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REVIEW ARTICLE

Management of inflammatory bowel disease in pregnancy

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Abstract

Background and Aims: Inflammatory bowel disease (IBD) is a chronic disease affecting mainly young people in their reproductive years. IBD therefore has a major impact on patients' family planning decisions. Management of IBD in pregnancy requires a challenging balance between optimal disease control and drug safety considerations.
This article aims to provide a framework for clinical decision making in IBD based on review of the literature on pregnancy-related topics.
Methods: Medline searches with search terms 'IBD', 'Crohn's disease' or 'ulcerative colitis' in combination with keywords for the topics fertility, pregnancy, congenital abnormalities and drugs names of drugs used for treatment of IBD.
Results: IBD patients have normal fertility, except for women after ileal pouch-anal anastomosis (IPAA) and men under sulfasalazine treatment. Achieving and maintaining disease remission is a key factor for successful pregnancy outcomes in this population, as active disease at conception carries an increased risk of preterm delivery and low birth weight.

Abbreviations 6-MP, 6-mercaptopurine; 6-TGN, 6-thioguaninenucleotides; AZA, azathioprine; BCG, Bacillus Calmette Guerin; IPAA, ileal pouch-anal anastomosis; MTX, methotrexate.

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Clinicians should discuss the need for drug therapy to maintain remission with their patients in order to ensure therapy compliance. Most IBD drugs are compatible with pregnancy, except for methotrexate and thalidomide. If possible, anti-TNF therapy should be stopped by the end of the second trimester and the choice of delivery route should be discussed with the patient.

Conclusions: Disease control prior to conception and throughout pregnancy is the cornerstone of successful pregnancy management in IBD patients.

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Contents

1. Introduction

As a chronic disease affecting mainly young people in their reproductive years, inflammatory bowel disease (IBD) has a major impact on patients' family planning decisions. When active disease is under control, clinicians need to take time to counsel IBD patients on topics such as fertility, pregnancy, and genetic aspects of IBD. Patients wishing to become pregnant need to be informed on pregnancy outcomes and therapeutic options in the preconception period and during pregnancy.

This article aims to summarize the current knowledge about the effect of IBD on fertility, the disease course of IBD during pregnancy, as well as pregnancy outcomes and drug treatment of IBD during pregnancy and lactation, to provide clinicians with a framework to guide their care of IBD patients in these challenging circumstances.

2. Effect of IBD on fertility

In Crohn's disease (CD), fertility is observed to be normal[1–3] or slightly reduced.[4] Subfertility is mainly reported in CD patients with active disease.[5]

In ulcerative colitis (UC) overall fertility rates are normal,[6,7] except after surgical resection with ileal pouch-anal anastomosis (IPAA).[8–11] A meta-analysis estimated the risk of infertility after IPAA to be increased by a factor three.[12] Colectomy with ileorectal anastomosis[13] or subtotal colectomy with an ileostomy and pouch creation after childbearing[14] may be reasonable alternatives for women wishing to become pregnant, as subfertility or infertility after IPAA is mainly attributed to postsurgical adhesions in the pelvic region with subsequent fallopian tube occlusion.[14,15] Laparoscopic IPAA could reduce adhesions and may be a suitable alternative for patients of child-bearing age.[16]

Men with IBD can experience reduced fertility or infertility when treated with sulfasalazine. This drug is known to cause reversible semen abnormalities (oligospermia, reduced motility, abnormal morphology) and infertility in up to 60% of men.[17–20] The mechanism by which sulfasalazine induces male fertility is not well known, but impaired sperm maturation and oxidative stress are thought to play a role.[21,22] Sperm quality is restored two months after sulfasalazine withdrawal. Switching to mesalazine also restores male fertility, indicating that the sulfapyridine component is the culprit in sulfasalazine-induced infertility.[20]

Azathioprine does not impair male fertility,[23] but its teratogenic potential, mainly attributed to its metabolite 6-mercaptopurine (6-MP), remains controversial. Two studies have reported an increased incidence in congenital malformations in children fathered by IBD patients on thiopurines,[24,25] whereas two other studies did not observe a significant effect of preconceptive thiopurine exposure of the father on pregnancy outcomes.[26,27]

Infliximab has been reported to increase semen volume with a trend towards decreased sperm motility. How these findings impact the fertility of men treated with infliximab is not known yet.[28] Potentially infliximab may also serve to counter the negative effects of TNF-α on sperm quality.[29] Data on the impact of other biologicals on male fertility are currently lacking.

