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Review Article

Update on pregnancy and breastfeeding in the era of biologics

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ABSTRACT

Inflammatory bowel diseases are chronic conditions that frequently affect patients during their child-bearing years. Considering the characteristics of disease and the medications used to treat it, several issues arise in the care of these patients when they attempt or achieve conception. We review the most current evidence concerning fertility and pregnancy outcomes in patients with inflammatory bowel diseases. With the exception of those women who undergo pelvic surgery, patients with inflammatory bowel diseases have no decreased fertility. Sulfasalazine decreases fertility in men. When looking at obstetrical outcomes, active disease at conception is associated with an increased risk of preterm delivery and low birth weight. While most medications used to treat inflammatory bowel diseases are low risk, some precautions need to be taken and the risk-to-benefit ratio needs to be considered on an individualized basis. In general, aminosalicylates and thiopurines should be continued, but methotrexate is contraindicated. Anti-tumour necrosis factor agents are considered safe to continue but full monoclonal antibodies do cross the placenta. As a general rule, the it is important to counsel women that conception is optimal when disease is in remission, as adverse obstetrical outcomes are directly associated with disease activity. Clinicians need to educate patients before, during and after conception, emphasizing treatment compliance.

1. Introduction

Inflammatory bowel diseases (IBD) are chronic conditions characterized by intestinal inflammation; Crohn's disease (CD) and ulcerative colitis (UC) are the 2 main recognized entities. The pathogenesis is not completely understood, but the most accepted hypothesis is that genetically susceptible individuals develop an aberrant response to luminal bacteria.

Most patients with IBD develop the disease between the second and forth decade, affecting patients during their child-bearing age [1]. Pregnancy is a major management concern in women with IBD and in the older literature it has been associated with poor obstetric outcomes. Several other issues in this area include fertility, fear of disease activity during pregnancy, teratogenicity, and limited knowledge of the long term effects that medications may have on offspring. These concerns previously made physicians discourage pregnancy in women with IBD, and prematurely discontinue medical treatments due to fear of potential side effects. The evolution of better treatments and population based research have resulted in better disease control and lower surgical rates in the general population with IBD [2]. As a result, patients are more willing to consider pregnancy and an uncomplicated gestation is a realistic expectation [3]. A recent study showed that among nulliparous woman with IBD, most are concerned about the effect that the disease can have on the gestation and the potential effects of pregnant to their disease, as well as issues with infertility [4].

The multidisciplinary team caring for the patient, including gastroenterologists, surgeons and obstetricians must work together to educate patients, guiding them through a successful pregnancy. In this article, we review the most current evidence concerning fertility and pregnancy in patients with IBD.

2. IBD and fertility

The obstetrical literature defines infertility as the inability to conceive after 1 year of unprotected intercourse in the fertile phase of the menstrual cycle [5]. Fecundability is the chance of being pregnant in a single menstrual cycle and fecundity is the probability of achieving a live birth within a single reproductive cycle [6].

Fertility is a concern to both men and women with IBD [7]. Most studies show that the rates of infertility in patients with CD are similar to those reported in the general population, although the data are conflicting [8,9]. It appears that disease location (particularly colonic) and a history of surgery for active disease are associated with a lower likelihood of conception [9].

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In women with UC that have not undergone surgical treatment, fertility is not affected. On the contrary, those women who have undergone colectomy with ileal pouch anal anastomosis (IPAA), fecundability is significantly reduced [10,11]. Two meta-analyses have since demonstrated this phenomenon [12,13]. The underlying mechanism for this finding is thought to be due to adhesions created in the pelvis during the creation of the pouch, as women who undergo subtotal colectomy preserve their fertility [14,15].

3. Pregnancy outcomes

When compared to healthy controls, most studies have shown that women with CD or UC are more likely to deliver prematurely and their infants have a higher risk of low birth weight [16]. They are also at a higher risk of having a caesarean section [17]. A recent Japanese study compared pregnancy outcomes before and after onset of the disease. They reported that patients with UC have similar pregnancy outcomes after disease onset when compared to the observed rates prior to disease onset, but those women with CD had higher rates of spontaneous abortion when conception occurred after the development of IBD [18]. However, another population-based including patients with UC in Denmark and Sweden showed no increased risk [19]. In Israel, researchers looked at long-term outcomes in the offspring of patients with IBD when compared to controls. At the time of analysis, the median age of the offspring was 14 years in the IBD group and 12 years in the control group [20]. The investigators found that children born to mothers with IBD had significantly more congenital anomalies as well as neurodevelopmental problems [20].

