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TOPIC HIGHLIGHT

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Pregnancy related issues in inflammatory bowel disease: Evidence base and patients' perspective

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Abstract

Inflammatory bowel disease (IBD) affects women of childbearing age and can influence fertility, pregnancy and decisions regarding breastfeeding. Women with IBD need to consider the possible course of disease during pregnancy, the benefits and risks associated with medications required for disease management during pregnancy and breastfeeding and the effects of mode of delivery on their disease. When indicated, aminosalicylates and thiopurines can be safely used during pregnancy. Infliximab and Adalimumab are considered probably safe during the first two trimesters. During the third trimester the placenta can be crossed and caution should be applied. Methotrexate is associated with severe teratogenicity due to its folate antagonism and is strictly contraindicated. Women with IBD tend to deliver earlier than healthy women, but can have a vaginal delivery in most cases. Caesarean sections are generally recommended for women with active perianal disease or after ileo-anal pouch surgery. While the impact of disease activity and medication has been addressed in several studies, there are minimal studies evaluating patients' perspective on these issues. Women's attitudes may influence their decision to have children and can positively or negatively influence the chance of conceiving, and their beliefs regarding therapies may impact on the course of their disease during pregnancy and/or breastfeeding. This review article outlines the impact of IBD and its treatment on pregnancy, and examines the available data on patients' views on this subject.

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Key words: Pregnancy; Breast-feeding; Nursing; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) predominantly affects the younger-aged population and therefore is prominent in women of child-bearing age. It often requires medication for maintenance of remission[1]. Literature on pregnancy in IBD has mainly utilized tertiary hospital cohorts and focused on pregnancy outcomes. Current guidelines emphasize the importance of inducing and maintaining disease remission prior to conception and during pregnancy[1,2]. Studies of patients' perspective of the influence of IBD on fertility, pregnancy and breastfeeding

are highly relevant and beginning to emerge. This review article summarizes this evidence and examines the currently available data describing the patients' views.

LITERATURE SEARCH

A literature search was conducted using Pubmed from 1980 to 2010 with the search terms "IBD", "Crohn's disease (CD)", "ulcerative colitis (UC)", "pregnancy", "breast feeding" and "nursing". Further relevant articles were identified from the reference lists of identified articles.

Fertility and fecundity

Factors determining fecundity and fertility in IBD include disease systemic effects (e.g., fatigue and anaemia) as well as libido and sexual inactivity, which, in turn, may be influenced by body image issues and dyspareunia[3]. Furthermore, concerns over the influence of disease activity or medications on a successful pregnancy may also influence fecundability. In UC, overall fertility is comparable to that of the healthy population[3-5], but women with ileo-anal pouches (IPAA) have reduced fecundity[6,7]. Fertility in CD in remission is equivalent to that of healthy women[4,8,9] but may be reduced in patients with active disease[9-12]. As in UC, women with CD also have reduced fecundity following extensive surgery involving the pelvis[5-7,13-18].

Disease behaviour during and after pregnancy

Disease activity during pregnancy is similar to that in non-pregnant women as reported by two Danish cohort studies. In 97 women with UC, flare rates were 34% per year during pregnancy and 32% per year outside pregnancy[19], while in 68 women with CD there was also no increased risk of a flare during pregnancy[20]. The vast majority of women have quiescent disease during pregnancy as shown in a population based cohort of 461 women from the Northern California Kaiser Permanente population[21].

Women with IBD might experience a more benign course of disease in the post-partum period. A significantly reduced number of flares in comparison to pre-pregnancy in a small cohort of 18 CD and 19 UC patients was reported by Castiglione *et al*[22]. A larger pan-European study of 93 women with CD and 173 women with UC confirmed this finding[23]. The reason for this phenomenon is unknown, but it has been proposed that disparity between maternal and foetal human leukocyte antigen class Ⅱ antigens leads to a state of immuno-tolerance or suppression that in turn leads to a more benign course of IBD[24].