Although fecundity in IBD patients is normal, except for women with a history of IPAA and men taking sulfasalazine, studies consistently find lower birth rates and smaller family sizes in IBD patients, as compared to the general population. This 'voluntary childlessness' was observed for both female and male IBD patients,[30] and illustrates the important impact of IBD on family planning. In a survey among 255 Australian IBD patients fear concerning IBD heritability, risk of congenital anomalies and medication teratogenicity were reported as factors contributing to decreased family size. Fear of infertility was reported by 42.7% of patients, although fertility rates and use of medical fertility advice among study participants were comparable to the normal Australian population.[31]

3. Effect of pregnancy on IBD disease activity

3.1. Disease activity during pregnancy

A retrospective study including 70 pregnancies in 61 patients with Crohn's disease observed a small but significant decrease in the Harvey-Bradshaw index of disease activity during pregnancy in comparison with the year preceding and following the pregnancy.[32] In this study, the reduced disease activity in pregnancy was partly due to reduced tobacco smoking during pregnancy. Smoking has a known negative effect on the course of Crohn's disease.[33]

A large European prospective study observed that 74% of CD and 67% of UC patients with active disease at conception achieved remission later during pregnancy.[34]

3.2. Risk of flare: comparable to that in non-pregnant patients

Clinical experience corroborates the early observations of Khosla et al.[1] that patients with active disease at conception, often continue to have symptoms during pregnancy, whereas a normal course of pregnancy can be expected in patients who conceive when in remission. In the literature, CD flare rates during pregnancy of 14–34% are reported, similar to that in non-pregnant patients.[7,34,35] A European cohort study with a 10-year follow-up period observed that if conception occurred during remission, flare rates were comparable to those in non-pregnant patients with IBD, whereas two-thirds of patients relapsed during pregnancy when conception occurred during a period of active disease. Of these, two-thirds will experience further deterioration.[5] In a study including 35 pregnancies in 23 women over a 12 year period, a 26% exacerbation rate during pregnancy was found, which is similar to that in the Crohn patient population at large.[36] A Danish study reported 40.3% of relapses during pregnancy in UC, as compared to 13.6% in the 6 months prior to pregnancy.[37]

Exacerbations of disease, particularly in the first trimester of pregnancy are often due to discontinuation of maintenance therapy.[38]

3.3. Lower risk of IBD relapse and complications after pregnancy

Whether disease flares are more likely to occur in the postpartum period remains controversial, but pregnancy seems to have a beneficial effect on the disease course of IBD. A small prospective study reported a decrease in relapse rate in CD as well as UC patients four years after pregnancy, in comparison with the 3 years before pregnancy.[39] Similar findings were reported in a large European cohort study, where yearly flare rates decreased from 0.34 to 0.18 in UC and from 0.76 to 0.12 in CD. Pregnancy did not influence the incidence of stenosis or resection rates in this cohort.[5]

Earlier studies reported reduced stenosis and resection rates in women with IBD after pregnancy.[40,41] The potential mechanism for reduced complication rate of IBD after pregnancy remains elusive, but the hormone relaxin, the effect of pregnancy on the immune response, as well as foetomaternal HLA disparity have all been mentioned as potential explanations.[41,42]

A retrospective study by Kane et al. observed that 43% of IBD patients who breastfed their infants experienced a postpartum disease flare, but after adjustment for medication cessation, the risk of postpartum flare in breastfeeding IBD mothers was not significant, indicating that discontinuation of therapy while breastfeeding was the main determinant of the high flare rate in this study.[43] A 2009 registry study on the other hand, found comparable postpartum flare rates in breastfeeding (26%, OR 0.58, 95% CI 0.24–1.43) versus not breastfeeding (29.4%) IBD mothers[44]

4. Effect of IBD on pregnancy outcome

Current evidence indicates that quiescent disease has minimal impact on the course and outcome of pregnancy in IBD patients, whereas patients with active disease at conception have increased rates of spontaneous abortion[1,36] and a significantly increased risk of preterm delivery and low birth weight.[35,45,46] Preterm delivery is further associated with disease flares during pregnancy.[36,47]

A recent European prospective study including 332 pregnant women with IBD from 68 centers in 12 countries concluded that overall pregnancy outcomes for women with CD or UC did not differ significantly from those in pregnant patients without IBD.[34]

A meta-analysis covering 12 studies in 3907 women with IBD found an increased odds ratio for premature delivery in IBD patients (OR 1.87, 95% CI 1.52–2.31), comparable in CD and UC. This study also described an elevated risk for low birth weight in CD (OR 2.82, 95% CI 1.42–5.60) but not in UC and a significant increase in congenital abnormalities (OR 2.37, 95% CI 1.47–3.82). The observed increased risk of congenital malformations was mainly observed in UC (OR 3.88, 95% CI 1.14–10.67), whereas the risk in CD was not significantly increased (OR 2.14, 95% CI 0.97–4.74).[48]

A study including newborns from 510 Crohn patients from 6 national registries and 3018 controls observed a significant, albeit modest decrease in birth weight, with babies of primiparous versus multiparous CD patients weighing on average 142 g and 105 g less than those of controls after adjustment for confounding factors.[49] A Swedish population study found 4.5% and 1.2% of children born to IBD patients had low and very low birth weight, as compared to 2.9% and 0.6% in the overall Swedish population. Neonates of Swedish IBD patients were small for gestational age in 4.0% of cases, against 2.9% overall.[50] Moser et al. additionally found an increased incidence of poor maternal weight gain during pregnancy in CD patients with quiescent disease at conception.[35]

