REVIEW

Inflammatory bowel disease in pregnancy

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Concerns about sexual health, fertility, and pregnancy are common in patients with inflammatory bowel disease (IBD). Fertility is usually normal, although may be decreased in women with active Crohn's disease. Women with active IBD (especially Crohn's disease) are at risk of having small and premature babies. In some patients with IBD it may be desirable to continue drug treatment during pregnancy in order to control disease activity. Early engagement in discussion of these issues is important and it should be possible for most patients with IBD to have a normal outcome of pregnancy.

Every prospective parent hopes to have a healthy baby. Young adults who have a chronic illness such as inflammatory bowel disease (IBD) may have increased concerns about sexual health, fertility, pregnancy, childbirth, and the future health of any children that they may have. Worries about whether the illness or its treatment may affect the fetus or whether a child will inherit IBD are commonly expressed in hospital clinics and general practitioners' surgeries (box 1). Until recently, there has been little in terms of evidence based medicine to inform IBD patients, their partners, and clinicians. This review will attempt to summarise the available information in this area.

RELATIONSHIPS AND SEXUAL HEALTH

Chronic IBD decreases quality of life.[1] The symptoms of IBD, including diarrhoea, problems with continence, and weight loss undoubtedly have an effect on body image particularly in adolescents and young adults. The side effects of treatment such as weight gain due to steroids may also cause feelings of unattractiveness and loss of self esteem. Children with IBD may experience delays in growth and puberty, and this also has a serious effect on confidence and body image. Young people with IBD may therefore experience difficulty in forming intimate relationships and worry that they may not be able to have a normal sex life. Stoma surgery is a major life event, particularly in teenagers.[2] The development of IBD may put great strain on a previously good relationship, and women who are in a relationship experience more difficulties in their sexual life than non-affected women of a similar age.[3 4] Dyspareunia and vaginal candidiasis are commoner than in healthy women, which may account for some of these difficulties.[5] It is important to remember, however, that women with IBD do not invariably experience relationship and sexual difficulties and people with IBD should be encouraged to expect to live a normal life.

In men with IBD the only area that has been studied in detail is the incidence of impotence after proctocolectomy.[6] Men with IBD have been shown to have fewer children than healthy men of comparable age and it is unclear whether this is due to decreased sexual function or to infertility.[7]

Box 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 it's 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?

INHERITANCE OF IBD

Many people with IBD are concerned that their children will inherit the disease. There is an increased empirical risk of IBD in families of affected individuals and this risk is greater for Crohn's disease than ulcerative colitis and in Jewish families. The lifetime risk for the child of an affected parent developing IBD is around 10.5% for all forms of IBD and 7.5% for Crohn's disease.[8] About 10% of patients with IBD have an affected first degree relative and if both parents have IBD, the risk of their children being affected is around 35%.[8]

FERTILITY

Fertility is probably normal in women with ulcerative colitis. In inactive Crohn's disease, the evidence also suggests normal fertility but Crohn's disease activity impairs fertility.[9] Men and women with IBD have been shown to have fewer children than unaffected individuals.[7] In one study which examined pregnancy in women with IBD who became pregnant before or after the diagnosis, women with ulcerative colitis were no older at the time of the first pregnancy and its outcome was no different, comparing conception before and after diagnosis. Women with Crohn's disease had a delayed age of first pregnancy after

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Abbreviations: CI, confidence interval; IBD, inflammatory bowel disease

Box 2: Fertility

In women with IBD:

- Fertility is usually normal in ulcerative colitis.
- In Crohn's disease, disease activity impairs fertility.
- Psychosocial issues are important.

