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REVIEW

Treatment of pregnant women with a diagnosis of inflammatory bowel disease

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Abstract

The frequency of diagnosis of inflammatory bowel disease (IBD) has increased in younger populations. For this reason, pregnancy in patients with IBD is a topic of interest, warranting additional focus on disease management during this period. The main objective of this article is to summarize the latest findings and guidelines on the management of potential problems from pregnancy to the breastfeeding stage. Fertility is decreased in patients with active IBD. Disease remission prior to conception will likely decrease the rate of pregnancy-related complications. Most of the drugs used for IBD treatment are safe during both pregnancy and breastfeeding. Two exceptions are methotrexate and thalidomide, which are contraindicated in pregnancy. Anti-tumor necrosis factor agents are not advised during the third trimester as they exhibit increased transplacental transmission and potentially cause immunosuppression in the fetus. Radiological and endoscopic examinations and surgical interventions should be performed only when absolutely necessary. Surgery increases the fetal mortality rate. The delivery method should be determined with consideration of the disease site and presence of progression or flare up. Treatment planning should be a collaborative effort among the gastroenterologist, obstetrician, colorectal surgeon and patient.

Key words: Pregnancy; Inflammatory bowel disease; Immunomodulators; Biologics; Breastfeeding; Treatment

Core tip: Active disease prior to conception and during pregnancy increases the rate of pregnancy-related complications; thus, special attention should be given to pregnancy during the disease remission period. The safest drugs for use during pregnancy and breastfeeding are 5-aminosalicylic acid complexes, thiopurines and corticosteroids. Methotrexate and thalidomide are contraindicated. Anti-tumor necrosis factor treatment should be avoided during the third trimester. The risk of venous thromboembolism is increased in patients with moderate-to-severe disease. The delivery method should be selected according to the region of the body involved and disease activity. In this article, the problems

encountered by patients with inflammatory bowel disease from pregnancy to breastfeeding are discussed, and appropriate management strategies are suggested.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, idiopathic diseases characterized by relapse and remission periods, and they constitute a major portion of the inflammatory bowel disease (IBD) spectrum. A multicentric epidemiological study performed in Europe found the incidence of UC to be 10.4/10000 and that of CD to be 5.6/10000[1]. The risk of IBD in children is increased 2-13-fold if one parent has IBD[2] and by 33%-36% if both parents have IBD[3,4]. The disease is most frequently diagnosed during the second and third decades of life. CD is diagnosed slightly more frequently in women than men (1.3:1), whereas the ratio is 1:1 for UC. Approximately 25% of female IBD patients are expected to become mothers during their disease period[5]. In other words, the disease affects prospective parents. For this reason, the effect of the disease on possible complications encountered during pregnancy and the effects of the treatment on the fetus, birth method selected and breastfeeding safety are sources of anxiety for patients. To alleviate such worries, physicians must increase their knowledge of and experience with such subjects and share this information with patients and their relatives.

Pregnancy does not cause IBD flare-ups; however, the disease can be exacerbated in IBD patients who become pregnant during the active phase of the disease[6]. Of those patients who become pregnant during the active phase, approximately two-thirds have active disease throughout their pregnancy term[7,8]. Approximately one-third of patients who become pregnant during the remission period experience a disease flare-up[9]. However, these proportions are identical to those in the general population. IBD flare-ups are often due to medication discontinuation during pregnancy, lactation and smoking resumption following birth[10]. Approximately one-third of patients have active disease during conception[11]. Nielsen *et al*[12] reported that the yearly exacerbation rate is 34% during pregnancy and 32% in non-pregnancy. Increased prevalences of premature birth, low birth weight, stillbirth, cesarean section and congenital anomalies have been reported in pregnant women with IBD[13,14]. Such complications are more frequent in patients with CD than those with UC. However, these meta-analyses did not take disease activity or medical treatments into consideration. Congenital malformation rates were increased in IBD patients in case-controlled studies conducted in Hungary[15] and Italy[16], as opposed to other studies that reported similar rates in IBD patients to those of the general population[17,18]. Some authors[19-21] suggest this difference is explained by disease activity, while others suggest it is due to the high numbers of low-activity patients included in the studies[10,22]. The prospective, case-controlled ECCO-EpiCom study[23] found no significant difference in pregnancy outcomes in pregnant IBD patients compared with the general pregnant population. In that study, logistic regression analyses showed that age > 35 years and tobacco smoking were risk factors for premature birth and congenital anomalies in CD patients and for premature birth in UC patients.

