Proper Use of Inflammatory Bowel Disease Drugs during Pregnancy

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Key Words

Counseling · Fertility · Inflammatory bowel disease · Pregnancy · Treatment

Abstract

Crohn's disease and ulcerative colitis, referred to as inflammatory bowel disease (IBD), are chronic, relapsing conditions. Patients are often diagnosed at a reproductive age, and therefore questions about fertility and reproductions often arise. Preconceptional counseling is the most important aspect in the management of IBD patients with a pregnancy wish. Patients should be counseled on the influence of IBD and IBD drugs on pregnancy. Most drugs are not related to adverse outcome while used during pregnancy. Active disease is related to adverse outcomes; therefore, it is of utmost importance to strive for remission before conception and during pregnancy.

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC), referred to as inflammatory bowel disease (IBD), are chronic, relapsing conditions. IBD typically arises at a reproductive age and because the maternal age during first preg-

nancy is increasing, an increasing number of IBD women will become pregnant after diagnosis. Although there are still misbeliefs with regard to pregnancy and IBD, it has been generally accepted that IBD or its treatment is no reason to advice against pregnancy. The most important risk factor for adverse pregnancy outcomes is the presence of disease activity. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery, thromboembolic events, emergency caesarean section and low birth weight, whereas the majority of pregnancies in women with quiescent IBD are uncomplicated. This indicates the necessity to maintain remission with the continuation of medication. Therefore, knowledge on the effects of IBD and IBD drugs on the child *in utero* is of utmost importance for IBD patients with a pregnancy wish.

Counseling IBD Patients with a Child Wish

Patients should be counseled on the influence of IBD and IBD drugs on pregnancy. Life style advice such as the necessity to stop smoking and the use of folic acid before conception should also be discussed. In general, it is advised to strive for disease remission at least 6 months before conception, since disease activity negatively influences fertility and pregnancy outcome.

IBD patients have fewer children compared to the general population [1, 2]. Incorrect beliefs and poor knowledge on IBD and pregnancy probably contribute to the high rate of voluntary childlessness within the IBD population, resulting in a lower average number of offspring [3, 4]. Recent studies show that fertility is not influenced by the presence of UC or CD [5, 6]. However, active disease is related to subfertility in both male and female patients [7]. Possible reasons are inflammation of the colon involving the fallopian tubes and ovaries, poor nutrition, depression, decreased libido and dyspareunia caused by perianal disease [8]. Female UC patients who underwent a colectomy with an ileal pouch anal anastomosis (IPAA) have a 3-fold increased risk of subfertility than female UC patients who did not [9–11]. The reason for subfertility after IPAA surgery is most likely destruction of fimbria, the higher rate of hydrosalpinx and tubal obstruction following pelvic surgery [12]. Recently, 2 small retrospective studies showed that infertility rates after laparoscopic IPAA surgery are lower than after open IPAA surgery [13, 14]. This might be explained by a reduced adhesion formation after laparoscopic surgery. Males with UC who had IPAA surgery may experience erectile dysfunction and retrograde ejaculation. However, studies show either no change or an improvement in sexual function after surgery in male patients [15, 16].

IBD Drugs and Fertility in Male IBD Patients

Sulfasalazine causes a reversible, dose-related, decrease in sperm count and motility in male patients [17, 18]. As a result, male patients using sulfasalazine are less fertile. Sulfasalazine should be switched to a different 5-ASA drug in case of a reproduction wish.

Corticosteroids can cause a reversible decrease in sperm motility and concentration [19]. However, there seems to be no link between steroid use and infertility [20, 21]. Methotrexate (MTX) causes oligospermia, which improves within a few months after stopping [22]. Moreover, MTX is teratogenic and contraindicated in both men and women wishing to conceive. It is advised to stop MTX 3–6 months before conception. Azathioprine (AZA) does not reduce semen quality and therefore fertility in male IBD patients [23]. A large prospective study including 115 pregnancies fathered by men using thiopurines (AZA/6-mercaptopurine (6-MP)) during conception showed no increased rate in major congenital anomalies [24]. Also, a meta-analysis published in 2013 showed no association between congenital abnormalities and the use

of thiopurines by the father at the time of conception [25]. Therefore, it is not recommended that male IBD patients stop thiopurine treatment before conception. The effect of anti-TNF on male fertility has not been extensively examined. Infliximab (IFX) seems to affect semen quality by reducing motility [66], but data are conflicting as men with spondyloarthropathies tended to have better sperm qualities when receiving anti-TNF therapy [26]. Few studies investigated the effects of male IFX use during conception upon the fetus, but these studies found no evidence of an increased risk of adverse birth outcome [27, 28]. Therefore, male IBD patients should not be advised to stop IFX treatment before conception. There have been no studies on the effect of adalimumab on male fertility.

