Digestion

Digestion 2012;86(suppl 1):45–54
DOI: 10.1159/000341941

Published online: October 5, 2012

Pregnancy and Breastfeeding in Inflammatory Bowel Disease

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Key Words
Pregnancy · Breastfeeding · Medical therapy benefits

Abstract
Inflammatory bowel disease (IBD) is frequent in women during their peak reproductive years. Accordingly, a significant number of questions and uncertainties arise from this population regarding the risk of transmission of IBD to the offspring, the impact of the disease and therapies on the fertility, the role of the disease on the course of the pregnancy and the mode of delivery, the impact of the therapy on the pregnancy and fetal development as well as breastfeeding. The safety of medical therapy during pregnancy and lactation is a major concern for both pregnant women and their partners as well as for physicians. As a general rule, it can be stated that the benefit of continuing medical therapy in IBD during pregnancy outweighs the potential risks in the vast majority of instances. This article will review recent developments on this topic consistent with the European Crohn's and Colitis Organization guidelines.

Introduction

Inflammatory bowel disease (IBD) affects a substantial number of patients during their peak reproductive years. With an estimated prevalence of 1 for 1,000 inhabitants in Europe, Crohn's disease (CD) and ulcerative colitis (UC) affect both sexes equally (the female to male ratio in major epidemiological studies varies from 0.51 to 1.58 and 0.34 to 1.65 for UC and CD, respectively [1]). Around half of all IBD patients are diagnosed before the age of 35 years [2], and about a quarter of patients are diagnosed before their first conception [3]. Accordingly, a significant number of questions and uncertainties have arisen for this population, with regard to the risk of transmission of IBD to the offspring, the impact of the disease and the therapies on fertility, the role of the disease on the course of the pregnancy and the mode of delivery, and finally, the impact of therapies on pregnancy, fetal development and breastfeeding.

The safety of medical therapy during pregnancy and lactation is a major concern for both pregnant women and their partners as well as for the physicians involved

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0012–2823/12/0865–0045$38.00/0

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in their treatment, such as obstetricians, general practitioners and gastroenterologists. Ideally, all women of reproductive age should receive pregnancy counseling (i.e. it should not only be offered after conception), in order to ascertain optimal disease control, to adapt a therapy if necessary and to ensure adequate nutritional status and supplementation.

In view of accumulated observational data from the literature on IBD in recent years, the following essential rule can be derived: the benefit of continuing medical therapy in IBD during pregnancy outweighs the potential risks in most instances [4–11].

This article, consistent with the European Crohn's and Colitis Organization (ECCO) guidelines, reviews the literature with regard to recent developments on the subject in order to help provide clear information to patients.

IBD and Heredity

Among the identified risk factors for IBD, such as smoking, ethnicity or appendectomy, cohort studies and family registries have observed that a positive family history is considered the likeliest to predict lifetime risk [7, 12]. The prevalence proportion ratios (division of observed IBD cases with expected cases in this population) are constantly higher amongst the offspring of CD patients [13]; this is also illustrated by the higher concordance rates for CD in twin studies [14]. The risk of transmission was found to be higher from mother to child than father to child in non-Jewish patients with CD; this distortion of transmission on the basis of sex was not observed in UC [15]. Compared to the normal prevalence, an approximately 10-fold increased risk for UC and CD was identified in a Danish study among the first-degree relatives of IBD patients [16]. A consecutive nationwide study identified prevalence proportion ratios of 2.6 for CD and 5.1 for UC in UC patients and 12.8 for CD and 4.0 for UC in CD patients, respectively [13]. When one parent is affected, the overall risk of IBD in the offspring appears to be 2–13 times higher than in the general population [13, 16, 17]. The risks of transmission appears to be higher in CD than in UC, estimated to be 5.2 and 1.6%, respectively, for the occurrence of IBD in the offspring of one affected parent. These risks are even higher in the Jewish population, and increase to 7.8 and 4.5%, for CD and UC, respectively. If both parents of an individual have the disease, the risk of occurrence of an IBD during their lifetime rises to 36% [18].