Retrospective analysis of 502 pregnancies before and 121 pregnancies after diagnosis of IBD observed an increased risk of low birth weight in IBD of both groups,[51] indicating that IBD has an influence on pregnancy, even in the preclinical phase. Birth weight in babies born to CD patients was significantly lower than that of UC offspring in this study, corroborating the earlier study by Dominitz et al., who reported increased risk for preterm delivery, low birth weight and small for gestational age births in CD but not in UC.[52]

The risk of congenital malformations may be slightly increased in children of IBD patients, mainly for patients with UC,[48] although a number of studies did not observe an increased risk of congenital abnormalities.[5,53] A population-based case control study in Hungary found no overall increased risk of congenital anomalies in offspring of UC patients (OR 1.3 (95% CI 0.9–1.8), but did observe elevated risks for the presence of limb deficiencies (OR 6.2, 95% CI 2.9–13.1), obstructive urinary anomalies (OR 3.3, 95% CI 1.1–9.5) and multiple congenital anomalies (OR 2.6, 95% CI 1.3–5.4) in children of UC mothers. Maternal UC was not associated with cleft palate or cardiovascular defects in this study.[54] A retrospective cohort study in Washington state reported congenital malformations in 7.9% of UC births (OR 3.8, 95% CI 1.5–9.8) versus 3.4% in CD and 1.7% in controls.[52] Another case–control study found congenital abnormalities in 5.5% of births in IBD pregnancies, but no difference between CD and UC.[51] The reported risks of congenital anomalies in UC are quite low and do not justify discouraging women with UC from becoming pregnant. Attentive prenatal monitoring is warranted, however.

Pregnancies in both CD (20.9% of cesarean sections) and UC patients (20.8%) ended more often with cesarean section in comparison with the general population (15%).[55] A more recent Californian cohort study found borderline differences in cesarean section rate between IBD patients and controls (13.5% versus 9.5%, p=0.05),[56] whereas a 2009 population-based study found that pregnancies of patients who needed to be hospitalized had a higher risk of ending in cesarean section for CD (OR 1.72; 95% CI 1.44–2.04) as well as UC patients (OR 1.29; 95% CI, 1.01–1.66), in comparison with patients without IBD.[57]

Active perianal disease at the time of delivery is an indication for cesarean section, whereas cesarean section without history of perianal disease or inactive perianal disease do not require a cesarean section.[55] In UC patients with IPAA cesarean section rates of almost 50% were reported, but the incidence of pouch-related complications was low and pouch function was found to be unrelated to the mode of delivery.[58] However, the most recent ECCO guidelines state that the presence of an ileoanal pouch in CD patients is an indication for caesarean section.[59]

5. Drug treatment of IBD during preconception, pregnancy and lactation

Most of the drugs used in the treatment of IBD are not associated with increased risk of congenital anomalies or adverse effects on the fetus and are thus compatible with pregnancy. Moskovitz et al. studied 207 conceptions in 113 IBD patients and found no evidence of an influence of drug treatment on pregnancy outcome.[60]

The 2010 ECCO guidelines state that 'medical treatment for Crohn's disease (except methotrexate) should generally continue during pregnancy, because the benefits outweigh the risks of medication'.[59] Moreover, as complications and adverse pregnancy outcomes mainly occur in patients with active disease, the main concern should be to achieve remission prior to conception and maintain quiescent disease during pregnancy.

Table 2 provides an overview of IBD drugs and the risk associated with their use during pregnancy and lactation.

Population-based studies in Denmark reported adherence to medical treatment in 72% of CD and 60% of UC patients prior to or during pregnancy. Fear of a negative effect on fertility or the fetus was stated as the main reason for non-compliance.[37,61] UC Patients who received counseling regarding medical treatment during preconception and pregnancy were more likely to remain compliant,[37] illustrating the important role of the clinician in informing IBD patients accurately on the benefits and risk of drug treatment prior to conception and during pregnancy.

5.1. Aminosalicylates

It is generally regarded as safe to keep using aminosalicylates during pregnancy (FDA category B drug), despite some reports noting a higher incidence of neural tube defects, oral cleft, and cardiovascular defects.[62]

A number of studies concluded that sulfasalazine use during pregnancy does not give rise to increased rates of birth defects in women with IBD, when compared with untreated IBD patients or the general population.[60,63] In a recent meta-analysis treatment of IBD patients with 5-ASA

Table 1 US Food and Drug Administration categories for drug safety during pregnancy.[134]