Box 3: Outcome of pregnancy

IBD is associated with:

- Low birth weight.
- Prematurity.
- No increase in fetal loss.
- Adverse outcomes are related to disease activity.

the diagnosis.[10] Women with Crohn's disease have been shown to have fewer children than might be expected after diagnosis and a higher rate of failure to conceive (42% *v* 28%).[11]

In recent years, concern has been expressed about fertility in men with IBD.[7] Men taking sulphasalazine experience azoospermia in 60%, although this is fully reversible within a few weeks of stopping the drug.[11 12] Azathioprine has rarely been shown to cause temporary impairment of fertility. There is no evidence that IBD itself causes infertility in men and the reduced size of families may be related to fears, inhibition, or a decision to limit family size rather than a physical factor.

OUTCOME OF PREGNANCY IN IBD

The initial impression looking at multiple, small observational studies of pregnancy in women with IBD was that the outcome was normal.[13–15] More careful examination of the evidence suggests, however, that there is an increase in preterm birth and small babies, particularly in women with Crohn's disease. A careful epidemiological study that examined the outcome of all pregnancies in Sweden over a two year period found that 756/239 773 births were to women with IBD. This study confirmed an increase in prematurity, odds ratio 1.81, (95% confidence interval (CI) 1.06 to 3.07) at less that 33 weeks and for 33–36 weeks, odds ratio 1.48 (95% CI 1.10 to 1.99). There was also an increase in low birth weight <1500 g, odds ratio 2.15 (95% CI 1.11 to 1.45). The caesarean section rate was also increased (15% compared with 10%) but showed no increase in small for dates babies, stillbirth, or perinatal death.[16]

In a large case-controlled study reported from Denmark, in Crohn's disease the relative risk of low birth weight was 2.4 and prematurity 1.4. Another study reporting the outcome of 150 pregnancies in 72 women, 108 before IBD was diagnosed and 42 after, showed no difference in the outcome of pregnancy in terms of prematurity and mean birth weight in women with ulcerative colitis but in Crohn's disease, affected women had more premature and smaller babies after diagnosis.[17]

It is disappointing that none of these studies have addressed disease activity, which is believed to be responsible for the adverse effect of Crohn's disease in pregnancy.[18]

EFFECT OF PREGNANCY ON DISEASE ACTIVITY

The course of IBD in pregnancy has been examined in small observational studies and the best evidence available is from meta-analysis data. These data are summarised in table 1. About a third of women with inactive IBD at conception (both ulcerative colitis and Crohn's disease) can be expected to relapse during the pregnancy or puerperuim. This means that the relapse rate is probably the same during that year as in any other year. It has been thought in the past that relapse was commoner in the first trimester and puerperium. It is not certain however, from more recent evidence that this is the case.[19] If however, conception occurs at a time when IBD is active, the disease will only settle in about a third of women with both ulcerative colitis and Crohn's disease.[20] Many patients will experience chronically active disease throughout the pregnancy (24% ulcerative colitis, 32% Crohn's disease). Active disease has been associated with miscarriage, prematurity, and low birth weight. It is therefore extremely important to emphasise that conception should be planned, if at all possible at a time when the disease is quiescent, in women with IBD.

Table 1 Influence of pregnancy on IBD activity; meta-analysis data (from 17)

Disease at conception	Ulcerative colitis	Crohn's disease
Inactive (likelihood of relapse in pregnancy)		
No of pregnancies	528	186
Relapse (%)	34	27
Active (pattern of disease activity in pregnancy)		
No of pregnancies	227	93
Better (%)	27	34
No change (%)	24	32
Worse (%)	45	33

INVESTIGATION AND TREATMENT DURING PREGNANCY

Given that active IBD, especially Crohn's disease, has an adverse effect on the fetus, in women with IBD, all efforts should be channelled into ensuring the disease is quiescent at conception and during pregnancy. This raises important issues relating to treatment, therefore, including the continuation of maintenance treatment around the time of conception and during pregnancy and the investigation and treatment of flare-ups of disease activity.