5-ASA during Conception and Pregnancy in Women

5-ASA drugs are considered low-risk drugs during pregnancy. However, formulations containing dibutyl phthalate coating are re-categorized from FDA category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women) to C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks) because animal studies have shown an increased risk of congenital defects in the male urogenital tract [30]. Furthermore, high-dose dibutyl phthalate exposure is possibly associated with precocious puberty [31–33]. Therefore, formulations containing dibutyl phthalate coating should be avoided if possible. Sulfasalazine interferes with the folate metabolism; therefore, 2 mg/day of folic acid supplementation is recommended in women contemplating pregnancy.

IBD Medication: Thiopurines during Conception and Pregnancy in Women

During pregnancy, the active metabolite 6-thioguanine crosses the placenta but the prodrugs AZA and 6-MP do not [34]. Recent studies showed no increased risk of adverse pregnancy outcome in the case of thiopurine use during pregnancy [35–37]. This is in contrast with earlier published studies that described adverse pregnancy outcomes in cases of thiopurine use [38, 39]. However, these earlier studies failed to take in to account the disease activ-

ity during pregnancy, as it is well known that disease activity during pregnancy increases the risk of preterm delivery and low birth weight. It is therefore recommended that thiopurine should be continued during pregnancy as the risk of active disease outweighs the risks associated with thiopurine use. With respect to growth and development in children exposed to thiopurines *in utero*, a normal growth and development was reported in children followed up to 6 years of age [40]. Furthermore, the ongoing prospective PIANO registry did not observe an increased risk of congenital anomalies or pregnancy complications among 337 children who were exposed to a thiopurine during pregnancy [41]. In case of longstanding remission using combination therapy with an anti-TNF agent, it may be considered to stop the thiopurine before conception. However, patient's medication history and disease severity should be taken into account. Additionally, thiopurines are not recommended to be started during pregnancy because of the relatively late disease response and risks of bone marrow suppression and pancreatitis.

Methotrexate

MTX and thalidomide are teratogenic [42, 43] and (barrier) contraceptive methods are strongly recommended during therapy. Patients treated with MTX who express a pregnancy wish should discontinue MTX 6 months prior to contraceptive cessation. Alternative maintenance therapy with a low-risk profile during pregnancy should be started. Patients should be carefully monitored for any recurrence of disease activity with the new medication regimen. If however unplanned conception occurs during MTX treatment, it needs to be stopped immediately and high-dose folate replacement should be started. In addition, patients should be referred to a specialized obstetrician to discuss the effects of MTX on the child.

Anti-TNF Agents

IFX and ADA are both IgG1 antibodies capable of crossing the placenta in the second and third trimester of pregnancy [44]. Drug levels in infants exceed maternal anti-TNF levels and are dependent on the timing of anti-TNF cessation during pregnancy [45]. A systematic review showed that anti-TNF therapy does not increase the risk of unfavorable pregnancy outcomes among women with IBD [46]. The long-term effects of *in utero* exposure to anti-TNF are not extensively explored. A recent study shows a normal health outcome and first year development in children exposed to anti-TNF, comparable to children of non-IBD controls [47]. Also preliminary re-

sults of 2 ongoing studies showed normal growth and development in anti-TNF exposed children in the first few years of life [48, 49]. It should however be mentioned that combination therapy with immunomodulators did increase the risk of infections in offspring in the ongoing PIANO registry. In addition, continuing anti-TNF during pregnancy may have consequences for the vaccination program of the child because live vaccines should be deferred until anti-TNF levels are undetectable in the child. Fetal exposure to high levels of anti-TNF treatment may be avoided by stopping anti-TNF treatment at the end of the second trimester if patients are in sustained remission. A prospective study, comprising 83 pregnancies exposed to anti-TNF, showed that early discontinuation before gestational week 25 did not increase the risk of a flare and resulted in significantly lower levels of anti-TNF in cord blood [50]. Certolizumab pegol (CZP) is a PEGylated Fab' fragment of a humanized anti-TNF α monoclonal antibody. This Fab' fragment crosses the placenta by passive diffusion and not by active transfer like IFX and ADA. Therefore, the drug levels reaching the fetus are probably lower. A recent study analyzed the pregnancy outcomes of *in utero* CZP exposure, suggesting a lack of harmful effect of maternal CZP exposure [51].