FDA category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	animal reproduction studies have not demonstrated a fetal risk but there are there are no adequate and well-controlled studies in pregnant women Or animal reproduction studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks Or There are no animal reproduction studies and no adequate and well- controlled studies in humans
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit

drugs IBD did not a significantly increase the risk of congenital abnormalities (OR 1.16), stillbirth (OR 2.38), spontaneous abortion (OR 1.14), preterm delivery (OR 1.35) or low birth weight (OR 0.93).[64]

Sulfasalazine therapy should be accompanied by extra folate supplementation, as this medication halts folate synthesis by inhibiting dihydrofolate reductase. Folic acid supplementation was shown to decrease the augmented risk of oral clefts and cardiovascular anomalies associated with folate antagonist treatment during pregnancy.[65] Caution should be applied regarding the use of some mesalamine formalations (e;g. asacol) which contain dibutyl phthalate

Table 2 Drug treatment for IBD and risks during pregnancy.[72]

Drug class	FDA category	ECCO rating	Clinical recommendations
Aminosalicylates	B	Safe	No increased risk Combine sulfasalazine with folate supplements
	C		Dibutyl phthalate-coated mesalamine formulations Increased risk of malformations in the male urogenital tract associated with DBP.
Metronidazole	B	Probably safe	No birth defects 1 population-based case-control study found that infants of women exposed to Metro in 2nd to 3rd months of pregnancy had higher rates of cleft lip with or without cleft palate
Quinolones	C	Probably safe	Musculoskeletal abnormalities in animal studies, human data do not show increased abortion or congenital malformation rates. Should be avoided in the first trimester due to potential increased risk of arthropathy
Anti-TNF	B	Probably safe	No transfer to the embryo/fetus in first trimester. Can be used in the first two trimesters of pregnancy and during lactation.
Natalizumab	C		Safety during pregnancy and lactation still unknown. Limited data available
Corticosteroids	C	Safe	Use during the first trimester associated with increased risk of oral cleft in the newborn Increased risk of adrenal insufficiency
Cyclosporine	C	Probably safe	Does not appear to be a major teratogen
Azathioprine	D	Safe	Can be continued to maintain remission during pregnancy.
Methotrexate	X	Contraindicated	Contraindicated in pregnancy. Discontinue 3–6 months before conception.
Thalidomide & lenalidomide	X	Contraidindicated	Contraindicated in pregnancy.

(DBP) as a coating agent. Use of DBP-coated medications produces measurable phthalate metabolite levels in urine. Prenatal exposure to DBP can cause congenital malformations in the male urogenital tract.[66]

The sulfasalazine metabolite sulfapyridine is secreted into breast milk. Aminosalicylates are generally considered safe during lactation, although a case of bloody diarrhea in an infant has been reported.[67–69]

5.2. Antibiotics

5.2.1. Metronidazole

Metronidazole is considered a low risk drug during pregnancy (FDA class B, Table 2). Several studies did not find an association between metronidazole treatment and birth defects,[70] but one population-based case–control study observed an increased incidence of cleft lip and/or cleft palate in infants of mothers exposed to metronidazole in the first trimester of pregnancy.[71] Metronidazole use in pregnant IBD patients is best limited to short-term use for the treatment of pouchitis. Metronidazole is excreted in breast milk and breastfeeding during metronidazole use is not recommended.[70]

5.2.2. Quinolones

Quinolone antibiotics are FDA category C drugs and should be avoided because they carry an increased risk of arthropathy due to their high affinity for bone and cartilage.

Musculoskeletal abnormalities have been observed after exposure to quinolones during pregnancy in animal studies, but human studies do not show an increased risk of spontaneous abortion or congenital malformations. Although the overall risk is considered limited, ECCO recommends to avoid quinolone use in the first trimester of pregnancy.[72]

Data on breastfeeding are limited, but quinolone use is probably compatible with breastfeeding.[73,74]

5.3. Biologics

5.3.1. Anti-TNF therapies

The recent London position statement on biological therapy for IBD states that anti-tumor necrosis factor (TNF) therapy is considered low risk and can be used in the preconception period and during the first two trimesters of pregnancy.[14] A 2009 survey among French gastroenterologists revealed that only 35.1% discontinued anti-TNF therapy at the time of conception.[75]

The cytokine TNF-α not only plays a pivotal role in the inflammation process underlying IBD, but also plays physiological roles in host defense mechanisms and pregnancy. Expression of TNF-α and its receptors is found in the uterus, placenta and the embryo, but knocking out expression of TNF-a in mice does not affect pup morphology, growth or litter size in mice.[76] During pregnancy, TNF-α probably plays a role in protecting the fetus against teratogenic stress, since exposure to the teratogen cyclophosphamide induced significantly more malformations in fetuses of TNF-α knockout mice than in wildtypes.[77]

Despite the role of TNF in pregnancy, treatment with anti-TNF antibodies can be considered safe in the preconception period and the first part of pregnancy, because IgG antibodies do not cross the placenta in the first pregnancy trimester, and transplacental IgG transport mainly takes place during the late second and third trimester of pregnancy.[78,79] Maternal transfer of IgG during the last trimester of pregnancy provides the neonate with sufficient acquired immunity to defend itself while its own immune system is becoming fully functional. Other types of immunoglobulins do not cross the placenta.