IBD and Fertility

Infertility is usually defined as the failure to conceive after 1 year of unprotected regular sexual intercourse. In general, IBD patients have fewer children than the general population. An adequate interpretation of the data on IBD patient fertility is hampered by the fact that some patients choose to not conceive, for a variety of reasons, such as concerns about their disease being inherited, a fear of teratogenicity of the medication, the impairment of general activity and their social and sexual life. The impact of medical advice against pregnancy with IBD from the lay literature or treating physicians [19] is also a factor. However, nowadays, there is a general consensus that overall, both male and female fertility is not significantly affected in nonoperated IBD patients when their disease is quiescent [20–23]. Population studies [6, 7] in CD estimate the rate of female infertility at 5–14% in patients in remission, which is similar to rates observed in the general population. On the other hand, an active disease decreases fertility significantly, via an inflammation which extends to the tubo-ovarian system, surgical sequels (adherences in the pelvis), a secondary amenorrhea or sexual dysfunction (frequent in the presence of anoperineal lesions). In UC, a significant drop in fertility rate is observed in women after proctocolectomy with ileal pouch anal anastomosis (IPAA). This impairs fertility significantly; decreases of up to 80% have been described [24, 25]. Other studies confirm these results [26], showing an infertility rate that increased from 13.3 to 38.6% ($p < 0.001$) after IPAA. However, this is ostensibly a mechanical infertility, and in vitro fertilization seems to be a valuable alternative to enable these women to conceive [27]. According to more recent studies, this impairment appears to be less profound. The time to successful conception after IPAA was shown to be significantly prolonged, but the absolute rates of conception were only moderately decreased with 72 and 88% of women having undergone IPAA and a non-IBD control, respectively, which points to a reduced probability of conception rather than to complete infertility [28, 29]. The logical choice of a laparoscopic procedure in order to reduce the risk of adhesions has recently demonstrated its efficacy compared to laparotomy [30]. Medical therapy does not appear to have a negative impact on reproduction [23], with the exception of the drug sulphasalazine. The nontherapeutic sulphapyridine content may induce oligospermia and adverse sperm motility and morphology [31, 32]. This effect is dose-dependent and is fully reversible 6 months after stopping the drug or switching to 5-ASA [33]. Other ami-

nosalicylates do not induce this effect. Methotrexate (MTX) is also a source of oligospermia which is reversible after a discontinuation of the therapy (this has to occur at least 4 months before conception).

The Effect of Pregnancy on the Course of IBD

When conception takes place during a period of quiescent disease, the probability of a flare during pregnancy is similar to the expected risk of a flare in nonpregnant women with CD and UC over a period of 9 months [34, 35]. Indeed, UC studies [36] report an annual exacerbation rate of 34% during pregnancy versus 32% out of pregnancy. The exacerbation rates for CD during a pregnancy or at other times were similar [37]. However, in both UC and CD, when conception occurs while the disease is active, it is estimated that two thirds of patients will have active disease during the pregnancy, and that two thirds of these, in turn, will present a worsening of the flare. [20, 22]. This underlines that achieving and maintaining remission prior to conception is of upmost importance [4, 7, 8, 37, 38].

The overall course of disease during pregnancy seems to be slightly milder in CD, although confounding factors such as smoking cessation may also play a role here [39]. In both CD and UC, a decrease in the rate of flares was observed in a 3-year [40] and in a 10-year [41] follow-up. Although these observations are in line with those for other immune diseases, the mechanisms behind a potential beneficial effect of pregnancy on disease course still remain to be elucidated. One explanation might be immunosuppression induced by a disparity of the human leukocyte antigens (HLA II), DRB1 and DQ between mother and fetus [42].