Investigation

Interpretation of blood investigations for IBD during pregnancy can be difficult. Due to haemodilution, the haemoglobin and albumin decrease as pregnancy progresses, and so they cannot be used in the assessment of disease activity. Imaging options are obviously limited and abdominal radiography should only be used in a sick patient suspected of intestinal obstruction or toxic megacolon. Sigmoidoscopy or colonoscopy may be performed safely if necessary.[21] Sigmoidoscopy may be essential to confirm a diagnosis of an active colitis. Colonoscopy can usually be deferred until after delivery. If required, sedation for endoscopy is generally thought to be safe but antispasmodics such as hyoscine butylbromide (Buscopan) are contraindicated.

Maintenance therapy

The management of IBD in pregnancy is a partnership between patient and clinician and as part of this, full discussion and planning before conception are required. Very few drugs are licensed for use in pregnancy, and the continuance of maintenance treatment needs to be discussed in full with the patient and possibly her partner before conception.

It is important to discuss all the issues relating to the evidence available about disease activity, the (small amount of) evidence about the safety of drugs, and the methodological difficulties in obtaining the evidence and the possible effects on the fetus of an ill mother, along with the background incidence of congenital abnormalities for any pregnancy. If possible therefore, a decision should have been made, involving the IBD patient and her partner, before the

Box 4: Treatment during pregnancy

- Education and planning required.
- Folic acid advised before conception.
- Maintenance treatment may be continued.
- Flare-up should be actively treated.
- Disease activity is more dangerous than most drugs.

pregnancy and some women will decide to discontinue treatment, despite advice that it might be better to continue it.[22]

The investigation and treatment of a flare-up of disease during pregnancy, or making a new diagnosis is perhaps more straightforward, because it is clear that an illness in the mother may have an adverse effect on the fetus.

Nutrition

Nutrition is an important consideration in any pregnant woman, but is of particular concern in IBD patients. Early nutritional intervention is indicated if there is failure of weight gain and enteral feeding as a primary treatment for active disease has been shown anecdotally to be associated with a normal pregnancy outcome.[23]

Folic acid supplementation before conception is recommended for all women.[24] In women with IBD this is of particular important because they may be folate deficient due to their disease (Crohn's disease) and sulphasalazine, used in maintenance treatment, is a folic acid antagonist. Supplementation with folic acid 5 mg daily rather than 400 μg is therefore recommended.

Surgical treatment

Women who have undergone surgical intervention for ulcerative colitis or Crohn's disease in the past can expect a normal outcome of pregnancy. Vomiting has been reported to cause stomal prolapse requiring revision after delivery, and opinions are divided about the preferred mode of delivery in women who have had ileoanal pouch surgery and those with perianal disease.[25] Many colorectal surgeons advise caesarean section for these women.

Emergency surgery during pregnancy has been reported to be associated with a high risk of fetal loss (60%). Elective surgery should be postponed until after delivery.

Drug treatment

Aminosalicylates have been used for many years and are widely reported to be safe during pregnancy. They are poorly absorbed and there is little placental transport from mother to fetus. The advice is that they should be used for maintenance or induction of remission as in non-pregnant patients. Recently, concern has been raised about the safety of folic acid antagonists in pregnancy, in terms of neural tube defects and other congenital abnormalities principally cardiovascular defects and oral clefts.[26] There is no evidence directly relating to sulphasalazine, but in view of this, folic acid supplementation around conception should be strongly advised and a change to an alternative aminosalicylate preparation considered.

Mesalazine is safe in conventional doses,[27] but high dose mesalazine has been associated with interstitial nephritis in a newborn infant[28] and is therefore inadvisable during pregnancy.

Corticosteroids are well tolerated in pregnancy and their use has not been associated with abnormal fetal outcomes. Corticosteroids cross the placental barrier but there is no convincing evidence of teratogenesis in humans and although theoretically possible, adrenal insufficiency in the neonate is exceptionally rare. There have been reports of intrauterine growth retardation but some of this effect may be due to the underlying disease. Corticosteroids are therefore indicated in moderate to severely active disease as in a non-pregnant patient.[29] Rectal preparations may be used until the third trimester unless there is a specific concern about miscarriage or premature delivery.