The chance of a normal birth is 85% in patients with UC and 83.5% in those with CD if the disease is in remission during conception[9]. Ideally, the patient should be in remission when trying to conceive.

The physician should inform the patient and her partner of the IBD-pregnancy interaction and its effects on pregnancy outcomes, the treatment risk to benefit ratio and the importance of remission maintenance in reducing fetal risk. It is essential to be aware of disease management protocols during pregnancy to alleviate patient fears.

In this article, our main objective is to evaluate the management of IBD patients during pregnancy by reviewing the effects of IBD treatment on the fetus and mother during pregnancy and lactation.

MEDICAL TREATMENT

Discontinuing medical treatment during pregnancy can further harm the fetus by causing a flare-up in the patient. The pregnancy risk profiles for conventional drugs used in IBD treatment, such as 5-aminosalicylic acid (5-ASA), steroids and immunomodulatory agents, are available. Experience with biological agents is also increasing. The United States Food and Drug Administration (FDA) has deemed almost all drugs safe for use during pregnancy and lactation, with the exception of methotrexate and thalidomide, which are pregnancy category X drugs (Tables 1 and 2).

5-ASA

All 5-ASAs (mesalazine, balsalazide, ipsalazide and sulfasalazine) are used to induce and maintain remission in patients with light-to-moderately active UC, and these drugs exert their effects by acting on the intestinal mucosa.

Sulfasalazine

Effect on pregnancy: Sulfasalazine and its metabolite sulfapyridine inhibit folate synthesis. Sulfasalazine and sulfapyridine cross the placental barrier and can be detected in umbilical cord blood at rates similar to those in maternal blood. For this reason, sulfasalazine

Table 1 Food and Drug Administration pregnancy categories

FDA category	Definition
A	Controlled studies in animals and women demonstrate no risks during the first trimester, and the possibility of fetal harm appears remote
B	Studies in animals have not demonstrated a fetal risk, but no controlled studies have been conducted in pregnant women, or animal studies have shown an adverse event that was not confirmed in controlled studies in women during the first trimester. Chance of fetal harm is remote but remains a possibility
C	No controlled studies have been conducted in women, and animal studies have shown adverse effects on the fetus, or studies in humans and animals are not available. Chance of fetal harm. Give only if potential benefit outweighs the risk
D	There are no controlled studies in women or animals, but positive evidence of fetal risk is available. It can still be used for life-threatening or serious diseases when there are no effective alternative drugs
X	Studies in animals or women have demonstrated fetal abnormalities. The drug is contraindicated in women who are pregnant or may become pregnant

FDA: Food and Drug Administration.

Table 2 Safety of inflammatory bowel disease medications during pregnancy and breastfeeding

Medication	FDA category	Comments during pregnancy	Comments during breastfeeding
Adalimumab	B	Low risk: Transported through the placenta late in the second and third trimester; avoid treatment in the last trimester	Compatible
5-Aminosalicylic acid preparations[1]	B	Low risk: Limited data for olsalazine; if using sulfasalazine, folic acid supplementation is mandatory	Enters breast milk; probably compatible
Amoxicillin/clavulanate	B	Low risk	Enters breast milk; probably compatible
Azathioprine/6-mercaptopurine	D	Low risk	Low transfer to infant; appears in the milk 4 h after ingestion
Budesonide/prednisone	C	Probably low risk, avoid during first trimester (potential risk of oral clefts)	Probably compatible; enters breast milk
Certolizumab	B	Low risk	Limited data; probably compatible
Ciprofloxacin	C	Limited data; not recommended	Compatible
Cyclosporine	C	Low risk	Contraindicated
Methotrexate	X	Contraindicated: Teratogenic	Contraindicated
Metronidazole	B	Low risk, avoid during the first trimester	Enters breast milk, not recommended
Natalizumab	C	Limited data; low risk	Limited data; probably compatible
Tacrolimus	C	Limited data; no increase in congenital anomalies	Contraindicated
Thalidomide	X	Contraindicated: Teratogenic	No data available; potential toxicity

