetal abnormalities following endoscopy in pregnancy. Radiographic imaging should obviously be avoided unless obstruction, perforation or toxic megacolon are suspected and if possible in this situation, plain abdominal films should be used rather than CT or barium studies which involve much higher radiation exposure. Ultrasound may be useful, for example to identify an intra-abdominal collection in patients with Crohn's disease.

Table 2 Influence of pregnancy on IBD activity
Meta-analysis data from Reference 17

INACTIVE disease at conception. Likelihood of relapse during pregnancy

	Ulcerative colitis	Crohn's disease
Number of pregnancies	528	186
Relapse	34%	27%

ACTIVE disease at conception. Pattern of disease activity in pregnancy

	Ulcerative colitis	Crohn's disease
Number of pregnancies	227	93
Better	27%	34%
No change	24%	32%
Worse	45%	33%

TREATMENT OF IBD IN PREGNANCY

Drug treatment

The safety (or risk) of drug therapy during pregnancy is of prime concern to any pregnant woman. In women with IBD, the most important factors in relation to treatment are to emphasise the importance of planned pregnancy when the disease is quiescent and the fact that, if conception occurs with active IBD, inducing remission with medical therapy carries less risk than continuing a pregnancy without treatment[26].

First line agents

Aminosalicylates and sulphasalazine have been widely used in pregnancy in IBD. They are safe in conventional doses and should be used for maintenance or induction of remission in the same way as in a non-pregnant individual. Both aminosalicylates and sulphasalazine are poorly systemically absorbed and there is little placental transfer from mother to foetus[27-29]. No evidence of teratogenicity has been demonstrated and the outcome of pregnancy has been shown to be similar to that in healthy women. There have however, been reports of nephrotoxicity in the foetus of a woman taking a high dose of mesalazine[30]. High dose aminosalicylates are not therefore advisable during pregnancy.

Corticosteroids are well tolerated in human pregnancy. They cross the placental barrier but there has been no convincing evidence of teratogenesis despite reports of cleft lip and palate in the past. Immune deficiency in the new-born infant is theoretically possible, but is very rarely reported in clinical practice. In IBD patients taking corticosteroids during pregnancy, no increase in foetal complications have been found compared to the general population[29]. It is, therefore, important to use corticosteroids in women with moderate to severe disease activity in pregnancy in the same way as in a non-pregnant patient.

Second line agents

Azathioprine and 6-mercaptupurine have never been demonstrated to be teratogenic in humans and do not have any effects on human interstitial cell function or gametogenesis in the doses used in clinical practice[31,32]. There is extensive experience of the use of these drugs in pregnancy in renal transplant recipients and in patients with systemic lupus erythematosus who are unable to discontinue immunosuppressive treatment, with very little evidence of adverse effect[33,34]. However, because of the theoretical possibility of teratogenesis in animals, gastroenterologists have been very cautious in advising discontinuation of azathioprine prior to pregnancy or even termination of pregnancy in women conceiving on azathioprine. In a small retrospective study on the use of azathioprine in pregnancy and IBD there were no serious adverse outcomes. All the women conceived while taking the drug and half of them continued to take it throughout gestation[35]. In a larger study, looking at pregnant women with IBD on 6-mercaptupurine, there were also no adverse outcomes of pregnancy[36], although in this study only a small number of patients actually continued to take the drug throughout their pregnancy.

In general therefore, if a patient is established and well on azathioprine or 6-mercaptupruine and it is felt to be essential to continue this drug to retain remission, after full discussion with the patient and her partner, it is reasonable to decide to continue treatment during pregnancy. It is essential that this decision is made by the patient who has been presented with the evidence. In view of the complications which may arise at the start of treatment with these agents, it is not advisable to commence treatment for the first time during pregnancy.

Cyclosporine has been used in patients with severe UC which has not responded to steroids in an attempt to avoid surgery which is said to carry a high risk of foetal mortality[37]. Cyclosporine is not teratogenic and has been extensively used in transplant recipients and lupus patients without increased adverse effects[38-41]. Cyclosporine is a highly toxic drug however, carrying the risk to the mother of hypertension, nephrotoxicity and hepatotoxicity and it would therefore appear to be undesirable in almost all circumstances except the avoidance of urgent colectomy in a patient with fulminant UC.

Methotrexate is mutagenic and teratogenic and is therefore contraindicated in pregnancy or immediately prior to conception. There are reports of women with IBD who have conceived while taking methotrexate, who had a high incidence of severe congenital abnormalities in the babies born from these pregnancies, with neural tube defects and other severe deformities[42,43]. In a woman who conceives on methotrexate and will not agree to a therapeutic abortion, however, the methotrexate must obviously be stopped immediately and high dose folic acid replacement is indicated.