Effect of IBD on Pregnancy Outcome, Fetal Evolution and Neonatal Prognosis

Multiple population studies suggest that IBD per se, independently from the disease activity level, is linked to an increased rate of pregnancy complications [43–46]. Indeed, the risk of preterm birth [i.e. birth before gestational week (GW) 37], low birth weight (<2,500 g), small-for-gestational-age babies and fetal losses (spontaneous or therapeutic) [35] were observed significantly more often in IBD patients than in the general population, with odds ratios between 1.4 and 2.2 [45]. It appears that the previously reported increased frequency of therapeutic abortions in IBD patients was rather related to psychosocial stress (coping with a double burden – chronic disease and offspring) or a fear of severe side effects from medical therapy [46, 47]. However, according to more recent data from Europe [11] and the USA [48], there is no increase in spontaneous or therapeutic abortion in women with IBD.

There is likely no increased risk of congenital malformations in the IBD population [49]. Resection surgery and disease of the ileum in the past were shown to be risk factors for a pregnancy course with complications [48, 50]. It is crucial to ensure these patients receive close obstetrical and fetal monitoring, especially if conception occurred when the disease was active.

Concerning the risk of maternal complications relative to pregnancy and labor (e.g. placental disruption, eclampsia or placenta previa), the data available do not enable a clear conclusion. The neonatal prognosis of infants born at term does not seem to be affected by the presence of IBD in the mother [48].

Any pregnancy occurring in an IBD patient should be considered as a high-risk pregnancy. It is thus crucial to ensure that these patients receive the close monitoring of a multidisciplinary team consisting of an obstetrician, a gastroenterologist, a visceral surgeon and a proctologist).

Mode of Delivery

Women with IBD more commonly undergo Cesarean section than the average population [51]; however, there is no firm evidence advocating it as the preferred mode of birth for these women. The decision to undergo a Cesarean section should rely on strictly obstetrical indications, with the exception of three conditions which represent contraindications to a vaginal delivery: active perianal CD, active rectal disease and in UC patients who have undergone a colectomy with IPAA [7, 34, 51]. In IPAA, the already challenged maintenance of continence heavily relies on an appropriate sphincter ani function, which is threatened by the mechanical forces involved in vaginal birth. An episiotomy should be avoided whenever possible in CD patients, as cases of secondary anoperineal lesions occur [52]. The presence of a colostomy or ileostomy is not a contraindication for a vaginal delivery. The basis for the decision regarding mode of delivery is the obstetric necessity, with individual patient preferences and interdisciplinary consensus between the visceral surgeon and the gastroenterologist being other components.

Table 1. FDA pregnancy categories

FDA pregnancy category	Controlled studies in pregnant women	Controlled studies in animals	Comment
A	+, no risk	+, no risk	Possible fetal harm is remote
B	– +, no risk	+, no risk +, adverse effect	Chance of fetal harm is still remote, but remains a possibility
C	– –	+, adverse event –	Chance of fetal harm. Use only if potential benefit outweighs risk
D	–, but evidence for risk *or*	–, but evidence for risk	Benefit may sometimes outweigh risk (i.e. when disease is life-threatening and there are no effective alternative drugs available)
X	+, risk demonstrated	+, risk demonstrated	Drug contraindicated (also in nonpregnant women who may become pregnant)

+ = Available; – = unavailable.

Endoscopy and Surgery during Pregnancy

Although concerns with regard to the safety of endoscopy during pregnancy are notoriously raised, this procedure generally appears to be safe and may be performed, presuming that there is a strong indication such as significant bleeding. If possible, colonoscopy should be performed in the second trimester. To avoid vena cava compression, which can impair uterine blood flow and cause fetal hypoxemia, the pregnant patient in the second and third trimester should be positioned in the left lateral or left pelvic-tilt position [34]. Performance or at least planning of the procedure should occur in conjunction with obstetrical support, including documentation of fetal heart beat prior to, during and after the endoscopy. If a minimal dose of sedation is used to ensure adequate comfort of the patient under appropriate monitoring, propofol and meperidine (both class B) appear to be relatively safe. Benzodiazepines (class D) should not be used especially in the first trimester, as these substances have been associated with congenital cleft palate [53].