IgG is actively transported across the placenta via an active transport mechanism consisting of pH-dependent binding of immunoglobulins by fetal Fc receptors. Fc receptors on the membrane of syncytiotrophoblast cells capture immunoglobulins from the maternal circulation, bind them in a pH-dependent manner during transcytosis and release them in the fetal circulation.[80–82] Neonatal Fc receptors have different binding affinities for the different IgG subclasses, with the most efficient transplacental transport for IgG1 and least efficient for the IgG2 subclass.[79,83]

The currently available TNF inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab) are all classified as FDA category B drugs, indicating that no teratogenic effects of these drugs were observed in animal reproduction studies, but adequate and controlled human safety data are still lacking. All current TNF inhibitors with exception of certolizumab are of the IgG1 isotype and contain an Fc fragment, implicating they will be transported to the fetus according to the active transport mechanism described earlier. Certolizumab is a pegylated Fab' fragment of an anti-TNF monoclonal antibody without Fc fragment and would theoretically be expected not to cross the placenta, although human data on this topic are still lacking.[84]

Review of the FDA drug surveillance database prompted concern that anti-TNF treatment might be associated with the so-called VACTERL syndrome, characterized by multiple birth defects: Vertebral, Anal atresia, Cardiac abnormalities, Tracheoesophageal fistula, Esophageal atresia, Renal abnormalities and Limb abnormalities.[85] However, none of the reported cases showed 3 of these anomalies, necessary for formal VACTERL diagnosis and several methodological criticisms to this study cast a doubt on the assumption that anti-TNF treatment carries and increased risk for birth defects of the VACTERL type.[86,87]

Several animal studies concerning the development of the immune system after exposition to anti TNF antibodies in utero have been published. Mice exposed to anti TNF antibodies in utero or at birth have growth retardation as well as a marked atrophy of the thymus, spleen and lymph nodes as well as a decreased expansion of B cells.[88,89] On the other hand, injection of golimumab in pregnant macaques does not affect the development and maturation of the immune system of the offspring, although golimumab levels remained detectable in offspring up to 6 months after birth.[89]

Transfer of anti-TNF antibodies to the fetus during the last part of pregnancy may mean exposure of the neonate in the first months after birth, raising potential concerns about infection and response to vaccines.[14] The immunosuppressive effect of maternal treatment with TNF inhibitors during pregnancy on their infants is sadly illustrated by a fatal case of disseminated BCG infection after BCG vaccination in an infant born to a mother treated with infliximab throughout

pregnancy.[90] Infants exposed to immunosuppressive drugs during pregnancy probably should be considered to be immunocompromised, as their mothers are. ECCO guidelines state that live vaccinations (BCG, rotavirus, mumps-measles-rubella (MMR) and varicella zoster) are contra-indicated until exposure to immunosuppressants has been discontinued for at least 3 months.[91] In view of the long half-life of TNF inhibitors in newborns,[89] further studies are required to determine whether this safety period is sufficient. Since spreading of vaccine virus to household contacts has been described after oral poliomyelitis and rotavirus vaccination, these vaccinations are therefore contraindicated in household contacts of immunocompromised individuals. Non-live vaccines can safely be given to immunocompromised individuals and mostly lead to an adequate humoral immune response.[92]

IgA is the predominant immunoglobulin in human milk, so secretion of TNF inhibitors in milk is likely to be very limited and breastfeeding under anti-TNF treatment can be considered safe.[84]

5.3.1.1. Infliximab. Accumulating clinical data indicate that infliximab use is safe in the preconception period and during at least the first two trimesters of pregnancy[14]

The TREAT registry describes 36 pregnancies in patients exposed to infliximab. No fetal malformations were observed, and rates of miscarriage (11.1 vs. 7.1%) and neonatal complications (8.3 vs 7.1%) were comparable between infliximab-treated patients and non-exposed patients.[93] The Infliximab safety database collected data on 96 pregnancies with infliximab exposure between 3 months before conception to the end of the first trimester of pregnancy, with rates of miscarriage and fetal complications comparable to those expected for the general population.[94] A recent observational study by Schnitzler et al. studying pregnancy outcomes of 42 pregnancies exposed to anti-TNF treatment (35 with infliximab treatment, 7 with adalimumab treatment) observed that pregnancy outcomes in exposed pregnancies were not different from those in pregnancies occurring before anti-TNF treatment or with anti-TNF treatment before but not during pregnancy, but worse than outcomes of pregnancies before diagnosis of IBD.[95]

