

Pregnancy and inflammatory bowel disease

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Introduction

The Inflammatory Bowel Diseases (IBD) Ulcerative colitis (UC) and Crohn's disease (CD) demonstrate a bimodal age distribution with a small secondary peak later in life but the majority diagnosed in adolescence and early adulthood, essentially the childbearing years. It is thus no surprise that the interface between IBD and pregnancy poses a common challenge. In order to adequately counsel and manage our IBD patients when they consider starting a family there are 6 issues with which we need to be familiar; the inheritance of IBD, the impact of IBD on fertility, the effect of pregnancy on the course of IBD and conversely the impact of IBD (and the surgical and medical therapies thereof) on pregnancy outcomes, the safest mode of delivery and the complexities of breastfeeding.

The inheritance of IBD

The familial nature of IBD has long been recognized and this predisposition is stronger for CD than for UC, as evidenced by higher concordance rates for CD than UC in monozygotic twins.¹ There is also a high degree of concordance for IBD subtype in affected members of IBD families, as well as some degree of concordance for disease location and behavior. It has been shown that if one parent has CD or UC there is a 5 and 1.6 % chance respectively of disease affecting offspring, with higher rates in individuals of Jewish descent.² This risk is increased substantially (to at least 36%) if both parents are affected, regardless of IBD subtype.³ The inheritance of IBD is however complex and does not follow Mendelian principles. Numerous IBD susceptibility genes have been identified and the strongest association to date is that of CD with 3 polymorphisms of the NOD2 gene on chromosome 16.¹ A recent meta-analysis determined the odds ratios for developing CD in carriers of 1 mutant allele, and found only a small (2 to 4-fold) increased risk.⁴ Furthermore in the Western Cape these polymorphisms are infrequent in patients with IBD, as well as in population controls.⁵ Given the poor predictive value for disease acquisition genetic testing in IBD is currently not recommended.

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IBD and fertility

Infertility is best defined as the inability to conceive within 12 months of unprotected intercourse. Generally patients with IBD have infertility rates approaching that of the general population.⁶⁻⁹ Certainly IBD per se has little effect on male fertility, with the exception of several drugs used to treat the disease. Infertility is reported in up to 60% of men taking salazopyrine. This is due to a dose-dependent reduction in sperm count. Sperm is also morphologically and functionally abnormal. Fortunately this is reversible within 2 months of drug discontinuation and substituting an alternative 5-ASA agent restores sperm function to normal. Methotrexate may also induce oligospermia and while infliximab use in men may affect semen quality, whether this alters fertility remains to be established.⁷

Woman with quiescent CD have normal fertility [6-9]. In contrast active disease, in particular ileitis and colitis, appears to reduce fertility which can be normalized by regaining disease control. In contrast UC, whether active or quiescent, does not impact on female fertility.⁶⁻⁹ The notable exception however is women who have undergone ileal pouch anal-anastomosis (IPAA). A recent meta-analysis reports a three fold increase in infertility following this procedure.¹⁰ Furthermore IPAA appears to impact on female fecundity, defined as the probability of pregnancy per menstrual cycle of unprotected intercourse. Before IPAA woman with UC have normal fecundity ratios. Following IPAA however female fecundity is reduced by an alarming 80%.¹¹ This is largely attributed to pelvic adhesions post surgery. Other factors such as the type of pouch, patient age and smoking status have not been shown to impact significantly. As this is a major complication of IPAA women need to be adequately counseled prior to surgery. A recent report suggests that ileorectal anastomosis may preserve fertility to a greater extent than IPAA.¹²

The impact of pregnancy on the course of IBD

Both UC and CD are governed by the "rule of thirds"; one third improves, one third deteriorates and one third remains unchanged during pregnancy. If patients flare it is usually in the first trimester. The major factor influencing disease course during pregnancy is activity at the time of conception. 60% of women with active disease will continue to flare during gestation and 50% of these will deteriorate. As such every effort must be made to achieve quiescence before

considering pregnancy.⁶⁻⁹ A second factor affecting disease course is HLA disparity between mother and foetus, and by inference disparity between maternal and paternal genes. The foetus is a foreign body and in order to prevent rejection the maternal immune system must aggressively down-regulate responses to foetal antigens. As such, pregnancy is a state of immunosuppression or immunotolerance. It has been shown that if HLA disparity is present at 2 HLA alleles the course of IBD in pregnancy fares better than if a single locus is affected.¹³

Previous pregnancies also impact on the future course of IBD. Women with CD who have previously given birth have fewer resections and longer intervals between procedures, when compared to their nulliparous counterparts. Furthermore the course of future IBD is improved, with fewer relapses in the years following pregnancy than before. Again this may reflect pregnancy induced alterations in maternal immunity [6-9].