[1]Asacol HD (due to the dibutyl phthalate content) and olsalazine are category C drugs. FDA: Food and Drug Administration.

treatment can be continued during pregnancy. However, since it results in folate deficiency, it must be supplemented with 2 mg folic acid daily[24].

A meta-analysis published in 2008 compared 642 pregnant women who used mesalazine, sulfasalazine or olsalazine with 1158 pregnant controls and found no increased risks of congenital anomalies, low birth weight or similar complications[25]. The rates of low birth weight, prematurity, spontaneous abortion, live births and birth defects were similar between sulfasalazine-using mothers and the general population[8].

Effect on breastfeeding: Sulfasalazine and its metabolite sulfapyridine pass into breast milk. However, although sulfasalazine replaces bilirubin, which is a serious issue, no clinically significant cases have been reported[26]. Diarrhea was reported in infants of mothers taking sulfasalazine[27]. In such cases, adjustment of the sulfasalazine dosage or discontinuing treatment is indicated.

Mesalazine

Effect on pregnancy: Although most 5-ASA drugs are pregnancy category B, olsalazine is category C. Mesalazine metabolites, especially N-acetyl mesalazine, cross the placental barrier[28,29]. The rate of congenital anomalies in babies of mesalazine-exposed mothers was no higher than that in babies of the general population[30,31]. Several studies have reported the use of 5-ASA during pregnancy to be generally safe[32-34].

Enteric-coated mesalamine with dibutyl phthalate (DBP) was reported to cause skeletal anomalies and negative effects on the male reproductive system in animal models[35]. Drugs that contain DBP and 5-ASA (Asacol or Asacol HD; Procter and Gamble Pharmaceuticals, Cincinnati, OH, United States) should be switched to another 5-ASA preparation during pregnancy. However, a study that compared 117 pregnant patients who used Asacol with 156 pregnant patients who used non-Asacol aminosalycilate drugs reported no significant differences in terms of congenital anomaly rates[36].

Effect on breastfeeding: 5-ASA is excreted at a low concentration *via* breast milk[37]. Infants of mothers using 5-ASA can develop diarrhea due to allergic reactions. In such cases, the treatment should be stopped immediately.

Steroids

Effect on pregnancy: Corticosteroids, particularly prednisolone, are classified as pregnancy category C drugs. Carmichael *et al*[38] reported increased incidences of cleft palate and cleft lip anomalies with the use of corticosteroids 1 mo before pregnancy or during the first trimester. However, other studies involving larger patient groups reported no such risk[31].

Several studies also suggest that high-dose corticosteroid usage might cause adrenal suppression by affecting the hypothalamus-pituitary-adrenal axis in newborns. However, one study also concluded that the long-term effects are unclear and the absolute effects on the fetus negligible[39].

The use of budesonide is also regarded as safe during pregnancy. Beaulieu *et al*[40] reported no side effects in eight pregnant patients with CD who used budesonide. Moreover, studies involving larger groups of patients who used budesonide for asthma treatment reported no increase in the rate of birth defects or stillbirths[41,42].

Effect on breastfeeding: As the concentrations of steroids that enter breast milk are low, steroid usage during breastfeeding is deemed safe[43]. However, no specific guidelines exist for prednisolone usage during lactation. If the mother is worried about breastfeeding during steroid treatment, she can stop breastfeeding during her steroid treatment and resume once the treatment is discontinued[44].