An important indication that the benefit of infliximab treatment to achieve or maintain remission of disease during pregnancy may outweigh the potential risks is a case series of CD patients intentionally treated with infliximab during pregnancy described by Mahadevan et al. in 2005. In a series of 10 CD patients treated with infliximab during pregnancy, 8 patients received infliximab throughout pregnancy, one patient was started on infliximab in the third trimester for a severe flare, and one received infliximab treatment in the first trimester of pregnancy. All 10 pregnancies ended in live births of children without congenital malformations or intrauterine growth retardation. Three births occurred before 37 weeks and one infant had low birth weight.[96]

A number of case reports indicate that placental transfer of infliximab leads to prolonged exposure of the neonate: serum levels in neonates often surpassed these in maternal serum and remained detectable up to 6 months after birth.[97,98] Immaturity of the reticuloendothelial system leading to slow antibody clearance is probably responsible for this effect. Discontinuing infliximab at the end of the second pregnancy trimester or early in the third trimester may help to reduce infliximab exposure in the newborn.[14,99] Kane et al. reported that infliximab levels in newborn infants were undetectable when infliximab treatment had been stopped around gestational week 30.[99]

Infliximab could not be detected in breast milk,[99–101] so infliximab treatment is considered to be compatible with breastfeeding.[99]

5.3.1.2. Adalimumab. Although clinical data are scarce up to now, adalimumab is also considered low risk during preconception and in at least the first two trimesters of pregnancy.[14]

Adalimumab has received an FDA category B label. It is a fully humanized antibody of the IgG1 isotype. The mechanism and rate of transplacental transfer are comparable to those of infliximab. A recent study has shown that infants born to mothers who have received adalimumab up to 56 days before delivery have therapeutic levels of adalimumab in cord blood and in serum up to 7 weeks after birth.[98]

A limited number of case reports in which adalimumab use during pregnancy is followed by the birth of a healthy child have been published to date.[14,102]

High levels of anti-TNF in the newborn who have been exposed in utero, are present at a crucial period for the development of the immune system. An ongoing study in the USA is assessing the development and the risk of infection in children who have received anti TNF and/or thiopurines in utero. Preliminary results of this study have been presented at the Digestive Diseases Week in 2010. These results are reassuring, in that they do not show any obvious adverse signal. Definitive results are awaited. More data are needed to study the immune status of children who have been exposed to anti TNF in utero.

5.3.1.3. Certolizumab pegol. Certolizumab is a pegylated Fab′ fragment of an anti-TNF monoclonal antibody without Fc fragment. Certolizumab would therefore be expected not to be transferred across the placental barrier according to the mechanism described above. Animal studies indeed report much lower placental transfer of pegylated Fab′ antibodies; data in humans are not yet available, but a case of certolizumab administration as rescue therapy in the third pregnancy trimester of an IBD patient had a favorable outcome.[102–104] However, it is possible that the small Fab′ fragment could cross the placenta passively after cleaving off the PEG-tail. The recent London position statement considers certolizumab pegol to be low risk prior to conception and during pregnancy. Certolizumab is compatible with breastfeeding.[79]

5.3.2. Natalizumab

Natalizumab is an α-4 integrin inhibitor approved for treatment of CD in the US, but not in Europe. It is a humanized antibody of the IgG4 isotype, which is actively transported over the placenta in the second and third trimester of pregnancy, but less efficiently than IgG1 antibodies.[70] Experience with natalizumab in the context of IBD is still limited, but this biological is widely used for treating multiple sclerosis. It has received an FDA category C label. A series of 164 pregnancies exposed to natalizumab

during the first trimester of pregnancy revealed no adverse outcomes.[79] Recent case reports likewise described no apparent negative effects of natalizumab use,[14] but a case series of 35 women revealed one child born with hexadactyly.[105,106] Data on the use of natalizumab during lactation are lacking at this time. So at present insufficient data is available to reach a definite conclusion on the safety of natalizumab during pregnancy and lactation.

5.4. Corticosteroids

Corticosteroids are FDA category C drugs. They are believed to be safe throughout pregnancy at doses up to 15 mg per day.[14] Higher doses increase the risk of infection and premature delivery.[107] Systemic treatment with corticosteroids during the first trimester of pregnancy was found to slightly augment the incidence of oral clefts, from 1 per 1000 live births to 1.3–3.3 per 1000 live births (OR 3.35, 95% CI 1.97–5.69). The overall risk of congenital malformations, however, is not significantly increased (OR 1.45, 95% CI 0.80–2.60).[108]

Pregnant women are preferably treated with prednisone or prednisolone, as the bulk of these compounds is inactivated by placental 11β-hydroxy steroid dehydrogenase, the physiological mechanism in place to protect the fetus from elevated maternal cortisol levels during pregnancy. For treatment of the fetus, dexamethasone or betamethasone are the steroids of choice, as they cross the placental barrier more efficiently.[109]

While the safety of inhaled or intranasal budenoside (FDA category B) in pregnancy has been extensively demonstrated,[110] no safety data are available on oral budenoside. No adverse pregnancy outcomes were observed in a limited case series covering 8 patients treated with oral budenoside during pregnancy.[111]

