Current opinion on treatment of inflammatory bowel disease in pregnant women

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Inflammatory bowel disease (IBD) refers to a relapsing and remitting disease representing as forms of ulcerative colitis (UC) and Crohn's disease (CD) [1]. The peak age of onset is between 20 and 40 years of age, and thus overlaps with child-bearing years [2]. Fear of the adverse effect of medication on pregnancy is highly established in women with IBD, yet awareness of the harmful effect of IBD relapse during pregnancy is poor [3]. Generally both the active disease and its treatment may affect pregnancy; however, the belief is that the risk of the active disease is always greater than its medications [4].

Active CD and UC during conception and pregnancy increase the risk of adverse prenatal outcomes such as low birth weight and preterm delivery. Therefore active treatment of the disease and establishing remission before conception is the main goal in young women. In a very recent study, Bortoli *et al.* evaluated pregnancy outcome in IBD patients in a prospective European multicenter case-control study. They demonstrated no significant difference in frequency of fetal abnormalities in IBD patients compared with non-IBD controls [5].

Van der Eoude *et al.* found that the risk of relapse after conception is the same as non-pregnant IBD patients but if pregnancy occurs during disease flare-up, the disease will remain persistently active during pregnancy [6]. Inflammatory bowel disease itself, especially CD, may increase the risk of adverse neonatal outcome [6]. The risk is not only related to the medications but also related to the disease severity. One of the most important improvements in the management of IBD over the past decade has been the finding that normal pregnancy outcomes can be accomplished when a woman enters pregnancy in remission [7]. New insights into the safety of a wider spectrum of drugs in these patients have a great role in increasing success in IBD management.

Various classes of drugs are used in disease management including aminosalicylates, corticosteroids, immunosuppressive drugs, antibiotics, and biologic agents. Also in recent years, the effectiveness of probiotics in maintaining remission and their efficacy in preventing relapse in IBD have been supported by concrete evidence [8, 9].

Aminosalicylates – the standard treatment for induction and maintenance of remission of mild to moderate forms of IBD (mostly UC) – are poorly absorbed into blood circulation but once in the blood can easily cross the placenta and reach the fetus [10-12]. They are relatively safe during pregnancy and are considered as class B by the Food and Drug Administration (FDA) but folic acid supplementation at 2 mg per day is recommended to overcome probable risks of folate deficiency and its complications in neonates. In a meta-analysis in 2007, Rahimi *et al.* reported a 1.16-fold increase in congenital malformations, 2.38-fold increase in stillbirth, 1.14-fold increase in spontaneous abortion, 1.35-fold increase in preterm delivery, and 0.93-fold increase in low birth weight in IBD pregnant women on aminosalicylate therapy [13] but they did not compare the risk in IBD pregnant women without drug therapy. A few studies reported the risk of neonatal interstitial nephritis with higher doses of mesalazine (more than 3 g/day) [14, 15].

Corticosteroids are classified as class C drugs in pregnancy. There is no evidence of teratogenicity of corticosteroids and they are prescribed for different forms of the disease [16]. Although there are differences between corticosteroids there is no report of maternal adrenal suppression, glucose intolerance, ocular side effects, hypertension, or congenital abnormalities with budesonide [17], which is commonly used in IBD, whereas an increase in the risk of oral cleft was found with prednisone in a meta-analysis [18]. Of course, the route of drug administration may affect drug plasma levels as well as its placental transfer [16]. Budesonide is mainly used as a rectal enema while prednisolone is used orally.

There is no consensus among practitioners on the adverse fetal consequences after immunosuppressive exposure. The use of mercaptopurine during pregnancy is not recommended because of miscarriage and preterm birth and it is considered as class D. Although some studies could not show adverse pregnancy outcomes with mercaptopurine and azathioprine (AZA) [19, 20], others reported congenital abnormalities [21]. Cleary and Källén indicated a moderate risk of congenital malformations, specifically ventricular/atrial septal defects as well as growth retardation [22], but they did not consider the effect of the disease on pregnancy. In contrast, Shim *et al.* found no association between AZA/mercaptopurine and risk of preterm birth, fetal adverse outcomes and congenital anomalies in IBD pregnant women [23]. Cyclosporine can be indicated in severe cases unresponsive to steroids because of serious health concerns [24]. There are reports of pros and cons of the association of cyclosporine neonatal exposure and adverse outcome [10]. To date, there are no conclusive data about its safety; nevertheless, its use in pregnancy is not recommended.