Thiopurines

Effect on pregnancy: Azathioprine is a pro-drug that is metabolized into 6-mercaptopurine (6-MP). Following its metabolism into 6-MP, it is again metabolized into its active 6-thioguanine (6-TG) and inactive 6-methylmercaptopurine (6-MMP) metabolites. These drugs damage chromosomes by disrupting nucleic acid synthesis. The FDA classifies these drugs as pregnancy category D, since animal models showed teratogenic effects at therapeutic or elevated dosages[45]. Yet, the significantly higher bioavailability of intraperitoneal or parenteral, compared with oral, thiopurines used for IBD treatment in animal models should not be overlooked. Intact azathioprine or 6-MP cannot cross the placental barrier, whereas 6-TG can[46]. In a prospective study that included 30 pregnant women, 6-TG levels decreased but 6-MMP levels increased during pregnancy; however, these changes did not cause myelotoxicity or hepatotoxicity[47]. After pregnancy, both metabolites returned to their pregestational levels. With the exception of a newborn whose mother had severe pre-eclampsia and pancytopenia during delivery and high alkaline phosphatase levels, 6-MMP was not detected in any of the newborns. No major congenital malformations were seen in those newborns. All newborns had normal Apgar scores, but 60% were diagnosed with anemia. Therefore, a complete blood count is advised for newborns whose mothers used thiopurines during pregnancy.

In daily clinical practice, gestational planning for IBD patients who take thiopurines and continuation of thiopurine usage during pregnancy pose a challenge for the physician. This is due to the numerous contradictory studies in the literature. Two more recent publications reported an increase in the risk of congenital anomalies with thiopurine usage[48,49]. However, these studies have been criticized for their small number of patients and other limitations, such as inclusion of both major and minor anomalies[50]. Other than the risk of congenital anomalies, other studies have reported a relationship between thiopurine usage and the incidences of preterm births and low birth weight[48,49,51].

However, a large number of recent studies showed no relationship between thiopurine usage and the risk of congenital anomalies. Goldstein[52] evaluated women who took azathioprine for various indications; after a review of birth defect records, no significant increases in malformation rates were found. The 20-year study by Ban *et al*[53] reported that neither MP nor any other drug is related to an increased risk of congenital anomalies. Beaugerie *et al*[54] and Coelho *et al*[55], *via* the CESAME study in France, compared 89 women exposed to thiopurine during pregnancy and 129 IBD patients without thiopurine exposure and found no increase in the risk of congenital anomalies in a sub-analysis. The meta-analysis published by Akbari *et al*[56] reported no increase in the risk of congenital anomalies or low birth weight but an increased risk of premature birth with thiopurine usage during pregnancy. Casanova *et al*[57] reported that thiopurine usage was not associated with pregnancy complications and actually predicted lower rates of obstetric complications and better pregnancy outcomes. The first results of the ongoing PIANO study[58], published in 2012, showed no increase in the rates of congenital anomalies or pregnancy complications in 317 pregnant women exposed to thiopurine during pregnancy. The infants of those exposed mothers were followed up and exhibited similar or better developmental parameters compared with infants of mothers who were not exposed to thiopurines[59]. This finding supports the results of another study in 2013 in which 30 babies of mothers taking thiopurines during pregnancy for both medical and psychosocial health reasons showed no differences compared with the control groups[60].

To summarize, thiopurine treatment should be continued during pregnancy to prevent flare-ups, as the risk of active disease outweighs the risk of thiopurine usage. A female patient using anti-tumor necrosis factor (TNF) therapy combined with thiopurines who

is planning to become pregnant can discontinue the thiopurines prior to pregnancy, considering the risk of infection[50]. Women who were not taking thiopurines prior to pregnancy are not advised to start thiopurine treatment during pregnancy, as thiopurines take a long time to act and pose a small risk of bone marrow suppression and pancreatitis[61].