While it may appear that patients with IBD may have worse obstetrical outcomes, the evidence points to disease activity as the main driver for these findings. When disease activity is taken into account, pregnancy outcomes other than small for gestational age and C-section do not appear to be higher [21].

4. Disease activity in pregnancy

In UC, the consensus is that pregnancy does not directly affect disease course, even though some studies relate discontinuation of medications and smoking as potential factors affecting disease activity [22]. For those women who have undergone an IPAA, most surgeons recommend that vaginal delivery be avoided. However, the literature suggests that there is no increased risk for pouch complications after delivery [23].

In CD, the influence of pregnancy on the natural course of disease has been a point of debate. One French study found that patients with CD did had a higher activity index the year before and after pregnancy, but these results were not significant when controlled for smoking [24]. A British study found that patients with CD who had been pregnant had a lower rate of surgical resection when compared to those were never pregnant [25]. In another European cohort study, the authors found no difference in the development of strictures or the rate of bowel resection. However when compared to the period of time before pregnancy, women in the study group had lower rate of flares after pregnancy [26]. An interesting study that was to look at maternal–foetal HLA discordance as a biologic mechanism for disease activity during pregnancy found that a combined disparity in loci DRB1 and DQ was associated with lower overall disease activity and an improvement of symptoms over time [27]. The mode of delivery in CD is based on the presence or absence of perianal disease. Current recommendations include C-section for those women with active fistulizing disease [28].

Endoscopic evaluation of disease may be warranted during pregnancy. Indications for a procedure do not differ from the non-pregnant state but if possible should be deferred to the second trimester. The obstetrical team should be involved in the risk-benefit assessment and the baby should be closely monitored. The experience with colonoscopy in pregnant patients is limited, even though seems to be viable and low risk if performed in the appropriate clinical setting [29–31]. The two main procedural concerns involve patient position and medication use. The patient should be in the left lateral position but in order to avoid vascular compression a pelvic tilt can be created by placing a pillow under the patient's right hip [32]. If lower endoscopy requires an oral lavage, one time use of polyethylene glycol solutions are considered low risk. When possible, patients should be done without any medications if a flexible sigmoidoscopy is anticipated. If a colonoscopy is required, then propofol with foetal monitoring is recommended [32].

The need for emergent surgery during pregnancy is done for the same indications as in the non-pregnant patient. Surgical maternal and foetal morbidity is high and thus surgery should be delayed if possible to the end of the second or third trimester, and be as limited as possible. One such intervention is a Turnbull blowhold colostomy where colonic decompression is performed as opposed to intra-abdominal surgery [33].

Many women with IBD are afraid to nurse as they are concerned about the effect of medications on breast milk. One study found that women with IBD were less likely to breastfeed, and that disease activity was related to medication cessation [34]. A second Canadian study found that women were not more likely to have disease activity if they nursed [35].

5. Medications

In general and due to several factors, medication adherence in pregnancy is poor [36], although patient counselling can reverse this effect [37]. Despite the fact that one of the most important risk factors for adverse obstetrical outcomes is disease activity, we frequently see patients and/or clinicians discontinue some or all the drugs when a patient is diagnosed as pregnant, mostly because of the potential teratogenic effect. The discontinuation of medications can have detrimental consequences for both mother and foetus, especially on those patients with severe disease [38].

Evaluating the effects of medication exposure during pregnancy is challenging mainly because large number of patients are needed to record rare events, and randomizing patients to test harm is obviously unethical. To complicate the problem even further, the pharmacokinetics of drugs are frequently altered in pregnancy, which can potentially affect the required dose and measurement of serum levels.