Treatment with corticosteroids is compatible with breastfeeding.[112,113] Less than 0.1% of the maternal dose of prednisolone is secreted into milk, corresponding to less than 10% of the infants endogenous cortisol level.[68]

5.5. Cyclosporine

Cyclosporine crosses the placenta but is rapidly cleared in the neonate and has no known teratogenic effects. FDA categorizes cyclosporine in pregnancy category C for lack of controlled studies in humans (Table 2), but cyclosporine does not appear to be a major teratogen. Extensive experience exists with use of cyclosporine in pregnancy, mainly in transplant patients.[67] A meta-analysis including 15 studies on the use of cyclosporine in pregnancy, showed that cyclosporine use in pregnancy was not associated with major malformations, but tended to decrease birth weight and duration of gestation, although these effects did not reach statistical significance.[73] In the context of IBD, cyclosporine use in refractory UC during pregnancy has been shown to be safe and effective. Its main use in pregnant IBD patients is the prevention of urgent colectomy in fulminant UC.[114,115]

Although a number of cases are reported where no overt adverse effects were observed in breastfed infants of mothers treated with cyclosporine, the use of this drug during lactation is generally not advised, as cyclosporine is secreted in milk at high concentrations, leading to potential nephrotoxicity and immunosuppression in exposed infants.[116]

5.6. Thiopurines

Azathioprine and 6-mercaptopurine are still designated as FDA category D drugs (Table 1), indicating that increased risk for the fetus exists, but the risk must be weighed against the possible benefits of the drug.

The FDA category D rating was originally given because in the 1960s teratogenic effects of azathioprine were observed in mice and rabbits after intraperitoneal administration at high doses, related to its use as cytostatic agent. Although skeletal and visceral malformations in rabbits and mice have also been observed with oral doses equivalent to the human dose, multiple case series and cohort studies in human pregnancy, mostly in transplant recipients and IBD patients, have not revealed increased incidence of congenital anomalies or recurrent patterns of congenital anomalies,[117] which is why currently almost 9 out of 10 experts continue azathioprine throughout pregnancy[118]).

A recent Danish cohort study, showed an increased risk of preterm delivery and low birth weight in women exposed to azathioprine or 6-mercaptopurine during pregnancy, but no significant increase in congenital malformations. Comparing the outcomes of 76 patients exposed to thiopurines during pregnancy to those in a cohort of pregnant women treated with azathioprine or 6-mercaptopurine before but not during pregnancy, showed that adverse birth outcomes in exposed pregnancies mainly depended upon the underlying disease state, rather than the drug exposure.[26,60,119–122] In the CESAME study, a cohort study comparing IBD patients exposed to thiopurine therapy during pregnancy with women receiving other treatments or women without any drug therapy, thiopurine therapy did not significantly increase the incidence of prematurity, low birth weight, or congenital abnormalities.[123]

Preliminary results from the PIANO study suggested a potential influence of thiopurines on postnatal development, as the percentage of developmental milestones reached by infants of mothers treated with thiopurines at 9 months was lower than in infants of untreated mothers or mothers treated with biologics (Mahadevan et al. DCC 2010 – Abstract #764).

Thiopurines undergo a complex metabolization process and the placenta forms a partial barrier to their metabolites, as the active metabolites 6-thioguaninenucleotides (6-TGN) are detectable in fetal red blood cells, whereas 6-methylmercaptopurine (6-MMP) is not.[124] Thiopurine metabolites may cause myelosuppression in mother and child. To avoid excessively high levels, dosing of 6-TGN at least once during pregnancy is recommended.[125] Thiopurine treatment is generally considered a contraindication for breastfeeding, but Christensen et al. demonstrated low 6-MP levels in breast milk and conclude that breastfeeding during treatment with azathioprine seems safe, with exposure of a breastfed infant estimated at <1% of the maternal dose (<0.008 mg 6-MP/kg). Since the majority of thiopurine metabolites are excreted in milk in the first 4 h after intake of the drug, they recommend reducing the infant's exposure to the drug by allowing a 4-hour time interval between thiopurine intake and breastfeeding or else discarding the first portion of the milk.[125]

5.7. Methotrexate

Methotrexate (MTX) has teratogenic properties and is contraindicated during pregnancy (FDA category X – Table 1). Since MTX is widely distributed and its metabolites have long tissue half-lives,[126–128] MTX administration must be stopped 3 to 6 months before conception.[129] Exposure to MTX in the first trimester of pregnancy is associated with the aminopterin syndrome, a combination of growth deficiency with major central nervous system, bone and cardiac abnormalities.[70,107] It is recommended to provide folic acid supplementation after MTX withdrawal, as MTX acts as a folate antagonist. MTX is excreted into breast milk at low concentrations,[130] but is contraindicated during lactation because of its potential accumulation in the child's tissues.