Anti-TNF antibodies There are currently no data about pregnancy in patients receiving therapy. By definition this therapy is used for people with severe active CD, and for the present pregnancy should be discouraged during this treatment.There is no evidence that it is safe to continue with the pregnancy if conception occurs during treatment with anti-TNF antibody.

Antibiotics: Metronidazole has not been shown to have

adverse effects and has been used extensively in pregnancy by gynaecologists to treat bacterial vagionosis. There is not any evidence of increased risk of spontaneous abortion or congenital abnormality in humans[44,45]. Ciprofloxacin and other quinolone antibiotics have been suggested to be associated with musculoskeletal problems in foetuses in animal studies but this has not been substantiated in humans. Ciprofloxacin has been used during pregnancy with no increased incidence of spontaneous abortion or congenital abnormality and follow-up of the children born from these pregnancies is ongoing[46].

Surgery

Patients who have undergone previous surgical intervention for UC or CD do not appear to have any increase in problems during pregnancy compared to the general population. Patients who have undergone colectomy and ileostomy or ileal pouch operations can expect a normal outcome of pregnancy. In women with an ileostomy, stomal prolapse has been reported following hyperemesis. This can cause discomfort and require revision of the ileostomy post-partum. Opinions vary about the need for delivery by caesarean section following pouch surgery. Some centres have published data suggesting that vaginal delivery is appropriate. There are no published long-term studies of the effect of vaginal delivery on pouch function although one study demonstrated no short-term deterioration of pouch function[7,8]. Some surgeons advise elective caesarian section to avoid risk of sphincter damage.

Surgery for acute indications during pregnancy has been reported to carry a high risk of foetal loss and is generally felt to be inadvisable. Reports of a 60% risk of foetal loss for urgent colectomy in UC may be an overestimate in the 21st century. A small case report from Manchester recently reported six women who had surgery for intraperitoneal sepsis in Crohn's disease during pregnancy. Five healthy babies resulted from these pregnancies although one miscarriage occurred in a patient with a surgical complication[47].

Breast-feeding

Breast-feeding is the best option for mother and baby in most circumstances. Concerns about breast-feeding are related to worries about the secretion of drugs in breast milk. Sulphasalazine and the aminosalicylates are poorly absorbed from the bowel and very small amounts are excreted in breast milk. It is safe to breast-feed while taking these medications with the small reservation that it is inadvisable to take high doses of amino-salicylates as there is one report of renal impairment in a child of a mother on a high dose of mesalazine[37].

Prednisolone is also concentrated poorly in breast milk and the amount received by the infant is minimal[48]. If breast-feeding is deferred until 4 hours after taking steroids, this further decreases the dose to the infant. It is therefore considered safe to breast-feed while taking these first-line agents.

There are almost no data on the safety of breast-feeding while taking other agents used to treat IBD. Breast-feeding is not recommended by the manufacturers of azathioprine or 6-mercaptopurine. Many transplant recipients and patients who take these drugs for rheumatological disorders and who must remain on azathioprine have breast-fed without reports of ill effect to the baby. This is another situation where full discussion with the mother and her partner may allow them to make an informed decision on the basis of what little evidence is available.

CONCLUSION

The key to the management of the pregnant IBD patient is to have discussed the issues relating to reproductive health prior to conception. Counselling from teenage years in young patients with IBD will help them to understand the importance of planned pregnancy. Fertility can be expected to be normal except in women with active Crohn's disease. The outcome of pregnancy is usually normal but the risks are associated with active disease and more strongly with Crohn's disease. Disease activity is definitely associated with premature delivery and low birth weight. Drug treatment should be discussed in advance of pregnancy and it would seem logical that women should be encouraged to continue maintenance treatment with aminosalicylates or sulphasalazine during pregnancy. If an attack occurs it should be investigated and treated as in a non-pregnant patient, except that use of x-rays should be minimised. Patients maintained on azathioprine may wish to continue with the drug if it is important to retain remission after full discussion. A patient with quiescent IBD can expect normal fertility, normal outcome of pregnancy and there is no contraindication to breast-feeding. The management of IBD in pregnancy is a good example of the therapeutic partnership between patient and doctor. Education and communication are key, active disease is the greatest risk to the outcome of pregnancy and drug therapy may be necessary and if so is safe.

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