5.1. Aminosalicylates

Neither sulfasalazine nor mesalamine have been found to increase the risk for congenital abnormalities [39–41]. In May of 2010, the Food and Drug Administration (FDA) issued a warning for 2 mesalamine preparations (Asacol and Asacol HD), as their enteric coating contains dibutyl phthalate (DBP), which in animals (at very high doses), has been associated with external and skeletal malformations and adverse effects on the male reproductive system [42]. Asacol is now rated a class C drug (Table 1), while other mesalamine preparations are rated as class B. Those patients receiving sulfasalazine require extra folate supplementation as sulfasalazine inhibits dihydrofolate reductase, which decreases body stores. Folic acid supplementation has been shown to reduce the risk of cleft palate and cardiovascular teratogenicity [42]. The amount of aminosalicylate metabolites excreted in breast milk is negligible, and is considered low risk for nursing [43].

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

FDA category	Definition
A	Controlled studies in pregnant women have not shown increased risk of foetal abnormalities if administered during the first trimester of pregnancy. If this drug is used during pregnancy, the possibility of foetal harm appears remote.
B	Animal reproduction studies have failed to demonstrate a risk to the foetus but there are no adequate and well-controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus during the first trimester of pregnancy.
C	Animal reproduction studies have shown an adverse effect on the foetus, and there are no adequate and well-controlled studies in humans or there are no animal reproduction studies and no adequate and well-controlled studies in humans.
D	Evidence of human foetal 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 foetal abnormalities and/or if there is positive evidence of foetal risk based on adverse reaction reports from investigational or marketing experience. The risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

FDA. Federal Register/Vol. 73, No. 104/2008.

In men, sulfasalazine induces oligospermia and abnormal sperm morphology and function, which can lead to impaired fertility. These changes resolve after discontinuation of medication. Switching to a mesalamine formulation is recommended to control disease [44–47].

5.2. Antibiotics

Even though antibiotics as a class are not recommended for the primary treatment of CD or UC, some agents are frequently used in IBD (e.g. quinolones and nitroimidazoles) [48]. They have a role treating septic complications, fistulizing disease and preventing post-operative recurrence of CD (nitroimidazoles) [49,50]. Short term metronidazole has been found to be safe in pregnancy, with no increased teratogenic risk and is a pregnancy category B drug [51–53]. Metronidazole can be detected in breast milk but does not appear to have an immediate effect in the neonate [54]. Nevertheless, the effects of long-term exposure are not clear, and breastfeeding while on this medication is not recommended.

Quinolones are also commonly used in patients with CD. Because they bind to bone and cartilage, quinolones pose a theoretical risk for arthropathies, even though this has not been proven in humans. They are rated as a category C medication [55–58]. Rifaximin is an oral antibiotic with minimal absorption that was recently shown to have some efficacy in the induction of remission in CD [59]. The clinical experience with this drug is limited and even though is considered a “non-systemic” antibiotic, there are no studies in animals or humans that assess safety in pregnancy. Rifaximin is a pregnancy class C drug.

5.3. Corticosteroids

Corticosteroids are frequently used in IBD, although their long term use is limited by the side effect profile. While most studies in humans point towards no increased risk of teratogenicity [60–62], some have found a possible association with cleft lip and palate [63–65]. It is also important to mention that the dose and time of treatment with corticosteroids may play an important role when addressing the risk of side effects. In patients with rheumatoid arthritis, studies have shown that prolonged treatment and/or doses greater than 15 mg of prednisone are associated with intrauterine infection and premature delivery [66]. In a case series that included pregnant patients receiving oral budesonide for CD, none of the 8 patients had complications or adverse foetal outcomes, but larger trials addressing the safety of budesonide are needed [67]. While corticosteroids are rated as pregnancy category C, the benefits and risks of the treatment need to be evaluated in a case-by-case basis. Prednisone, prednisolone and methylprednisolone are the agents of choice as their metabolism by the placenta is higher than other formulations. Studies on patient receiving prednisone or prednisolone have found that the concentration in breast milk is low [68]. Overall, mothers can breastfeed while on these medications.