Effect on breastfeeding: Thiopurines were detectable in breast milk 4 h after their ingestion, albeit at very low levels compared with serum plasma levels[62]. Thiopurine metabolites are almost undetectable in infants breastfed by mothers taking thiopurines[63]. Furthermore, no increase in the risk of infection was evident in babies of mothers treated with thiopurines[64]. Therefore thiopurine-using mothers have no issues during breastfeeding. However, mothers of infants with weak immune systems should exercise caution while breastfeeding during thiopurine treatment[10].

Methotrexate

Effect on pregnancy: When taken during the organogenesis period, methotrexate can cause methotrexate embryopathy or fetal/methotrexate syndrome, which is characterized by congenital extremity and craniofacial anomalies[65]. When taken during the third trimester, methotrexate can cause fetal toxicity, retardation of development and loss of the fetus[66,67]. Since it remains in the body for a prolonged period, the drug should be discontinued 3-6 mo before conception[68]. It is recommended that men also stop taking methotrexate 3 mo before conception. In addition, folic acid supplementation should commence 3 mo prior to and be continued during pregnancy.

While on methotrexate, the patient should be warned about its toxic effects on the fetus and advised to use at least two contraception methods to prevent pregnancy[69].

Effect on breastfeeding: Methotrexate is present in breast milk and can cause immunosuppression and neutropenia by accumulating in neonatal tissues. Therefore, it should not be used during pregnancy[70].

Cyclosporine

Effect on pregnancy: Cyclosporine is a pregnancy category C drug. Because cyclosporine can cross the placental barrier, it may exert adverse effects on the fetus[71]. In renal transplant patients, cyclosporine caused premature birth, low birth weight, gestational diabetes, maternal hypertension, pre-eclampsia and fluctuations in the levels of other drugs[72]. Another meta-analysis of the effects of cyclosporine usage on pregnancy (15 studies, 410 patients) reported the incidence of premature birth to be 56% and that of congenital anomalies to be 4.1%. However, the rate of congenital malformation is not significantly different from that in the normal population[73]. In a smaller study that included eight pregnant patients, seven were treated successfully for steroid-refractory ulcerative pancolitis, while one required infliximab (IFX) treatment and was treated successfully. Seven patients delivered healthy infants, and one fetus died in utero. Two newborns were premature, and no congenital anomalies were detected in any of the infants[74].

Effect on breastfeeding: Since very small amounts of cyclosporine pass the placental barrier, it is safe to use in nursing mothers. However, the possibility of immunosuppression in the infant must not be overlooked. If treatment with this drug is planned, the potential risks should be discussed with the mother.

Tacrolimus

Effect on pregnancy: Tacrolimus, like cyclosporine, is classified as a pregnancy category C drug by the FDA. A study that followed 37 female liver transplant patients for 13 years with 49 recorded births reported an increase in the rate of premature births but not in the rate of congenital anomalies[75]. In another report, a female patient treated with tacrolimus during pregnancy delivered a healthy baby[76]. As with cyclosporine, there are few data regarding tacrolimus, so the risk to benefit ratio should be evaluated before using this drug.

Effect on breastfeeding: Tacrolimus is reported to enter the breast milk at a rate of 0.05%. Therefore, there is no clear evidence that it must be stopped during breastfeeding[69].

Biological agents

The use of synthetic TNF inhibitors such as IFX, adalimumab, certolizumab pegol and golimumab for the treatment of IBD is increasing. These drugs are classified as pregnancy category B. Natalizumab, which is rarely used, is a pregnancy category C drug. Clinical experience with the use of anti-TNF agents during pregnancy is limited[77,78].

Effect on pregnancy: Transplacental transmission has been reported mostly for monoclonal antibodies (IFX, adalimumab and golimumab) and rarely for fusion proteins (etanercept). Transplacental transmission of monoclonal antibodies increases during pregnancy, and their concentration in umbilical blood becomes equal to or higher than that in maternal blood during the last trimester.