Surgery may be indicated in UC (for refractory acute severe colitis requiring colectomy) and CD (for perforation, abscesses, severe hemorrhage or obstruction) in pregnant women. When there is an appropriate indication, the risk of the ongoing illness generally outweighs the periprocedural risk for the fetus [4]. In non-life-threatening cases, a carefully balanced approach in intensifying medical treatment to avoid surgery may be appropriate [7]. With endoscopy, there are concerns about spontaneous abortion (first trimester) or induction of preterm labor (third trimester). However, due to the emergent setting, postponement to the second trimester or postpartum are not possible in the majority of instances [54]. A temporary ileostomy is advocated instead of primary anastomosis [54].

Medical Therapy during Pregnancy and Breastfeeding

As a general rule, medical therapy for CD and UC should generally be continued during pregnancy as the benefits of stable remission for the mother and fetus largely outweigh the potential risks in most cases [4–11]. In other words: it is the active disease that poses the greatest risk for the mother and unborn child, not the medical therapy. However, there are no drugs used to treat gastrointestinal diseases with pregnancy category A [Food and Drug Administration (FDA) pregnancy categories are depicted in table 1], implying that the use of any medical treatment option for IBD in pregnancy is at best associated with a remote but possible chance of fetal harm. Hence, the slight potential or theoretical risk that remains must be discussed with the mother and preferably both parents individually.

It is paramount to note that with regard to drug safety in pregnancy, the number of high-quality studies (i.e. controlled trials) is very limited and that most of the human data available originates from large retrospective databases or case series. Concerning animal models, it has to be borne in mind that neither safety nor harm observed in animals necessarily translates to a similar outcome in hu-

mans. A significant number of women do not recognize pregnancy up to weeks 6–8, when organogenesis is already mostly completed; this underlines that the optimal time to discuss medical therapy is certainly prior to conception.

Lactation itself does not seem to independently affect the course of disease in IBD [34]. The necessity of weighing up risks and benefits also applies to breastfeeding, where the availability of human data is even more limited. Uncertainty and the fear of potential adverse effects appear to translate into significantly lower rates of women with IBD opting to breastfeed. In a US study, only 29% of women with CD breastfed their babies compared to an average of 60% amongst unaffected women [55].

An overview of FDA pregnancy categories of the most important IBD drugs and their safety during pregnancy and lactation is provided in tables 1 and 2. Concerning thiopurines and biological therapy, we review a specific development below.

Thiopurines

Six-mercaptopurine (6-MP) and its precursor azathioprine (AZA) are purine analogs which cross the placenta. Animal studies have observed risk of teratogenicity with an increased frequency of cleft lip and palate and skeletal and urogenital abnormalities. However, the low oral bioavailability of these drugs associated with the fact that the immature liver of the fetus lacks the enzyme inosinate pyrophospohorylase necessary to convert AZA to its active metabolite 6-MP, confer a protection to the fetus during the organogenesis period. Besides this, the large and reassuring studies available on transplanted and rheumatologic populations on AZA, allow us to consider these drugs as safe and compatible with pregnancy. In IBD, different population studies [56] and especially the CESAME cohort [57] did not observe any increased risk of congenital abnormalities when exposed to thiopurines during pregnancy. A recent multicenter prospective study on more than 1,000 IBD pregnant patients [58], 324 of whom were on thiopurines, has confirmed this observation and did not show any increased risk of growth or developmental problem in the newborns. Lactation when on thiopurines is theoretically contraindicated, because of the potential risk of myelotoxicity, infection and pancreatitis for the newborn. But given the fact that the major part of 6-MP is excreted in the breast milk if the mother breastfeeds within 4 hours after drug intake, some authors have proposed shifting the breastfeeding to 6 hours after the drug intake. In men, there is no need to stop the therapy before conception, as no effects on spermatogenesis have been observed.