5.4. Azathioprine/6-mercaptopurine

6-Mercaptopurine (6-MP) and its pro-drug azathioprine (AZA) are frequently used alone or in combination to treat IBD [69]. Its metabolism is complex, and the pro-drug can follow different pathways, which is also variable from patient to patient. In animals that received parenteral AZA, most studies have found an increased risk for several malformations, including cleft palate, skeletal anomalies, decreased thymic size, limbic malformations, ocular and urological anomalies [70,71]. However, the doses used in these studies as well as route of delivery (intraperitoneal, subcutaneous) produce much higher drug concentrations than used in humans.

Most of the data in regards to the thiopurines suggest its safety in pregnancy. The placental concentration of AZA ranges from 64 to 93% of the maternal blood level, even though the concentration in foetal blood only reaches 1–5% of their respective maternal blood levels [70]. A case series looking at the concentration of thiopurine metabolites in the umbilical cord artery found that 6-thioguaninenucleotides (6-TGN) are detectable at 22–91% of the maternal blood levels. 6-Methylmercaptopurine (6-MMP) was undetectable in all three cases. Interestingly, in two of the three cases, the metabolites were also measured in the umbilical cord vein, finding similar levels to the umbilical artery [72]. Most studies in humans have shown no increased rate of spontaneous abortion, congenital malformations, neoplasia or infections [73–79] however others have shown an increased risk of congenital malformations, perinatal mortality and pre-term birth in children born to women exposed to AZA/6-MP during pregnancy [80,81]. Another study found a specific association between AZA use in early pregnancy and cardiac malformations (ventricular/atrial septal defects) [82]. It is likely that those adverse outcomes seen are due to active underlying disease and are not a direct effect of the AZA or its metabolites. Given the weight of evidence for their safety and the known effects of active disease on pregnancy outcomes, the current recommendation is to continue AZA/6-MP while attempting or after conception.

Breastfeeding while on thiopurines is another controversial topic. A study from Denmark with 8 patients found that excretion of 6-MP in breast milk is extremely low (<0.008 mg/kg body-weight/24 h) and is present only within the first 4 h after medication intake [83]. Another study from Austria with 11 patients found that the offspring of patients receiving AZA did not have an increased rate of infections when compared to those who were not [84]. The same study found no difference in general development or hospitalization rate of infants nursed. While thiopurine methyltransferase enzyme activity is higher in newborns when compared to adults [85], the clinical significance of this phenomenon is unknown. The current recommendation is that nursing is low risk

in women taking thiopurines, and to further minimize infant exposure nurse with milk produced only after 4 h of drug ingestion.

Another issue that has been an issue of debate is the use of thiopurines by men wishing to father children. Whereas an early retrospective study done in the United States showed an association between paternal use of 6-MP within 3 months of conception and both congenital abnormalities and spontaneous abortions [86], larger studies done in Spain and another in Germany refuted these initial findings [87,88]. Azathioprine does not appear to affect male fertility [89].

5.5. Methotrexate

The teratogenic effect of methotrexate is well known (even at low doses). Prenatal exposure in the first trimester increases the risk of hydrocephalus, anencephaly, cranial dysostosis, cerebral anomalies, dysmorphic facies, skeletal malformations and limb defects [90]. In later stages of pregnancy, there is an association with growth retardation and functional abnormalities [90]. Methotrexate is a category X drug and should not be used in pregnant women or on those considering conception. There should be "washout" period between drug exposure and conception, most often the recommendation is 3 months. An Israeli study done in patients who received methotrexate for ectopic pregnancy and conceived within 6 months of methotrexate demonstrated no increase in congenital abnormalities. Methotrexate is excreted in breast milk [91] and should not be used while breastfeeding [92].

As with AZA, there is a concern regarding the use of methotrexateon fertility and risk of teratogenicity in men that want to conceive. To date, there is no evidence of unfavourable pregnancy outcomes in pregnancies fathered by men with recent exposure to methotrexate. Some reports have found that it can cause reversible oligospermia, but most of those studies are confounded by the fact that patients had been exposed to several anti-neoplastic drugs [93]. In view of the limited information and the theoretical risk of sperm mutation, it is suggested that a washout period for men be 3 months before attempting conception.