Effects of IBD and IBD disease activity on pregnancy

Active disease during pregnancy has been linked to adverse pregnancy outcomes of low birth weight, pre-term birth and foetal loss[19,25-27]. Population-based studies have, however, reported conflicting results. In 461 women (300 with UC) of the Kaiser Permanente population in North America, no correlation between adverse pregnancy outcomes and disease activity was found[21], while a study of 157 Danish women with CD revealed that active disease increased the risk of pre-term birth[28]. The higher proportion of patients with active disease in the Danish study (45% *vs* 20% in the Kaiser Permanente population) may explain this difference.

Some studies, including a meta-analysis by Cornish *et al*[29], reported an increase in pre-term births in IBD patients[21]. Other studies, however, that differentiated UC from CD found an increase in pre-term birth rates for patients with CD only[30,31]. CD women also delivered lower birth weight babies than healthy controls and UC women[30,31]. It is important to recognise that all studies examining pregnancy outcomes in IBD used healthy women controls rather than those with other chronic diseases.

Congenital abnormalities in offspring of mothers with IBD

Congenital abnormalities of variable severities occur in 3%-7% of babies of healthy mothers[32]. Studies of congenital malformations in the offspring of mothers with IBD have reported conflicting results. In a population based cohort of 262 women from Washington state, North America, an increased risk of congenital malformations was found in the offspring of UC patients (7.9% *vs* 1.7% in healthy controls; $P < 0.001$) but not in those of CD patients (3.4%; P = NS)[30]. The study did not control for medication use[30]. In contrast, the Hungarian Case Control Surveillance of Congenital Anomalies (HCCSCA) (1980-1996) found no increase in the risk for "any" malformation [odd ratio (OR): 1.2, 95% (confidence interval) CI: 0.9-1.8] in the offspring of 79 UC mothers compared to 95 control mothers after adjusting for parity, age and medication use[33]. Specific malformations of the limb (OR: 6.2, 95% CI: 2.9-13.1), urinary tract (OR: 3.3, 95% CI: 1.1-9.5) and multiple malformations (OR: 2.6, 95% CI: 1.3-5.4), however, were significantly increased[33].

An Italian case-control study reported a significantly increased risk of congenital anomalies in the offspring of 90 women with IBD (5.5% *vs* 0% in 240 healthy controls) and that CD and UC had equivalent risks[31]. The reported 0% incidence of congenital abnormality rate in healthy controls, however, was unusually low given this rate can approach 7%[32].

The risk of congenital malformations in the offspring of 461 women with IBD from the Northern California Kaiser Permanente population was not increased in comparison to 493 healthy controls[21]. Cornish *et al*[29] found in a meta-analysis of four studies an increased risk (OR: 2.37, 95% CI: 1.47-3.82) of reporting congenital abnormalities for UC, while for CD the risk increase was not statistically significant (OR: 2.14, 95% CI: 0.97-4.74; P = 0.06).

Data on congenital malformations may be contradictory due to differences in study design, the inclusion of cohort *vs* population subjects, and sample sizes. The majority of studies, however, report an increased risk for malformations in UC, but not in CD. Further prospective

Table 1 Food and Drug Administration categories of drug safety during pregnancy

FDA category	Definition
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 pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies 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 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

FDA: Food and Drug Administration.

studies adjusting for disease activity, medication and age of the mother are needed.

Medication during pregnancy

The risks and benefits of medication need to be considered on an individual patient level, since active disease poses a risk to the pregnancy[26-28]. The European Crohn's and Colitis Organisation (ECCO) guidelines state the risk of adverse pregnancy outcomes from active disease to be higher than the risk of using most IBD medications[2]. The United States Food and Drug Administration issued a categorisation of drugs safety in pregnancy (Table 1)[34].

Aminosalicylates: Sulfasalazine, mesalazine and balsalazide are category B medications, while olsalazine is category C. Initial case reports[35-37] suggesting sulphasalazine teratogenicity was refuted by a Danish cohort study demonstrating no adverse outcomes in 17 pregnant CD patients exposed to sulfasalazine[28]. Another study of 181 pregnant patients with IBD exposed to sulfasalazine reported lower rates of adverse outcomes than those expected in the general population[38]. Sulfasalazine impairs folate absorption, which is vital for neural tube development. Therefore folate supplementation is mandated[2].