Anti-TNF-α Therapy

Infliximab (IFX) and adalimumab (ADA) are monoclonal immunoglobulin G 1 (IgG1) antibodies, which are actively transported through the placenta via specific fetal receptors. This transport starts from the end of the first trimester but is weak at this time, so that the total IgG remains low until the end of the second trimester. From GW 30, an important transplacental passage takes place. Case studies, including 1 recently [59], have shown the detection of therapeutic levels of IFX in the newborns of mothers whose therapy was interrupted at GW 26. It is interesting to note that in these newborns, the IFX levels exceeded the levels detected in the mother. Important to note is that these antibodies can stay in the newborn's blood for six months after birth, which strictly contraindicates a vaccination with a live or attenuated vaccine (i.e. measles, rubella, mumps, chickenpox, rotavirus or BCG). The recommendations are to wait at least 6 months or to obtain a negative dosage of the antibodies in the newborn blood before such vaccinations are administered. Although normal levels of lymphocytes B and T have been observed in these newborns, the long-term effects of anti-TNFs on their immune system development are unknown. In regards to maternal-fetal complications, the main available registries [47, 58, 60–62] include the recent GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif) study [60] involving IBD women directly exposed to anti-TNFs (of 136 pregnancies, 24 of the women were on a combotherapy with thiopurines) and the latest PIANO (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes) study [58] (preliminary results: of 161 pregnancies directly exposed to anti-TNF, 59 of the women were on a combotherapy with thiopurines). These two studies, the largest to date, do not report an increased risk of adverse pregnancy and fetal outcome linked to anti-TNFs. In the GETAID study, the rate of complicated pregnancies (fetal losses whether spontaneous or therapeutic, prematurity and metabolic or infectious complications) was 30% including miscarriages (9%) and prematurity (20%) among completed pregnancies. This is similar to earlier cohorts of IBD patients who had not used anti-TNFs. Neonatal complications ranged from 3 to 20% in the different studies. Accordingly, if the disease is in remission, stopping IFX or ADA therapy at GW 30 is recommended. Otherwise, the therapy should be pursued until term, and precautionary measures should be applied concerning vaccinations in the newborn.

Table 2. Overview of the most important drugs for the treatment of IBD during pregnancy and breastfeeding