5.6. Cyclosporine and tacrolimus

Both cyclosporine and tacrolimus are calcineurin inhibitors widely used to avoid organ rejection after transplantation and have some role in some clinical scenarios within IBD (123). Cyclosporine crosses the placenta, with foetal circulation levels ranging from 10 to 50% of maternal level [94]. No studies have shown an increased risk of malformations, even though there are some reports of low birth weight [95]. A meta-analysis done with studies in transplanted patients found no statistical significant increase in teratogenicity [96]. In UC, the experience is limited to case reports and one retrospective study [97–100]. Cyclosporine is present in the foetal circulation during gestation at similar concentrations to those in the mother and breastfeeding needs to be avoided [101].

Tacrolimus has been shown to be useful improving fistula discharge in patients with CD [102]. As with cyclosporine, most of the experience is with post-transplant patients; studies have not shown worse obstetrical outcomes [103]. Prenatal growth for gestational age and postnatal infant growth for postpartum age have been found to be similar to the general population [104], but tacrolimus use during pregnancy has been associated with hyperkalaemia in the neonate [105]. Tacrolimus is detectable in breast milk, but at very low concentrations (0.06 μg/kg/d) [106]. Even though several reports have found that breastfeeding is safe, the data is scarce [105,107]. It is also important to mention that the pharmacokinetics of tacrolimus during pregnancy is altered, with an increased unbound tacrolimus concentration [108].

6. Biologics

6.1. Infliximab and adalimumab

Infliximab is a chimeric mouse/human monoclonal IgG1 antibody against tumour necrosis factor alpha (TNF-α) approved by the FDA for the treatment of CD and UC in 1998 and 2005 respectively. Adalimumab is a fully human IgG1 antibody that also antagonizes TNF-α. Both been found efficacious in the treatment of CD and UC and have been classified by the FDA as a pregnancy class B [109–111].

There is an abundance of TNF and its receptors in endometrial, decidual and placental tissue, having a pivotal role in the reproductive system [112]. Also, in animal models, TNF-α has been found to protect embryos exposed to teratogenic stress [113]. Conversely, there is evidence that overexpression of TNF (e.g. a maternal infection) will induce placental damage, foetal loss, growth retardation [114,115].

IgG is transported across the placenta to confer immunity to the foetus. Documentation of serial levels during pregnancy demonstrates that placental transport of IgG increases with gestational age, starting with a negligible transport in the first trimester to the highest transfer during the third trimester [116]. IgG is transported across the human placenta through an active transport mechanism mediated by foetal Fc receptors located in the syncytiotrophoblast [117]. Both infliximab and adalimumab have been found in the newborns in higher levels than in the peripheral blood of their mothers, and they remain detectable for up to 6 months after birth [118,119]. Another case series found that when stopped before 30 weeks of pregnancy, the levels in the newborn (but not in the mother) were undetectable [120]. It is currently recommended that if not detrimental to maternal health, that biologics be held after week 28 or thereabouts to minimize foetal exposure to therapy.

The concern is that exposure to TNF-α will alter the maturation of the infant's native immune system [121], and that the presence of these antibodies will increase the risk of malformations, infections and/or decrease the response to vaccines. The offspring of animal models who received an anti TNF-α throughout pregnancy have not develop abnormalities in the development or maturation of the immune system in the offspring [122,123]

A European observational study compared pregnancy outcomes in several groups: direct exposure to infliximab or adalimumab (within 3 months prior conception and/or during pregnancy until the second trimester), indirect exposure (the mother received an anti TNF-α before pregnancy), those who were naïve to anti TNF-α and before the diagnosis of IBD. They found no difference in outcomes among patients with a diagnosis of IBD irrespective of anti TNF-α exposure [124]. This again supports the fact that the disease itself (and not the treatment) is the main responsible for worse outcomes.

A report from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry showed that when compared to the data from the general U.S. American population, those patients that were exposed to infliximab during pregnancy had similar outcomes [125]. An update from the same registry showed that among maternal and paternal live births, 92.4% had no defects and 90.2% had no adverse events [126].