Several studies have demonstrated the safety of mesalazine[39-41]. Robust data from a Danish population-based cohort and a prospective controlled trial of 165 pregnant women with mesalazine exposure reported no increased risk of congenital abnormalities[42,43]. It is unclear whether an excess of stillbirth and preterm birth in 88 pregnancies of women with CD on mesalazine reported in the population based study[43], occured as a result of IBD itself rather than the medication since this study incorporated 19 418 pregnancies of healthy women without any chronic illnesses and medication exposure as the control group. Thus, sulfasalazine and mesalazine are considered safe in pregnancy.

Antibiotics: Antibiotics play an important role in the management of perianal CD[2]. Metronidazole is a category B medication. In a population based case-control study using HCCSCA data (1980-1991), metronidazole exposure during the second or third trimester was associated with cleft defects[44]. Other studies including two meta-analyses and a prospective controlled study, however, found no increased risk of congenital abnormalities relating to metronidazole use[45,46]. Quinolones can induce congenital abnormalities in animals due to their accumulation in bone and cartilage[47]. In 2 human studies totalling over 250 patients without IBD, no increased risk of adverse pregnancy outcomes or foetal malformations was found[48,49].

Short-term antibiotic use in pregnancy appears safe in largely non-IBD cohorts. In IBD, however, exposure to antibiotics can be prolonged and the associated risks may therefore be higher[2]. A small series of IBD patients found no adverse pregnancy outcomes in 27 patients exposed to metronidazole and 18 to ciprofloxacin[50].

Tetracyclines (retardation of foetal skeletal development) and sulphonamides (interferes with folic acid metabolism) should both be avoided in pregnancy[2].

Corticosteroids: Prednisone and budesonide have category C ratings. Corticosteroids cross the placenta and some adverse data exist in humans. A meta-analysis of ten cohort and case-control studies totalling 50 845 patients without IBD found no increase in overall risk of major congenital abnormalities, but there was a significant risk of oral clefts[51]. In contrast a prospective study of 262 women found that neither the overall risk for malformations nor the risk for clefts was increased[52]. No human data exist on orally administered budesonide, but studies looking at women exposed to inhaled or intra-nasal budesonide have found it to be safe during pregnancy[53,54]. Due to oral budesonide's high first pass hepatic metabolism, significant foetal exposure is less likely.

Thiopurines: Mercaptopurine and its pro-drug azathioprine are category D due to previous links with spontaneous abortions[55,56]. Animal studies, using doses of 1.5-2.5 mg/kg, have not reported any adverse outcomes apart from low birth weights[57,58]. Transplant and rheumatology cohorts demonstrated the safety of thiopurines[59-61]. Most studies in pregnant IBD patients report no adverse outcomes[62,63], but a Danish study reported a increased pre-term birth, low birth weight and foetal abnormalities in a cohort of only 10 patients[64]. That study compared pregnancy outcomes in thiopurine exposed patients to those of the general population rather than non-exposed IBD patients. It is therefore unclear whether the increased risk detected in the study was due to medication or IBD itself. In contrast, a prospective Austrian abstract of 33 women[65] and a French study on 86 women show no increase in adverse outcomes[66]. Paternal thiopurine exposure within 3 mo prior to conception led to a higher

rate of pregnancy related complications in one study[67], but another study reported no increased risk of adverse outcomes[68].

Thus, studies comparing outcomes of thiopurine exposed and unexposed IBD patients demonstrate no association with adverse outcomes. The single study showing a possibly increased risk is small and compares exposed patients to the general population[64]. Based on the overall evidence and despite the category D classification, the ECCO guidelines therefore consider thiopurines safe and well tolerated in pregnancy[2].