Infliximab

IFX is an IGG1-type monoclonal antibody that inhibits TNF-α. It cannot pass the placental barrier during the first trimester but is transmitted effectively during the third trimester[79]. Therefore, the fetus is not exposed to the drug during the organogenesis period, but following transplacental transmission during the third trimester, IFX remains in infant blood for a few months following

birth. Neither teratogenicity nor toxicity was detected in a study involving 35 pregnant women who used IFX[80]. No difference was seen in terms of pregnancy outcomes between patients using IFX and healthy controls[81]. However, neonatal death caused by intracerebral and pulmonary hemorrhage, premature birth and Fallot's tetralogy have been reported[82].

The TREAT Registry and IFX Safety Database are the two largest studies on this subject[83,84]. In the TREAT Registry, a prospective study involving CD patients, patients on IFX were compared with those not taking IFX. Thirty-six of 66 pregnant women were treated with IFX during pregnancy. Fetal malformations were not detected. In addition, there was no significant difference between the two groups in terms of neonatal complications and miscarriage.

The IFX Safety Database is a retrospective review of 96 patients using IFX. The treatment was generally stopped during the first trimester after the patients realized they were pregnant. Pregnancy outcomes were not different between patients who did and did not take IFX.

The IFX levels of six neonates of mothers taking IFX were higher than those of the mother, but IFX was cleared from the bloodstream of the infants after 2-7 mo[85]. This shows that IFX crosses the placental barrier easily during the third trimester. Moreover, the reticuloendothelial system of the infant is not sufficiently developed to clear the antibodies effectively.

The latest prospective PIANO study[58] included 1232 pregnant women, of whom 264 were treated with IFX, 151 with adalimumab, 67 with certolizumabpegol and 29 with combined biological agent-immunomodulatory therapy. No differences in parameters such as birth defects and infection rates were detected during the first year, but differences in weight and height were detected between infants who were exposed to anti-TNF therapy and those who were not[58]. The odds ratios for developing complications and for preterm birth with combined IFX-immunomodulatory therapy were 1.7 (1.0-2.2) and 2.4 (1.3-4.3), respectively. No difference was seen in the pregnancy outcomes of CD patients according to drug exposure, but increased risks of preterm birth and low birth weight and a prolonged stay in the intensive care unit were seen in UC patients taking combination therapy.

To summarize, IFX can be used during the first two trimesters of gestation. Patients are advised to stop IFX prior to the last trimester (30 wk). In patients with a flare-up caused by IFX treatment discontinuation, short-term corticosteroid treatment can be administered. Discontinuing IFX during the third trimester or at the end of the second trimester decreases IFX transportation to the placenta, reducing the level to which the neonate is exposed. Exposure to IFX during the third trimester can result in infections or a suboptimal response to vaccinations during the neonatal period. Live vaccines should not be administered during the first 6 mo in infants exposed to anti-TNF therapy[79]. Other vaccinations may proceed according to schedule.

Effect on breastfeeding: IFX is found in minute amounts in breast milk, and its oral absorption is minimal; thus, systemic adverse effects are rarely diagnosed[24,86]. IFX levels in an infant whose mother was taking IFX until 4 wk prior to birth decreased after 6 mo even though the mother continued to take IFX while breastfeeding[87].

However, data regarding the safety of IFX during breastfeeding and its local immunosuppression in the gastrointestinal system are insufficient.

Adalimumab

Adalimumab is an antibody targeting IGG1 that is actively transported through the placenta during pregnancy[79,88]. Similar to IFX, adalimumab crosses the placental barrier during the third trimester. Small observational studies on adalimumab during pregnancy have been conducted. It can be used from the time of conception through the first two trimesters of pregnancy. No increased risk of congenital malformation, spontaneous abortion or preterm birth was detected in pregnant women exposed to adalimumab. Although clinical experience with this drug in pregnant women is limited, the Organization for Teratology Information Specialists, which conducted a prospective study on adalimumab involving 27 pregnant women as well as a review of the birth outcomes of 47 pregnant women who used adalimumab during pregnancy, reported that the rates of spontaneous abortion, stillbirth, preterm birth and congenital anomalies were similar to those in the general population[89]. As this medication is used in weekly doses, it is difficult to discontinue treatment at the beginning of the third trimester as this might result in disease flare-ups. It is suggested to discontinue adalimumab 6-8 wk prior to birth.