The Pregnancy in IBD And Neonatal Outcomes (PIANO) registry is a prospective multicenter study aiming to determine whether exposure to AZA/6-MP and/or anti TNF-α during pregnancy worsens obstetrical outcomes [127]. In a preliminary report, the authors described no increased risk for congenital abnormalities by drug exposure, even though the offspring of mothers who were receiving combination therapy with adalimumab or infliximab plus AZA/6-MP had a 35% (95% CI 10–80%)increase in risk of infection at 9–12 months of age when compared to those who were receiving

monotherapy. The secondary outcomes (infant height, weight and developmental milestones) were similar among groups.

While most studies and case reports have shown no association between anti TNF-α and pregnancy complications or foetal malformations, a review of reports for adverse foetal outcomes submitted to the FDA found a high rate of malformations on those pregnant patients exposed to infliximab or etanercept. The authors described that most of these congenital abnormalities were part of the VACTERL syndrome (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limp abnormalities) [128]. The interpretation of those results needs to be done carefully as the study had several limitations including reporting bias. In addition, cardiac defects are very common, and a population based study done 2 years after the initial study did not replicate these findings [129].

The administration of live vaccines in the newborn deserves special attention. Levels of infliximab and adalimumab can be detected in the baby up to 6 months after delivery [119], and the use of live vaccines (Bacillus Calmette-Guérin [BCG], rotavirus, mumps-measles-rubella and varicella zoster) are contraindicated during this period of time. A case report from England described a healthy baby that was exposed to infliximab in utero (not breastfed) and subsequently received the BCG vaccines at age 3 months. The child developed disseminated BCG, ultimately causing death [130].

The available information on whether infliximab or adalimumab can be detected in breast milk has been limited to case reports or case series. While some studies have not found levels (160,161), others using different methodologies have found detectable amounts, albeit very low (162,163). It is unclear as to the clinical significance of antibodies that might be present in milk, as oral ingestion should result in infant gastric acid degradation. The current recommendation is that nursing is low risk with maternal use of either of these agents.

There is no evidence that infliximab or adalimumab affect male fertility, even though a study done in 10 men found that after infliximab infusion, sperm motility and the number of normal oval forms decreased [131]. Other studies have shown an improvement in sperm motility and vitality, which presumably is due to a decrease in disease activity [132].

6.2. Certolizumab pegol

Certolizumab pegol is a humanized monoclonal antibody Fab fragment linked to polyethylene glycol (PEG) with activity against TNF-α [133]. Unlike infliximab or adalimumab, certolizumab pegol does not have a Fc region, which theoretically would impede the transport across the placenta. A recent study examining anti TNF-α drug levels in infants showed that certolizumab levels in infants of mothers receiving the drug was below the level of assay detection [119]. Out of 10 newborns studied, all had certolizumab concentrations of <2 μg/ml.

The clinical experience of certolizumab during pregnancy has been limited to case reports [134], even though in the PIANO registry, the use of certolizumab pegol throughout the pregnancy was not associated with an increased risk of malformations or infections, even when in combination with an immunomodulator [127]. Because of the above findings, the label has been changed to reflect that it does not appear to cross the placenta, as do the other anti-TNF agents. Certolizumab pegol is likely safe to use while breastfeeding.

6.3. Natalizumab

Natalizumab is a humanized monoclonal IgG 4 antibody to alpha-4 integrin and has been found to induce remission and response in patients with CD and high levels of C-reactive protein [135]. Because of its association with an increased risk for the development of progressive multifocal leukoencephalopathy it is reserved for patients with moderate to severe Crohn's disease refractory to other agents. The FDA rated natalizumab pregnancy level C.

In animal models, natalizumab does not increase the risk of spontaneous abortion or teratogenicity [136]. In guinea pigs, its use did not affect the fertility of males but did reduce the pregnancy rate in females treated with a very high dose (30 mg/kg) [137]. Most of the experience in humans has been in patients with multiple sclerosis. A German study found that out of 29 cases, 28 were healthy children and only one presented with a minor malformation (hexadactyly) [138]. There is no experience with lactation, and currently nursing is not recommended.