Methotrexate: Methotrexate is rated category X as it is clearly teratogenic and an abortifacient due its biological action as a folate antagonist. It is associated with numerous foetal abnormalities and high risk of foetal mortality and absolutely contraindicated for women attempting pregnancy[69,70].

Other immunosuppressants: Data on cyclosporine and tacrolimus mainly stems from the transplant and rheumatology literature and both are rated category C[2].

Biological agents: Infliximab has been classed as category B. It does not cross the placenta during the first trimester and hence there is no exposure in this critical phase of development[71]. Infliximab crosses the placenta in later stages of pregnancy and may be present in the newborn for several weeks[71]. Safety data for infliximab are provided by three large scale studies. The Crohn's Therapy Resource, Evaluation and Assessment Tool registry-a prospective, North American observational multi-centre study-enrolled infliximab-exposed and unexposed CD patients from 1999 to 2004[72]. No differences in miscarriages and neonatal complications were found between infliximab-exposed (117 pregnancies) and unexposed (49 pregnancies) women[72]. The retrospective Infliximab Safety Database (maintained by Centocor) found no differences in adverse outcomes between 96 pregnancies in women with infliximab exposure compared to the general population[73]. The Leuven group in Belgium treated 29 women treated with infliximab during 35 pregnancies and six women with adalimumab during seven pregnancies. In comparison to IBD patients without infliximab or adalimumab exposure, no increased risk of adverse events was found[74].

Adalimumab is also classed as a category B drug and expected to have the same placental transfer as infliximab. Apart from the Leuven experience[74] there are few reports on IBD patients exposed to adalimumab during pregnancy[75,76]. The organisation for teratology specialists' registry of women with rheumatoid arthritis compared 34 adalimumab-exposed pregnancies to 52 pregnancies of healthy women and found no increased risk of adverse pregnancy outcomes[77]. Certolizumab and natalizumab are category B and C drugs respectively, but there is currently little data on their effects in pregnancy[2].

Infliximab use in pregnancy resulted in the death of a 3 mo old child with disseminated Bacillus Calmette-Guérin (BCG) after receiving the live BCG vaccination[78]. Live vaccinations are contra-indicated for immuno-compromised patients. Newborns to mothers exposed to infliximab and adalimumab mothers should have their vaccination postponed[78].

Mode of delivery

Patients with IBD (especially CD) were more likely to have a caesarean section in Cornish's meta-analysis of six studies (OR: 1.5, 95% CI: 1.26-1.79; $P < 0.001$) compared to the general population[29], but there was no difference in caesarean rates between UC and controls[29]. Concerns regarding the preservation of the anal sphincter function and the development of perianal disease after traumatic injuries occurring during vaginal delivery may partially explain this phenomenon. However, the chance of developing perianal disease in women with CD without prior perianal involvement is low; in a population based cohort study from Mannitoba, Canada only one of 27 women without prior perianal disease developed perianal disease after vaginal delivery and episiotomy[79]. Conversely, in a self-report survey of 179 women without perianal disease, 18% reported perianal involvement after delivery[80], but it is possible that selection bias, that is, more women with than without perianal disease may have responded, and recall bias may have occurred[80].

A population based cohort study from Mannitoba of 11 patients with inactive perianal disease and two single case reports from France and United States, revealed that inactive perianal disease may tolerate a vaginal delivery with episiotomy if needed without risking a flare[79,81,82]. However, women with active perianal disease should be advised to have a caesarean section as a high risk of deterioration is anticipated. Delivery trauma can lead to poor-healing in the perineum. ECCO guidelines advise that elective caesarean section is indicated for all women with perianal involvement[2] even though there is little evidence suggesting harm from a vaginal delivery in cases of inactive disease.