Biologic agents are considered as a useful class of drugs in the course of IBD in unresponsive and severe forms. Infliximab, a monoclonal anti-tumor necrosis factor-α antibody, is an effective biologic agent for induction and maintenance of remission of CD and is classified as a class B drug in pregnancy. It crosses the placental barrier at week 20 and thereafter in a linear fashion can be detected in newborns [25]. There are a few reports of infliximab-induced malformations [26] but the results of most of the studies are in favor of infliximab [27, 28]. Animal studies did not show adverse fetal effects [29]. Adalimumab is also considered as a class B drug for use in pregnancy and no congenital abnormalities were reported [30, 31]. The safety of certolizumab in pregnancy is not fully known. A recent observational study on the risk/benefit assessment of anti-TNF treatment with infliximab and adalimumab in 212 pregnant women determined the incidence of adverse outcomes as not higher than for IBD [32].

Zelinkova *et al.* assessed 4 pregnant IBD patients under infliximab treatment and determined 2-3-fold higher infliximab concentrations in the cord blood than peripheral blood of mothers. After stopping infliximab, the pregnant women were followed for 3-6 months and normal neonatal development was observed; however, this study raised a debate on the unknown effects of infliximab on the developing immune system [33].

Biological therapy may cause serious side effects including pneumonia, tuberculosis, lymphoma, drug-induced lupus, and hepatotoxicity in a small percentage of patients, and the balance between their risks and benefits seems to be good [34].

Antibiotics are also used in IBD patients, especially CD, on some occasions and even have been even proposed effective in irritable bowel syndrome (IBS) [35]. They include metronidazole, ciprofloxacin, tetracyclines and sulfonamides, which are associated with high risk of neonatal anomalies or contraindicated while ampicillin, cephalosporin and erythromycin are associated with low risk of adverse pregnancy outcomes [36].

Probiotics that are recently approved in management of IBD and even IBS [37] do not appear to cause any safety concerns for pregnant women [8, 9]. Systemic absorption is rare when probiotics are used, and the current literature does not indicate any increase in adverse pregnancy outcomes [38].

There is a great fear of adverse medication effects on pregnancy outcomes among IBD patients while there are a few conflicting and controversial studies which reported the adverse effects of IBD medications on pregnancy outcomes. In contrast,

the knowledge of IBD patients about the deleterious effects of the disease on pregnancy outcome is inadequate while the disease activity carries the highest risk.

Expert opinion

Taking all the evidence into consideration, the prescribers should consider the risk-benefit assessment of each class of drugs during conception and pregnancy. Defining the best therapeutic approach in pregnancy, different scenarios must be considered in IBD pregnant women including planning pregnancy in patients in remission; unplanned pregnancies in patients with active disease; planning pregnancy in patients with active disease; and unplanned pregnancy in patients in remission. In each of these scenarios, the clinician must evaluate the patient's drug regimen and plan to change some of its components if necessary. It should be noted that drug discontinuation because of the fear of adverse pregnancy outcomes worsens the situation and the mother will be at a high risk of flare-up. Generally, aminosalicylates and corticosteroids are routinely used for moderate to severe forms and data about their safety are growing. Although the risk of serious adverse drug reactions during pregnancy is low, during pregnancy methotrexate and thalidomide are contraindicated and after pregnancy if the patient is on treatment with these two drugs, changing medications is necessary. The most important issue regarding anti-TNF agents is their probable side effect on the developing immune system, which needs more investigations, and for this purpose and according to a study there is the possibility of stopping infliximab in the third trimester and resuming drug administration after delivery. Notably, infliximab does not reduce the rate of colectomy in patients with IBD while colectomy and surgical resection with ileal pouch anal anastomosis (IPAA) have an important role in induction of infertility in IBD patients [39, 40]. In UC, overall fertility rates are normal except after surgery. Therefore considering more effective and safe management to prolong remission and protection of patients to reach the phase of surgery are very important. Most medications in the treatment of IBD are safe for the fetus and should be continued throughout pregnancy in order to maintain maternal health. It should be emphasized that maintaining fertility of patients and safety of pregnancy are dependent on remission of patients. Therefore, more effective and not risky agents such as probiotics could stay in the center of interest.

There are still questions about new medications such as monoclonal antibodies for which data are rare and time is needed to gather case reports. Notably, conducting clinical trials is unethical in pregnant patients and thus researchers should rely on observational studies, which are still rare.

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