Golimumab is a fully humanized monoclonal antibody, very similar to ADA. There is limited data on pregnancy outcomes when used during pregnancy, although the safety profile is probably similar to the other anti-TNF drugs.

Data on anti-TNF initiation during pregnancy remain scarce, although several successful cases have been reported [52, 53]. In specific cases, it could be considered to start an anti-TNF agent in the case of steroid-refractory disease during pregnancy, as it is known that active disease cause maternal and fetal risks.

Vedolizumab

Data on the outcome of children exposed *in utero* to vedolizumab are still limited. As vedolizumab is also an IgG1 antibody, this drug is likely to be transferred through the placenta during the second and third trimester of pregnancy. A recent report showed the outcomes of 24 women exposed to vedolizumab, which resulted in 11 live births [54]. No teratogenicity was reported in animals exposed to high doses of vedolizumab [55]. Because vedolizumab is gut specific, a hypothetical concern might be an increased risk of gastrointestinal infections, such as the rotavirus in the newborn. However, more results are needed to adequately counsel patients using vedolizumab.

Treatment of a Disease Relapse during Pregnancy

Corticosteroids, particularly prednisolone, may be necessary for induction of remission during pregnancy. Before initiating new drugs during pregnancy, it is of importance to estimate the severity and extensiveness of the disease activity. However, clinical and laboratory results may fail to prove real active disease and fecal calprotectin is not validated during pregnancy. Therefore, performing a lower endoscopy might be warranted. Recently, a systematic review concluded that lower endoscopy is of low risk for mother and child in all 3 trimesters of pregnancy [56]. Additionally, a prospective study comprising 42 pregnant women who underwent 47 lower endoscopies during pregnancy showed no adverse outcome related to the endoscopy in all 3 trimesters [57]. Therefore, lower endoscopy can be performed during all trimesters when strongly indicated. With respect to the treatment of a relapse during pregnancy with corticosteroids, recent data from a large population-based cohort showed no increased risk of malformations [58]. Although an earlier meta-analysis showed an increase in children with a cleft palate [59], it seems that using corticosteroids during pregnancy is of low risk. There have been reports of neonatal adrenal suppression following exposure to corticosteroids in the late third trimester. Therefore, a pediatrician should carefully examine neonates exposed to corticosteroids *in utero* after birth. Furthermore, corticosteroids are known to increase the risk of gestational diabetes and hypertension, and pregnant women should be followed up stringently by a gynecologist [60]. Prednisolone is the preferred corticosteroid during pregnancy, because of the limited transplacental passage [61, 62]. No ad-

verse pregnancy outcomes following budesonide use during pregnancy has been reported [63] and should be considered alongside treatment with prednisolone. Dexamethasone, betamethasone and hydrocortisone are best avoided. Other drugs that might be initiated for the treatment of a relapse during pregnancy include the above-mentioned drugs, mesalazine and anti-TNF. Cyclosporine-A treatment is used as rescue therapy for severe, refractory UC. Data on safety profile during pregnancy mainly come from organ transplant patients who became pregnant. A meta-analysis assessing the use of cyclosporine-A during pregnancy showed no adverse pregnancy outcomes [64]. Small case series in UC women with severe disease activity during pregnancy who were treated with cyclosporine-A showed no increased risk of adverse pregnancy outcomes or malformations [65].

Conclusion

Most drugs are not related to adverse outcome while used during pregnancy. Active disease is related to adverse outcomes; therefore, it is of utmost importance to strive for remission before conception and during pregnancy. Because knowledge on pregnancy, drugs and IBD seems limited in IBD patients, counseling of patients who are planning pregnancy is advised before conception.

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No disclosure.

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