Effect on breastfeeding: There are insufficient data on the safety of adalimumab use while breastfeeding. The drug passes into breast milk in small amounts, but no adverse effects have been reported[86]. However, discontinuing treatment while breastfeeding should be decided after reviewing the health of the mother and her IBD status.

Certolizumab

Certolizumab is a PEGylated Fab' fragment of an anti-TNFα monoclonal antibody. As opposed to IgG1 antibodies, Fab' fragments pass through the placenta by passive diffusion; therefore, placental transfer is minimal during the third trimester, unlike the cases with IFX and adalimumab[79]. Certolizumab levels in umbilical blood were very low (less than 2 ng/mL) in 10 pregnant women exposed to certolizumab[90]. In theory, it can be used from conception until birth, but the data are insufficient. Certolizumab excretion *via* breast milk is

minimal[78].

Natalizumab

Information regarding the safety of natalizumab use during pregnancy and lactation is insufficient. No increased risk of congenital malformation was detected in a study involving 164 pregnant women treated with natalizumab for CD or multiple sclerosis[91].

Golimumab

Golimumab is a new anti-TNF inhibitor, approved in 2013. Its effects on pregnancy are unclear. Lau *et al*[92] reviewed 42 pregnant women exposed to golimumab (10 pregnant UC patients) for congenital anomalies. These pregnancies resulted in 19 live births, 13 spontaneous abortions (miscarriages) and 6 elective abortions. Of the 13 mothers who experienced miscarriages, 30.8% received simultaneous methotrexate treatment. As golimumab is a new drug, information on the safety of its use during pregnancy is insufficient, and no evidence of its presence in breast milk is available.

Anti-diarrheal agents

Anti-diarrheal agents should be avoided during pregnancy, especially during the early period. Teratogenicity was detected in neonates exposed to diphenoxylate/atropine and loperamide, but whether this was due to chance or to the drugs was unclear[93,94].

Cathartics

A colon cleanse is necessary for sigmoidoscopy during pregnancy. No study has specifically addressed the teratogenic effects of cathartics; however, no congenital anomalies were seen among 22843 pregnant women treated with laxatives[95]. The FDA reclassified cathartics and laxative agents from category B to category X. Cathartics are associated with a risk of dehydration and electrolyte imbalance.

Magnesium citrate

Magnesium citrate has an FDA category B rating and thus is safe to use for constipation or prior to sigmoidoscopy. It might cause electrolyte imbalance and dehydration when used long term.

Polyethylene glycol solution

Polyethylene glycol (PEG) has a FDA category C rating. No data on the safety of PEG use during pregnancy are available.

COMPLICATIONS AND RISKY SITUATIONS IN PREGNANT IBD PATIENTS

Patients who underwent IBD-related surgery prior to pregnancy may experience a temporary increase in stool frequency. Incontinence can be seen especially during the third trimester, but this disappears after birth. Ileostomy can prolapse during the third trimester. Patients with a history of abdominal surgery and ileostomy reported subileus and ileus attacks[96]. The study by Nguyen *et al*[19], which used data from the Nationwide Inpatient Sample (NIS), compared pregnant women with CD or UC with healthy pregnant women without IBD. The frequencies of venous thromboembolism (VTE) and blood transfusions were increased in pregnant women with IBD. The risk of VTE is fourfold greater in pregnant than in non-pregnant IBD patients[97]. The risk of VTE is especially high during the first 6 wk postpartum[98]. Subcutaneous low-molecular-weight heparin is indicated during the peripartum period in high-risk (relapsed and hospitalized patients with moderate-to-severe disease activity) pregnant IBD patients. Heparin prophylaxis is also advised in pregnant IBD patients who are hospitalized for other reasons. VTE is common among UC patients, while the risk of antepartum hemorrhage is at least twofold higher in CD patients[99]. In another study, placental abruption was seen in 2% of IBD patients[19].