Table 2
Medications used in inflammatory bowel diseases and their safety during pregnancy.

Drug class	FDA rating	Recommendations for pregnancy
Drugs used in the treatment of IBD and/or its complications		
Aminosalicylates	B	No increased risk for worse obstetrical outcomes Preparations containing DBP are FDA class C (risk of urogenital malformations)
Adalimumab and infliximab	B	Minimal transfer to the embryo/foetus in first trimester but high transfer during the third trimester. Increased risk of neonatal infections when combined with thiopurines
Azathioprine/6-mercaptopurine	D	Category D rating historical from use of higher doses for leukaemia, data for IBD low risk
Certolizumab pegol	B	Minimal transfer to the embryo/foetus throughout the pregnancy
Corticosteroids	C	Possible association with cleft lip and palate. Prednisone, prednisolone and methylprednisolone are the agents of choice
Cyclosporine	C	Crosses the placenta but there is no evidence of increased risk of teratogenicity
Natalizumab	C	Very limited experience in pregnancy but probably safe
Metronidazole	B	No increased teratogenic risk
Methotrexate	X	Absolute contraindication. Should be discontinued at least 3 months before conception
Quinolones	C	Theoretical risk for arthropathies but has not been proven in humans, likely safe
Tacrolimus	C	No increased teratogenicity, but its use during pregnancy has been associated with hyperkaelemia in the neonate
Drugs commonly used in endoscopy		
Benzodiazepines	D	Midazolam can be used, but should be avoided. Other alternatives for sedation should be considered
Fentanyl	C	There are reports of toxicity to the embryo/foetus. Should be avoided
Meperidine	B	No evidence of teratogenicity
Propofol	B	Appears to be safe and is the agent of choice. Should be administration by a trained anaesthesia provider

Abbreviations: DBP: dibutyl phthalate. FDA: food and drug administration. IBD: inflammatory bowel disease. TNF: tumour necrosis factor.

Table 3
Medications used in inflammatory bowel diseases and their safety during lactation.

Drug class	Recommendations for lactation
Aminosalicylates	Excretion of aminosalicylate metabolites is minor, and is considered low risk for breastfeeding
Adalimumab and infliximab	May be detected in breast milk in insignificant amounts, nursing is low risk with maternal use
Azathioprine/6-mercaptopurine	Insignificant amounts if measured 4 h after ingestion
Certolizumab pegol	Likely safe to use while nursing
Corticosteroids	The levels in breast milk are very low
Cyclosporine	Breastfeeding should be avoided as drug detected in milk and can be transferred to newborn
Natalizumab	No data, currently not recommended for nursing
Metronidazole	Can be detected in breast milk and long-term exposure are not clear, nursing not recommended
Methotrexate	Excreted in breast milk and should not be used while breastfeeding
Quinolones	Limited data, likely safe but the long-term exposure is unknown
Tacrolimus	Is detectable in breast milk at very low concentrations, likely safe

7. Conclusions

Fertility and pregnancy in patients with IBD is a clinically important topic. Every woman with IBD with childbearing potential should be asked about her reproductive plans in order to provide appropriate education. The majority of pregnancies in IBD patients have good outcomes; however success can only be achieved after careful preconception preparation, assessment of risk factors, and close management and monitoring of both the disease and the health of the foetus. Women with quiescent IBD should not be discouraged from becoming pregnant, but need to be counselled and closely monitored throughout the pregnancy. Clinicians need to explain to the patients whether and how active disease could affect foetal growth and gestational outcome. The patients must be also informed about the potential effects of the medications with the majority considered of benefit during pregnancy and nursing to control inflammation (Tables 2 and 3). Considering the lack of controlled data for several important questions, treating physicians and patients need to make decisions considering the risks and benefits. The key message to the population of patients with IBD is that they can have children but pregnancy should be planned when the disease is controlled. Women should know that treatment using "safe" drugs must be continued during gestation in order to prevent disease flares that may be harmful to both them and the baby. Given that there is an increased risk for low birth weight and small for gestational age, consultation with a high-risk obstetrician should be strongly considered.

Conflict of interest statement

The author of the manuscript declares that there is no conflict of interest.

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