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Pregnancy and breastfeeding in inflammatory bowel disease

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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.

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Pregnancy and breastfeeding in IBD

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INTRODUCTION

Inflammatory bowel disease (IBD) affects a substantial fraction of patients during their peak reproductive years. With an estimated prevalence of 1 for 1000 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 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 pregnancy course and the mode of delivery, the impact of the therapy on pregnancy and fetal development and breastfeeding.

Safety of medical therapy during pregnancy and lactation is a major concern for both pregnant women and their partners as well as physicians involved in their treatment, such as obstetricians, general practitioners and gastroenterologists. Ideally, counseling with regard to pregnancy should not take place after conception but rather in any woman in the reproductive age, in order to ascertain optimal disease control, to adapt the therapy if necessary and to ensure adequate nutritional status and supplementation.

These questions are essential and gastroenterologists are more and more faced with them, especially since the incidence of IBD tends to increase in the recent decades and since major therapeutic advances made with more and more effective therapies enable to encourage an increasing number of patients not to retain a desire for pregnancy. In view of accumulating observational data from the literature on IBD from recent years the following essential rule can be derived: The benefit of continuing medical therapy in IBD during pregnancy outweighs the potential risks in the vast majority of instances [4–11].

This article, which is consistent with the European Crohn's and Colitis Organization (ECCO) guidelines, will review recent developments of the literature on the subject in order to help us to provide clear information to our patients.

MAIN TEXT

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 strongest to predict lifetime risk [7, 12]. The prevalence proportion ratios (PPR; division of observed IBD cases with expected cases in that population) are constantly higher in the offspring of CD patients [13], also illustrated by the higher concordance rates for CD in twin studies [14]. The risk of transmission also appears to be higher from the mother to child compared to father to child in non-Jewish patients with CD, whereas this distortion of transmission on the basis of sex was not observed in UC [15]. Compared to the normal prevalence an around 10-fold increased risk for UC and CD was identified in a Danish study among first-degree relatives of IBD patients [16]. A consecutive nationwide study identified PPRs 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, they have been estimated to 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% respectively for CD and UC. If both parents have the disease, the risk of occurrence of an IBD during lifetime would rise to 36% [18].

IBD and Fertility

Infertility is usually defined as the failure to conceive after one year of unprotected regular sexual intercourse. In general, IBD patients have fewer children than the general population. An adequate interpretation of the data on fertility of patients with IBD is hampered by the fact that several patients may not conceive by choice, because of a variety of reasons, such as concerns about inheritance of their disease, fear of teratogenicity of the medication, impairment of general activity as well as social and sexual life including even medical advice against pregnancy with IBD from the lay literature or treating physicians [19]. However, there is nowadays a general consensus, that overall fertility in both male and female is not significantly affected in non-operated IBD patients when their disease is quiescent [20–23]. Population studies (6,7) in CD estimate the feminine rate of 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 significantly the fertility through inflammation which can reach the tubo-ovarian system, eventual surgical sequels (adherences in the pelvis), a secondary amenorrhea or also sexual dysfunctions, which are frequent in the presence of ano-perineal lesions. In UC, a significant drop in fertility rate is observed in women after proctocolectomy with ileal pouch anal anastomosis (IPAA), fertility is significantly impaired with a described decrease in fertility of up to 80% [24, 25]. These results are confirmed by other studies [26] showing an infertility rate increasing from 13.3% to 38.6% ($p < 0.001$) after IPAA. However, this is mainly a mechanical infertility, and in vitro fertilization (IVF) 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. Time to successful conception yet was shown to be significantly prolonged after IPAA but the absolute rates of conception are only moderately decreased with 72% and 88% of women having undergone IPAA and a non-IBD control, respectively, pointing to rather a reduced probability of conception than complete infertility [28, 29]. The logical choice of a laparoscopic procedure in order to reduce adhesions risks 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 sulphasalazine. The non-therapeutic sulphapyridine content may induce oligospermia and adverse sperm motility and morphology [31, 32]. This effect is dose-dependent and fully reversible 6 months after stopping the drug or switching to 5-aminosalicylic acid (5-ASA) [33]. Other aminosalicylates are not concerned by this effect. Methotrexate (MTX) is also a source of oligospermia which is reversible after discontinuation of the therapy (this has to occur at least 4 months before conception).