The effect of MTX on spermatogenesis and male fertility remains somewhat controversial, as some studies report reversible oligospermia under MTX treatment. No increase of congenital abnormalities in children conceived by fathers on MTX have been reported. A cautious course of action would be to wait 3 months before conception after withdrawal of MTX.[67]

5.8. Thalidomide and lenalidomide

Thalidomide and its analogue lenalidomide partly counteract the effects of TNF-α and have been used in patients with refractory Crohn's disease, although currently available systematic evidence does not clearly demonstrate the benefit of these drugs.[131] In view of its well-documented teratogenicity, including limb defects, central nervous system defects and congenital abnormalities in the cardiovascular, respiratory, gastrointestinal and genitourinary tract, thalidomide is absolutely contraindicated in pregnancy (FDA category X). Patients taking thalidomide are advised to use two complementary contraceptive methods.[132,133] Although lenalidomide appears less teratogenic in animal studies, exhibiting only teratogenic properties in rabbits at doses with maternal toxicity,[73] its structural analogy with thalidomide and the lack of studies demonstrating its safety, are absolute contraindications for using this drug in pregnant patients or patients wishing to become pregnant.

6. In summary

General recommendations for treating IBD patients before and during pregnancy and after delivery are summarized in Table 3. IBD patients have normal fertility, except for women after IPAA and men under sulfasalazine treatment. It is of the utmost importance to try and achieve disease remission prior to conception, as patients with quiescent disease can expect normal pregnancy outcomes, whereas active disease carries an increased risk of preterm delivery and low birth weight. Babies born to mothers with ulcerative colitis may have a limited increased risk of congenital malformations.

Clinicians should discuss the need for drug therapy to maintain remission with their patients in order to ensure therapy compliance. Most IBD drugs are compatible with pregnancy, except for methotrexate and thalidomide. If possible, anti-TNF therapy should be stopped by the end of the second trimester and the choice of delivery route should be discussed with the patient. Cesarean section is indicated in case of active perianal disease and if obstetrical difficulties are expected in patients with an IPAA pouch. After delivery women who wish to breastfeed their children should be placed on lactation compatible treatments.

Table 3 General recommendations on pregnancy in IBD patients.

Before conception
Achieve disease remission
Discuss necessity of drugs to maintain disease remission
Check and treat nutritional deficiencies (Folate, B12, Iron, Vitamin D)
Folic acid in all in anticipation of a pregnancy
During pregnancy
Monitor patient 8–12 weeks (lab tests when AZA or anti-TNF)
Stop anti-TNF if possible around week 20–22
Discuss way of delivery: C-section in perianal CD or IPAA pouch
Treat flares with IV steroids and anti-TNF
Preferentially use amoxicilline clavulanic acid if complications necessitate the use of antitbiotics
After delivery
Discuss with patient if and when drugs should be restarted
Be careful for flare in weeks following delivery
Discuss breastfeeding
Notify pediatrician of in utero exposure to TNF inhibitors and discuss implications for vaccination of the newborn

6.1. Practical aspects and personal recommendations

6.1.1. Medical treatment recommendations

We always advocate patients to avoid pregnancy when the disease is active or unstable. In case of longstanding stable inactive disease, we try to discontinue any treatment during pregnancy. If not we discuss on a case by case basis the benefit/risk of treatment. We usually advocate patients to continue purine analogues or mesalazine. Patients under anti-TNF therapy will continue until week 20 when the anti-TNF will be stopped for the remaining of the pregnancy.

6.1.2. Treatment of disease flare during pregnancy

When a disease flare occurs during pregnancy, the approach taken depends on the duration of the pregnancy and on the previous therapy of that patient before pregnancy. When the flare occurs in the last weeks of pregnancy, the option of delivery, hence avoiding medication exposure to the baby, is preferred. This option is of course not possible when the flare occurs in the first or second trimester. In the latter scenario, IV steroids or anti-TNF therapy are good options and both are discussed with the patients. Women should be made aware of the placental transfer of anti-TNF from week 20–22 onwards, as this has implications on the vaccination of the baby (BCG and Rotavirus in particular). This should also be communicated to the pediatrician in charge of the baby.

When a serious complication occurs where antibiotics are needed (abcess…), quinolones will be avoided and we prefer using drugs as amoxicilline-clavulanic acid instead.

6.1.3. Obstetric care for the pregnant IBD patient

We do not feel all patients with IBD should be referred to high risk pregnancy clinics. Patients whom we do refer for specialized obstetrics care are pregnant patients with active IBD necessitating steroid and/or anti-TNF treatment, patients with ileostomies and patients with ileoanal pouches. We do not have joint gastroenterology-obstetric clinics, but there are staff members in our department of obstetrics dedicated for high-risk pregnancies. Patients with IPAA surgery in the past will always be advised to undergo caesarian section, and our abdominal surgeon will be present during the delivery.

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SV, FC, PGC, VG, JMWH and EL aggregated the content of the article, outlined the manuscript and provided subject expert opinion; PLM, FDK and EL conceived the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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