ECCO guidelines recommend mandatory caesarean sections after IPAA[2]. Changes in anal sphincter function are temporary and long-term disturbances seem to be independent of the mode of delivery in patients with IPAA[14,16,83]. The largest study of 232 females with pregnancies after IPAA found no difference in pouch-related complications between women undergoing vaginal delivery or caesarean section[84]. In another survey, functional pouch outcomes of 85 women with vaginal deliveries after IPAA were no different to those of 343 age matched women who did not have children after IPAA[85]. A Finish survey study of 39 women with IPAA found no differences in pouch function after 19 vaginal deliveries in comparison to 21 caesarean sections and the rate of 5 tears after vaginal delivery was similar to a healthy control group[86]. In a cohort of women investigated four years after IPAA at the Cleveland clinic, United States no clinical differences were demonstrated between 20 women

Table 2 Medication recommendation for pregnancy and breast feeding

Class	Drugs	FDA category	Pregnancy advice	Detection in breast milk
Aminosalicylates	Sulfasalazine, balsalazide, mesalazine	B	Safe to use (folate supplementation for sulfasalazine)	Low levels detectable
Aminosalicylates	Olsalazine	C	Safe to use	
Antibiotics	Metronidazole	B	Safe to use	
Antibiotics	Ciprofloxacin		Limited data; probably safe	
Corticosteroids	Prednisolone, budesonide	C	Safe to use	Detectable
Thiopurines	Azathioprine, 6-mercaptopurine	D	Safe to use	Very low levels detectable
Folate antagonist	Methotrexate	X	Absolutely contraindicated	
Biological agent	Infliximab	B	Probably safe (avoid during 3rd trimester)	Not detectable
Biological agent	Adalimumab	B	Probably safe (avoid during 3rd trimester)	Very low levels detectable

FDA: Food and Drug Administration.

with at least one vaginal delivery compared to 62 women who only had caesarean sections[87]. Subclinical differences in anorectal physiology were however demonstrated as women with vaginal deliveries had significantly lower squeeze pressure on anorectal manometry and significantly more anal sphincter defects detected by anorectal sonography than those women with caesarean sections[87].

The ECCO guidelines state that women are at borderline incontinence after IPAA surgery and that any further disruption by a vaginal delivery might compromise this[2]. This theoretical concern is supported by sonographic and manometric evidence of sphincter dysfunction, but this does not translate to clinical differences in pouch function or quality of life. Precautionary caesarean sections are however recommended[2].

Thus, mandatory recommendation for caesarean sections in IBD is only for very specific indications and decisions should be made on a case by case basis.

Breast feeding

Breast milk provides ideal nutrition and has positive effects for the immune system of the newborn[88]. Data on the protective effect of breastfeeding against the development of IBD report are conflicting. Study design, recall bias, definition of breast feeding (especially duration) and the design bias often inherent in retrospective case-control studies may explain some of the differences[89]. A meta-analysis of 17 studies found reduced ORs of 0.67 (95% CI: 0.52-0.86) for CD and 0.77 (95% CI: 0.61-0.96) for UC. The relevance of a French case-control study reporting an increased risk (OR: 2.1, 95% CI: 1.3-3.4) of developing CD[90] remains unclear, in light of previous studies showing no effect or a protective effect[89,91].

Fewer patients with IBD breastfeed compared to the general population, and this may relate to fears about adverse effects of maternal medication[92]. Most maternal medications can be detected in breast milk, but this does not always lead to biological effects in the infant.

Based on two case reports of bloody diarrhoea in newborns breastfed by mothers taking sulfasalazine and 5-aminosalicylates respectively, the American Academy of Pediatrics advises against breastfeeding by mothers taking these medications[93-95]. In contrast, several studies demonstrate the safety of sulfasalazine and 5-aminosalicylates while breastfeeding by detecting low levels of drug in breast milk or the infant's serum[39,96,97]. Based on above evidence mothers on sulfasalazine and 5-aminosalicylates should not be discouraged from breastfeeding unless the infant develops diarrhoea.

Since corticosteroids are found in human breast milk in low concentrations, women are advised to avoid feeding within 4 h of taking an oral dose to reduce exposure[2,98]. Thiopurine and associated metabolite levels are either at undetectable, or extremely low levels, in human breast milk[99-101], while infants' levels were undetectable[102,103]. Infliximab can not be detected in infants of breastfeeding mothers[104], but adalimumab has been found in miniscule concentrations in breast milk in a single case[105]. Methotrexate should be avoided as it is found in breast milk[106]. Sulfasalazine, 5-aminosalicylates, steroids and thiopurines are all considered advisable during breast feeding[2] (Table 2).