Effect of Pregnancy on course of IBD

When conception took place during a period of quiescent disease, the probability of a flare during pregnancy is similar to the expected risk of a flare in a non-pregnant woman with CD and UC through nine months [34, 35]. Indeed, UC studies [36] report an annual exacerbation rate of 34% during pregnancy vs 32% out of pregnancy. In CD also the exacerbation rates during and out of pregnancy were similar [37]. However, in both UC and CD, when conception occurs while the disease is active, it is estimated that two third of patients will keep an active disease during pregnancy and among them two third will present a worsening of the flare. [20, 22]. This underlines, that achieving and maintaining remission prior to conception is of utmost importance [4, 7, 7, 8, 37, 38].

Overall the course of disease during pregnancy seems to be slightly milder in CD, although confounding factors, such as smoking cessation may have played a role [39]. However, in both CD and UC a decrease in the rate of flares has been observed in a 3-year [40] and 10-year [41] follow up. Although these observations are in line with those in 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 HLA II (DRB1 and DQ) antigens between mother and foetus [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 pregnancy complication rate [43–46]. Indeed, the risk of preterm birth (birth before gestational week (GW) 37), low birth weight (weight < 2500g), small for gestational age and fetal losses (spontaneous or therapeutic) [35] were significantly more often observed in IBD patients compared to the general population, with odds ratios between 1.4 and 2.2 [45].

There is likely no increased risk of congenital malformations in the IBD population [47]. A past resection surgery and disease of the ileum were shown to be risk factors for complicated pregnancy course [48, 49]. It is crucial to ensure to these patients a close obstetrical and fetal monitoring, especially if conception has occurred when disease was active.

Concerning the risk of maternal complications relative to pregnancy and labour (placental disruption, eclampsia, placenta previa), data do not enable a clear conclusion. The neonatal prognosis of infants born at term does not seem to be affected by the presence of an 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 a close monitoring to these patients through a multidisciplinary team (obstetrician, gastroenterologist, visceral surgeon and proctologist).

Mode of delivery

Women with IBD more commonly undergo C-section than the average population [50]. However, there is no firm evidence to advocate C-section as the preferred mode of birth in women with IBD. The decision to

undergo a C-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 UC patients having undergone colectomy with ileal pouch anal anastomosis (IPAA) [7, 34, 50]. In IPAA the already challenged maintenance of continence heavily relies on an appropriate sphincter ani function, which is threatened by mechanical forces involved in vaginal birth. An episiotomy should be avoided whenever possible in CD patients, since cases of secondary ano-perineal lesions have occurred [51]. The presence of a colostomy or ileostomy is no contraindication to a vaginal delivery. The primary basis on the decision of mode of delivery is obstetric necessity, while individual patients' preferences and interdisciplinary consensus involving visceral surgeon and gastroenterologist constitute further elements.

Endoscopy and Surgery during pregnancy

Although concerns with regard to safety of endoscopy during pregnancy are notoriously raised, it generally appears to be safe and may be performed, presuming that there is a strong indication, such as significant bleeding. If anyhow possible, colonoscopy should be performed in the second trimester. To avoid vena cava compression, which may 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 sounds prior to, during and after endoscopy. If the minimal dose of sedation is used to ensure an adequate comfort of the patient under appropriate monitoring, Propofol (class B) and Meperidine (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 [52].

Surgery may be indicated in UC (refractory acute severe colitis, requiring colectomy) and CD (perforation, abscesses, severe hemorrhage, obstruction) in pregnant women. In case of an appropriate indication, risk of the ongoing illness generally outweighs the peri-procedural 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]. As it is the case 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 will not be possible in the majority of instances [53]. The application of a temporary ileostomy is advocated instead of primary anastomosis [53].

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 for the mother and fetus of stable remission largely outweigh the potential risks in the vast majority of cases [4–11]. In other words: it is active disease that poses the greatest risk for the mother and unborn child, not medical therapy. However, there are no drugs used to treat gastrointestinal diseases with pregnancy category A (FDA pregnancy categories are depicted in Table 1), implying that the use of all medical treatment options for IBD in pregnancy is at best associated with a remote but possible chance of fetal harm. Hence, the slight potential or theoretical risk remaining has to be discussed with the mother or expecting parents, respectively, on an individual basis.