The impact of IBD on pregnancy outcomes

Five endpoints are evaluated in clinical trials; the incidence of congenital malformations, stillbirths or spontaneous abortions, small for gestational age (SGA), preterm delivery (<37 weeks of gestation) and low birth weight (LBW) of less than 2.5kgs. Overall IBD fathers have normal outcomes. In contrast woman with both CD and UC have an increased risk of adverse events.⁶⁻⁹ This appears to relate to disease activity rather than the use of specific medications. A recent meta-analysis has shown that overall both UC and CD are associated with a significant incidence of prematurity (OR 1.87, 95% CI 1.5-2.3). CD but not UC is associated with LBW (OR 2.8, 95% CI 1.4-5.6) and UC (but not CD) has an increased incidence of birth defects (OR 3.88, 95% CI 1.4-10.6). In contrast neither disorder appears to increase SGA or stillbirth/abortion rates.¹⁴

IBD surgery and pregnancy

IBD surgery in pregnancy should be restricted to major complications such as haemorrhage, perforation, obstruction and fulminant colitis. Maternal and foetal risk, which is substantial, correlates with the underlying disease severity, rather than the procedure itself. Emergency colectomy for UC carries an abortion rate of 60% while emergency surgery for CD has an 18-40% foetal loss.⁶⁻⁹ The second trimester is the safest time to operate. Given risk to mother and child active disease in pregnancy must be aggressively treated with medical therapy in attempt where ever possible to avoid surgery

The safety of IBD medications in pregnancy.

The FDA stratifies drug safety in pregnancy into 5 categories (see Table 1).¹⁵

Category	Interpretation
X	Contraindicated
A	Controlled studies show no risk (No category A IBD meds)
B	Generally safe in pregnancy
C	Risk cannot be ruled out (animal or human studies lacking)
D	Possible evidence of risk (can use if benefit outweighs risk)

Aminosalicylates are our mainstay of therapy for colonic disease. Generally these drugs are safe in pregnancy and have an FDA category B rating.¹⁵ A wealth of retrospective data has not shown any significant association of these drugs with adverse outcomes (up to 3g/day). The use of salazopyrine requires additional folic acid replacement (2g/day).⁶⁻⁹

In contrast salazopyrine use in prospective fathers is associated with an increased incidence of congenital abnormalities in their offspring.¹⁶ This together with the well recognized effects on fertility suggest we should either stop the drug or replace it with an alternative 5-ASA preparation at least 3 months before attempting conception to allow spermatogenesis to return to normal.⁶⁻⁹

Corticosteroids have an FDA category C rating.¹⁵ Overall they pose a low risk to the developing foetus. Some but not all studies have shown an association with oral clefts in the newborn. There are also reports in the transplant literature of premature rupture of membranes, as well as a theoretical risk of adrenal insufficiency in the newborn, which fortunately is rare in clinical practise. As in the non-pregnant IBD patient, steroids should only be used if truly indicated.^{6-9,15}

Antibiotics are often used to manage perianal and luminal CD. The usual suspects, ciprofloxacin and metronidazole, are considered safe in pregnancy after the first trimester. However in the setting of IBD prolonged courses are usually required and furthermore evidence of true benefit is lacking. As such chronic use should be avoided. Short courses if appropriate are acceptable.^{6-9,15}