Drug	FDA class in pregnancy	Safety	Comments – use in pregnancy	Comments – use during breastfeeding
5-Aminosalicylates	B (except olsalazine and Asacol: C)	Sulfasalazine and mesalazine (up to a dose of 3 g) are considered safe during pregnancy and breastfeeding. No risk [63] or slightly increased risk [46] of congenital malformations (the latter may be a confounder due to increased disease activity)	If using sulfasalazine, administration of folic acid, about 2 mg/day is mandatory. Enteric coating of Asacol, dibutylphthalate, associated with external and skeletal malformations and adverse effects on male reproductive system in rodents [64], until no human data available switching to an alternative 5-ASA preparation may be considered.	Generally considered safe. Only very low levels of 5-ASA occur in breast milk. As 5-ASA may cause (bloody) diarrhea in infants, stopping of the drug is recommended in case of severe diarrhea.
Corticosteroids (including budesonide)	C	Low risk. Probable slight increase in incidence of oral clefts [65], although not reproduced in a prospective study [66]. Not sufficient data available for budesonide, only small case series finding. No significant pregnancy adverse events [67].	Preferred therapy in conjunction with 5-ASA in case of relapse during pregnancy. If possible do not use during first trimester (potential risk of oral clefts). Short-acting agents (prednisone, prednisolone or methylprednisolone) are more efficiently metabolized by the placenta and should therefore be preferred (dexamethasone and betamethasone are not sufficiently metabolized). Topical steroids (enemas, foams or suppositories) may be used up to the third trimester (thereafter there is the potential of premature delivery).	Only low levels of steroids occur in breast milk (depending of the preparation between 5 and 25%). Hence, an interval of at least 4 h between intake and breastfeeding is recommended. Consider monitoring for adrenal insufficiency in infant if maternal doses are high [68].
Thiopurines (AZA, 6-MP, 6-thioguanine)	D	Despite category D, which is predominantly extrapolation of animal data, AZA and 6-MP are generally considered safe. Fetal abnormalities not consistently increased [69, 70], although a slight increase is suggested by some studies [71, 72]. In some [69, 73], but not all [74] studies, spontaneous abortions, preterm delivery and low birth weight are reported. No safety data for 6-thioguanine, hence it is not recommended.	ECCO and American Gastroenterological Association recommend continuation of AZA during pregnancy (there is a risk of flare with stopping). Most safety data are from the transplantation and rheumatology literature. No inosinate phosphorylase, that converts AZA and MP to 6-thioguanine in the fetus; in addition oral bioavailability of AZA (47%) and 6-MP (16%) is generally low, both may offer some protection.	Concerns of bone marrow suppression and immunosuppression (WHO advocates against breastfeeding). However, only very small amounts of AZA and 6-MP appear in breast milk [75], major part within 4 h after drug intake [76]. No increased risk of severe infections was found in a recent study [77]. Although still controversial and discussion with mother important, breastfeeding is generally supported by ECCO guidelines [4].
Anti-TNF (IFX, ADA, CTZ)	B	Generally considered safe. Most of the literature is from rheumatology. However, 2 recent multicenter studies in IBD [58, 60] showed no increased risk of adverse pregnancy and fetal outcome with anti-TNFs. In addition, a recent large single-center series identified similar pregnancy outcomes in IBD patients on anti-TNF treatment compared to pregnancies before such treatment became available, although pregnancy outcome after diagnosis of IBD was worse than prior to diagnosis [61].	IFX and ADA are IgG1 antibodies, actively transported through the placenta late in the second and third trimester (active transfer of immunity from the mother to the child) and higher levels of IFX and ADA (compared to serum in mothers) are still detectable in the cord-blood several months after birth. Although the implications hereare still are not quite clear, avoidance of anti-TNF treatment in the last trimester is often suggested [4], unless the disease is unstable with an increased risk of flare during conception after drug withdrawal. Active placental transport does not seem to occur with CTZ (an antibody fragment). Life vaccines are contraindicated in the first 6 months after delivery (at least in ADA- and IFX-exposed babies). Case report of fatal disseminated BCG infection after BCG vaccination and IFX exposure [78]. However, administration of inactivated vaccines at normal schedule is recommended and response in anti-TNF-exposed babies was shown to be normal.	IFX is neither detected in breast milk nor in the infant's serum level. Hence, breastfeeding under IFX treatment appears acceptable. In contrast, very low levels of ADA were reported in breast milk, with questionable relevance (achievement of serum levels in infant is unlikely, due to presumptive prompt proteolytic digestion in the stomach).

Table 2 (continued)