It is paramount to note, that with regard to drug safety in pregnancy the amount of high quality studies (i.e. controlled trials) is very limited and most of the human data available originates from large retrospective databases or case series. Concerning animal models it has to be bared in mind, that neither safety nor harm observed in animals necessarily translates to a similar outcome in humans. A significant number of women do not recognize pregnancy up to week 6-8, when organogenesis is already mostly completed, what underlines that the optimal time of discussing medical therapy certainly is prior to conception.

Lactation itself does not seem to independently affect course of disease in IBD [34]. The necessity of weighting risk and benefits also applies to breastfeeding, where limitedness of available human data is even more of an issue. This uncertainty and fear from potential adverse effects appears to translate into significantly lower rates of breastfeeding women with IBD, with only 29% of women with CD compared to an average of 60% in unaffected women in a US study [54].

An overview of FDA pregnancy categories of the most important IBD drugs and their safety during pregnancy and lactation is provided in *Table 1 and 2*. Concerning thiopurines and biological therapy, a specific development will be reviewed below.

Thiopurines

Six-mercaptopurine (6-MP) and its precursor azathioprine (AZA) are purine analogues which cross the placenta. Animal studies have observed risk of teratogenicity with an increased frequency of cleft lip and palate, of skeletal and urogenital abnormalities. However the low oral bioavailability of these drugs associated to the fact that the immature liver of the fetus lacks the enzyme inosinate pyrophosphorylase necessary to convert AZA to its active metabolite 6-MP, confer a protection to the fetus during the organogenesis period. Besides that, 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 [55] and especially the CESAME cohort [56] have not observed any increased risk of congenital abnormalities when exposed to thiopurines during pregnancy. A recent multicenter prospective study on more than 1000 IBD pregnant patients [57], of whom 324 were on thiopurines has confirmed this observation and did not show any increased risk of growth or developmental problem in the newborns. Lactation on thiopurines is theoretically contraindicated, because of the potential risk of myelotoxicity, infections and pancreatitis in the newborn. But given the fact that the major part of 6-MP is excreted in the breast milk within four hours after drug intake; some authors have proposed to shift the breastfeeding of six hours from the drug intake. In men, there is no need to stop the therapy before the conception since there has been no observed effect on spermatogenesis.

Anti-TNF- α therapy

Infliximab (IFX) and **Adalimumab (ADA)** are monoclonal anti-IgG1 antibodies, which are actively transported through the placenta via specific fetal receptors (FcRns). This transport starts from the end of the first trimester but is weak at that time, so that total IgG remain low until the end of the second trimester. From GW 30, an important trans-placental passage takes place. Case studies including one recent [58] have shown the detection of therapeutic levels of IFX in newborns of mothers in whom the 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. It is important to note that these antibodies can stay in the newborn's blood during six months after birth, which strictly contraindicates a vaccination with live or attenuated vaccines (ie. measles, rubella, mumps, chicken pox, rotavirus, BCG). The recommendations are to wait at least six months or obtain a negative dosage of the antibodies in the newborn blood before such vaccinations. Although normal levels of lymphocytes B and T have been observed in these newborns, long-term effects of anti-TNFs on their immunity system development are unknown. In regards to maternal-fetal complications, the main available registries [57, 59–62] include especially the recent GETAID study [59] involving IBD women directly exposed to anti-TNFs (136 pregnancies

directly exposed to anti-TNFs, of whom 24 had a combo-therapy with thiopurines) and the latest PIANO study [57](preliminary results: 161 pregnancies directly exposed to anti-TNF, of whom 59 had a combo-therapy 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, metabolic or infectious complications) is of 30% including essentially miscarriages (9%) and prematurity (20%) among completed pregnancies, which is similar to historical IBD cohorts of patients without anti-TNFs. Neonatal complications ranges from 3 to 20% in the different studies. Accordingly, it is recommended to stop IFX or ADA therapy at GW 30 if and only if the disease is in remission. Otherwise the therapy should be pursued until term, and precautionary measures should be applied concerning the vaccination in the newborn.

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 be thus pursued during the entire pregnancy. However, given its recent use the experience with CTZ is limited during pregnancy. 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, making 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 in safe conditions. The pre-condition to this is to make patients aware of and helping them to wait for and reach a remission before considering pregnancy and to deploy all means to keep them in remission during the gestational period. It is thus licit to treat these patients intensively if necessary, since the expected benefits for the mother and fetus clearly outweigh the eventual risks associated to the therapies. As developed above, the majority of therapies are safe during pregnancy; however the question of the long-term impact of immune-modulators and anti-TNFs on the newborn immunity remains still unclear.

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