Much of the controversy of prescribing in IBD pregnancy revolves around the thiopurines, azathioprine and 6-mercaptopurine. These drugs have an unfortunate FDA category D rating, based largely on animal and early human studies that showed an increased risk of birth defects and spontaneous abortions with these agents. However extensive retrospective evidence in the transplant, rheumatology and IBD literature suggests that these drugs are generally safe in pregnancy. Certainly no specific patterns of congenital abnormalities have emerged and furthermore the foetus is relatively protected during organogenesis by low bioavailability, as well as inability of the immature foetal liver to convert azathioprine to active 6-MP. It certainly appears that foetal exposure to thiopurines is preferable to active and uncontrolled maternal disease. As such most recommendations in the literature suggest continuation in woman effectively established on these drugs prior to pregnancy.^{6-9,15} In contrast there is no place for commencing these drugs after conception, given the category D rating, the prolonged time to efficacy and the dose adjustments in pregnancy reflecting fluctuations in BMI.

There are conflicting reports that exposure of IBD fathers to thiopurines within 3 months of conception is associated with a risk of adverse outcomes. Evidence to date is however insufficient to recommend discontinuation of azathioprine or 6-MP for this indication.¹⁷

Cyclosporine and **tacrolimus** both have FDA category C ratings. Evidence of safety and efficacy in IBD pregnancy has been reported in several cases of fulminant or refractory colitis. More extensive evidence from the transplant literature suggests little teratogenicity and certainly intrapartum cyclosporine exposure would be preferable to an emergency colectomy.^{6-9,15}

Infliximab (IFX) has a category B FDA rating and is generally considered safe in pregnancy. Over the past 3 years, analysis of the TREAT registry as well as the Centocor IFX safety database has identified numerous cases of unintentional exposure to IFX in both IBD mothers and fathers. Birth defects and adverse pregnancy outcomes have not been shown to differ significantly from subjects not exposed to the drug.^{6-9,15} More recently 10 cases of intentional exposure to maintenance IFX during pregnancy were described. All 10 pregnancies resulted in live births with no congenital abnormalities or SGA.¹⁸ As an IgG1 monoclonal antibody, IFX does not cross the placenta in any significant amounts during the first and second trimester, and thus exposure during organogenesis is minimal. Transplacental transfer of IFX does however occur in the third trimester and as effects on neonatal immunity are currently unknown it may be prudent to discontinue IFX in the last 2 months of pregnancy.

Safety of adalimumab in pregnancy is limited to a few case reports.

Delivery

Epidemiological studies have shown an increased caesarean section rate for both UC and CD. This likely reflects patient and practitioner concern, rather than true evidence based medicine. It is becoming increasingly apparent that the mode of delivery should be dictated by obstetric need only, and not the underlying IBD.⁶⁻⁹ One exception is woman with active perianal disease who will benefit from elective caesarean section.¹⁹ In contrast inactive perianal disease does not appear to pose a risk of perianal complications following normal vaginal delivery (NVD). IAPP is also not a contraindication to NVD.⁶⁻⁹ Several studies report good preservation of pouch function up to 4 years post NVD. This however is somewhat controversial given the risk of occult sphincter damage with NVD, especially in primigravids, which may impact on future continence and pouch function. Long-term follow up studies are required to address this question.

Breastfeeding and IBD

Breast feeding is obviously the preferred form of neonatal nutrition. Certain medications should however be avoided, due to high concentrations in breast milk and potential toxicity to the baby.^{6-9,15} Table 2 summarises current recommendations on safety of IBD medications in breast feeding.

Table 2: Safety of IBD drugs in breast feeding^{6-9,15}

Safe	Limited data Appears safe	Limited data Not advised	Contraindicated
mesalazine salazopyrine corticosteroids	IFX	azathioprine 6-MP	thalidomide methotrexate cyclosporin metronidazole ciprofloxacin

Conclusion

Pregnancy in IBD poses a common clinical challenge. In order to optimise management of both mother and foetus, every effort should be made to strive for remission before conception. Not only will this improve fertility rates in women with CD, but is a major factor influencing the course of IBD during gestation. Furthermore flares during pregnancy must be managed aggressively to prevent surgery and to improve pregnancy

outcomes. The true enemy of the IBD baby is active and uncontrolled disease, and not the medications used to treat it. With the notable exception of methotrexate and thalidomide, and salazopyrine in prospective fathers, the majority of IBD medications pose little overt risk to the foetus.

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