Women's beliefs and attitudes

Few studies have evaluated the perspectives of patients with IBD on fertility, pregnancy, breast feeding and pregnancy outcomes. Women with IBD may have fewer children as more stay "voluntarily childless"[107]. A survey of Crohn's and Colitis Foundation of America members reported that 18% of females with CD and 14% of females with UC decided to stay childless compared to 6% of the general population ($P = 0.001$ for CD, $P = 0.08$ for UC). Notably, the decision to stay childless amongst IBD patients contrasts to the much lower "involuntary" childlessness rates (inability to conceive) (5% in CD, 1.7% in UC and 2.5% in the general population, P = NS)[107]. Concerns about the effect of pregnancy on their disease, about passing on IBD to their children and about their ability to look after children were given as the main reasons for voluntarily childlessness[107]. IBD patients have expressed a high interest in genetic testing to determine their future health or that of their family members[108], but there are no data whether women with IBD would base decisions to have children on the results of genetic testing should a reliable test become available.

Data from an Australian IBD cohort were recently described by Mountifield *et al*[109,110] in two studies. The first postal questionnaire study evaluated the experience and views regarding fertility in 255 women with IBD and

found live birth rates of 1.0 for CD, 1.2 for UC, which are considerably lower than those of the general population of 1.8[109]. This coincided with a fear of infertility in 42.7% of patients, which was particularly apparent in women with CD or previous surgery[109]. Unfortunately, the study did not report whether women fearing infertility were indeed experiencing problems conceiving. Conversely, women sought fertility advice only as often as the general population[109]. The study highlights a difference between the medical evidence and patients' perception of infertility as patients overestimate their risk of infertility largely. The second study examined the experiences and views of 219 women after pregnancy[110]. The patients' main concern related to potential harm towards their pregnancy from IBD medication (84%) rather than the need to control active disease[110]. "Free text" responses suggested that women would rather "put up with the disease than harm my baby with medications". The main concerns regarding side effects of IBD medication related to congenital abnormalities rather than more common adverse outcomes of pregnancy such as pre-mature delivery or low birth weight[110]. Of note, some patients considered steroid "rescue" therapy safer than continuation of IBD maintenance medication[110]. The authors suggested their findings reflected a lack of patients' knowledge in the field of IBD and pregnancy'[110]. The study provides insight into patients' views: many opinions were contrary to current medical evidence, and women may make decisions based on incorrect perceptions.

Two population based Danish studies have examined adherence to IBD medication prior and during pregnancy in 58 women with CD and 63 women with UC. Adherence, measured by retrospective self-reporting, was relatively high in both CD (72%)[111] and UC (60%)[112] as adherence in the non-pregnant IBD population ranges from 55%-70%[113]. It is, however, difficult to interpret the study findings since there was no direct control group of non-pregnant patients included and selection bias (responders *vs* non-responders) and recall bias (the questionnaires were sent years after the pregnancies) may be likely. Furthermore, adherence was assessed using a simple question rather than a validated tool. Reasons for non-adherence were quiescent disease (59%) and a fear of negative effects on the unborn child (50%), while forgetfulness was uncommon (5%)[112]. These studies highlight that unwanted effects of medication play an important part in women's views and influence decision making.

CONCLUSION

IBD affects women of childbearing age and may have an effect on their offspring. Fertility is reduced in active CD and after surgery. The risk of active disease during pregnancy carries a significant risk to baby and mother. The limited data available on patients' beliefs and attitudes suggest that many women hold views contrary to medical evidence. Women with IBD are therefore at risk of making uninformed choices that could in turn lead to adverse outcomes. There is a need for further studies examining women's views in more detail and to investigate whether these beliefs are driven by a lack of knowledge. In the meantime, women with IBD should receive advice and counselling by their physician prior and during pregnancy.

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