Drug	FDA class in pregnancy	Safety	Comments – use in pregnancy	Comments – use during breastfeeding
Cyclosporine	C	Low risk, although most literature comes from transplantation and rheumatology. No significant increase of malformations reported in a meta-analysis [79].	Several case reports during pregnancy in UC. In general, the low risk of the drug has to be weighed against the risk of acute severe disease or colectomy.	Cyclosporine can be detected in breast milk [80]. Breastfeeding should be avoided (potential toxicity and immunosuppression in infant).
Tacrolimus	C	Most data come from the transplant literature, although less data available than with cyclosporine [81].	So far, only 1 case of an uneventful pregnancy in UC reported [82].	Only limited human data available, potential toxicity. In a single case, only a very low level of tacrolimus in breast milk was detected [83].
MTX, thalidomide	X	Teratogen is contraindicated. Effective contraception is essential. MTX should be stopped in both males and females at least 3 months (6 months is better) prior to conception.	In case of accidental pregnancy, therapeutic abortion should be discussed, MTX immediately stopped and a high dose of folic acid prescribed. Abortion is however not mandatory, as normal pregnancy outcome has been reported in some women exposed to MTX.	MTX is contraindicated. No data on excretion of thalidomide in breast milk available.
Antibiotics Met, FQL such as Cip, amoxicillin ± ACL, RIX, Tet such as Dox, SA such as TSM.	B (Met, ACl) C (Cip and other FQL, TSM, RIX), D (Dox)	Met generally considered safe, however risk of cleft palate probably slightly increased if used in the first trimester [84]. Potential risk of damage of cartilage and bone due to high affinity with FQL.	As with all GI medications in pregnancy, shortest possible antibiotic treatment course possible should be used, e.g. short courses of Met or ACL may be beneficial for perianal disease or pouchitis. FQL, and if possible Met, should not be used during first trimester. Avoid Tet and SA during entire course of pregnancy.	Met: limited human data and potential toxicity FQL: limited human data, breastfeeding probably safe ACL: probably safe RIX: probably safe, although so far no human data available Tet, Dox, TSM: safe:
Varia esomeprazole, panoprazole, lansoprazole	B, (C: omeprazole)	Limited data suggesting low risk	Antacids and sucralfate are considered safe	Human data not available (potential toxicity)
MCP, ODS, vitamin B_6	B, (C: domperidone)	Considered safe		MCP: limited human data, potential toxicity, ODS: limited human data, probably safe, Vitamin B_6: insufficient data, probably safe in dose not exceeding RDA
Lop, Cho	B (Lop), C (Cho)	Lop can probably be considered safe Coagulopathy due to decreased fat absorbed vitamins in infant may occur (Cho)		Lop: limited data, probably safe Cho: compatible

Met = Metronidazole; FQL = fluoroquinolones; Cip = ciprofloxacin; ACL = clavulanic acid; RIX = rifaximin; Tet = tetracyclines; Dox = doxycyclines; SA = sulfonamides; TSM = trimethoprim-sulfamethoxazole; MCP = Metoclopramide; ODS = ondansetron; Lop = Loperamide; Cho = cholestyramine.

Certolizumab

Certolizumab (CTZ) is a PEGylated Fab fragment of a monoclonal humanized antibody and not an entire IgG1 antibody. It can therefore not actively cross the placenta and can thus be continued during the entire pregnancy. However, given its recent use, experience with CTZ during pregnancy is limited. Nevertheless, no adverse pregnancy outcome has been reported.

Regarding breastfeeding, it is still unclear whether anti-TNFs are excreted in the breast milk or absorbed by it. Nevertheless, available studies do not report any toxicity associated with lactation, which makes anti-TNFs compatible with lactation.

Conclusion

The major therapeutic advances observed in the field of IBD allow a large majority of patients to conceive and carry a pregnancy under safe conditions. The precondition to this is patient awareness and helping them to wait for and attain a remission before considering pregnancy, and to deploy all means to keep them in remission during the gestational period. Intensive treatment of these patients, if deemed necessary, is legitimate, as the expected benefits for the mother and fetus clearly outweigh the eventual risks associated with the therapies. We maintain that the majority of therapies are safe during pregnancy. The question of the long-term impact of immunomodulators and anti-TNFs on the newborn immunity of newborns is still not clear.

Acknowledgements

Grant support: This research was supported by grants from the Swiss National Science Foundation to S.R.V. (Grant No. 320000–114009/3 and 32473B_135694/1), by the Zurich Center for Integrative Human Physiology of the University of Zurich, and the Swiss IBD Cohort (Grant No. 3347CO-108792).

Disclosure Statement

The authors declare no conflicts of interest.

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