Azathioprine and 6-mercaptopurine have no effect on human interstitial cell function or gametogenesis in the doses used in clinical practice. They do not interfere with folic acid metabolism. There has never been any demonstration of teratogenicity of these agents in humans, but because of a paucity of clinical data, many patients have been advised to discontinue azathioprine before pregnancy. Extensive experience of the use of azathioprine in pregnancy in transplant recipients and patients with systemic lupus erythematosus has not shown any adverse effect,[30 31] and small retrospective studies in patients with IBD have not observed any increase in complications of pregnancy or adverse outcomes.[32 33] If essential to maintain remission, after full discussion, it is reasonable to continue these agents. In view of the side effects and complications that may arise with the use of these agents in the first few months of treatment, initiation of therapy during pregnancy is not advisable.

Cyclosporin is a potent immunusuppressant with a significant incidence of serious side effects in any patient. Cyclosporin has not been associated with increased adverse effects to the fetus,[34 35] but the risks to the mother of renal and hepatic toxicity make its use limited to patients with fulminant colitis, not responding to steroids, in order to try to avoid a colectomy, which carries a high risk of fetal loss.

Methotrexate is mutagenic and teratogenic and is contraindicated in pregnancy or anyone considering conception. Patients starting methotrexate therapy should be advised to use reliable contraception. If conception occurs, there is a high risk of serious neural tube defects. If termination of pregnancy cannot be contemplated, high dose folic acid therapy should be administered for the remainder of the pregnancy.[36]

Antitumour necrosis factor antibodies have recently been used in the treatment of Crohn's disease.

Post-marketing surveillance of patients treated with infliximab has identified 59 pregnancies in patients before conception or during pregnancy. There was no increase in miscarriage and there were two complications of pregnancy, one premature birth and one child born with Fallot's tetralogy.

The outcome was therefore not different from that expected in the population and although further data are required, there is no theoretical or actual evidence of adverse effect.[37]

Antibiotics are sometimes used in the treatment of IBD patients. There are theoretical concerns about mutagenicity with *metronidazole*. This drug has been extensively used in the treatment of bacterial vaginosis in pregnancy and shown to be safe,[38] but there are no data about the effects of increased length of treatment, which would generally be the case in those with IBD.

Ciprofloxacin and other quinolones have been used during pregnancy and have not been associated with any evidence of congenital or musculoskeletal abnormalities in children subsequently.[39] Further prospective information about possible long term musculoskeletal effects are not yet available.

BREAST FEEDING

Breast feeding is encouraged for its beneficial effects. There is obviously concern if a mother is on any medication as to whether there may be any adverse effects on the baby from the drug secreted into breast milk. Sulphasalazine and the other aminosalicylates are excreted in breast milk in small amounts. No harmful effects have been observed from breast feeding on sulphasalazine or conventional doses ($\leq$3g) of mesalazine. Corticosteroids are poorly excreted in breast milk and if possible a four hour delay after oral dosing should be observed. However in practical terms breast feeding for mothers on steroids appears to be safe.[40] The manufacturers do not advise

Box 5: Breast feeding

- Breast feeding should be encouraged.

Box 6: Key references

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breast feeding in patients on azathioprine and 6-mercaptopurine, but there is extensive clinical experience of mothers who have breast fed on these agents with no apparent adverse effects. This is another situation where full discussion and informed decision are appropriate.

CONCLUSION

Discussion and education about sexual health, fertility, and pregnancy is an essential component of the management of any young person with IBD. This should allow informed descisions to be made before conception. In general, disease activity appears to be the most dangerous factor and is associated with premature delivery and low birth weight especially in women with Crohn's disease. Drug treatment should be discussed in full and the evidence suggests that aminosalicylates and steroids should be used as in the non-pregnant patient and that azathioprine may be continued to maintain remission, after full discussion. A woman with quiescent IBD can expect normal fertility, a normal outcome of pregnancy, there is no contraindication to breast feeding, and their pregnancy would be managed as a partnership between patient and physician.

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