Gestational diabetes is another issue. The risk of gestational diabetes did not differ between IBD patients not on steroids and a control group[100]. However, the risk of gestational diabetes was increased in IBD patients who used steroids during pregnancy in the PIANO registry study, which included more than 1000 pregnant IBD patients[58]. Therefore, a pregnancy in a patient with IBD must be considered risky.

NUTRITION AND SUPPLEMENT TREATMENTS

Although nutrition is crucial for all pregnant women, it is especially so in pregnant women with IBD. The prevalence of malnutrition was sixfold higher in pregnant IBD patients compared with healthy controls[19]. A retrospective study in Canada reported less weight gain during pregnancy in IBD patients compared with the general pregnant population[17]. Since malnutrition during pregnancy poses a risk to the fetus, although enteral nutrition is preferred, parenteral nutrition should be used as soon as the need arises. There is no solid evidence of the benefits of specialized diets in terms of IBD remission[101]. A randomized controlled study reported that consumption of fish oil supplements increased the rate of pregnancy without affecting fetal growth[102]. In patients with anti-phospholipid antibody syndrome, fish oil supplements can be used to prevent miscarriage[103]. They also reduce the risk of preterm birth and miscarriage in pregnant IBD patients. Since fish oil is not classified as a drug, it has not been categorized by the FDA for use during pregnancy. Folic acid supplementation is essential during pregnancy for prevention of neural tube defects. If the patient is on sulfasalazine, daily folic acid intake should be increased accordingly (2-5 g/d)[96,102]. Calcium and vitamin D supplementation is advised in patients using steroids to prevent bone

loss. The patient should also be advised not to smoke. Smoking has a negative effect on pregnancy outcomes, particularly for patients with CD.

ENDOSCOPY

Endoscopic retrograde cholangiopancreatography can be performed if indicated[104].

SURGICAL TREATMENT

Surgical treatment indications in both UC (acute, severe or refractory colitis) and CD (perforation, abscess, severe hemorrhage or bowel obstruction) are identical in pregnant and non-pregnant patients. Surgical interventions should be conducted during the second trimester. However, surgeries performed due to acute indications in pregnant patients with IBD carry a high risk of losing the fetus[105]. Few studies have addressed the effect of surgery on maternal morbidity. Ileostomy should be performed in place of primary anastomosis during surgery[106]. Live and healthy births have been reported despite poor prognoses, intraperitoneal sepsis and surgical interventions[107].

There are case reports of colectomy surgery performed during the third trimester in combination with vaginal birth or cesarean section[108-110]. However, medical treatments are preferred to surgical treatments in non-emergency situations.

DELIVERY METHOD

Delivery by cesarean section is more frequent in IBD patients compared with the general population. Indeed, compared with the general population, the frequency of cesarean delivery is 1.5-fold higher in pregnant patients with CD but similar in those with UC[13,19]. Another study reported that the risk of elective cesarean section was twofold higher in pregnant patients with UC and even higher in those with CD[99]. This is likely due to the increased frequency of perianal diseases in CD patients. A retrospective questionnaire study reported that the risk of developing perianal disease was 18% in patients without prior perianal disease who gave birth vaginally (especially in episiotomy cases)[111]. This may also explain the increased preference for cesarean section. However, other studies involving larger patient groups did not support these findings[112,113]. There are insufficient data to recommend this delivery method for IBD patients[85]. Cesarean section is not thought to prevent disease flare-up or development of perianal diseases. It should be performed only when vaginal birth is contradicted in an individual patient. Vaginal birth exacerbates the disease in pregnant CD patients with active perianal disease and in UC patients with active rectal disease with a history of ileal pouch anal anastomosis (IPAA) with colectomy[85,114]. It is vital to prevent pouch dysfunction in IPAA patients and maintain sphincter functionality. Sphincter integrity can be disturbed by mechanical pressure during vaginal birth. Episiotomy has a risk of causing rectovaginal fistulas and non-healing wounds during periods of active perianal disease[115]. Forceps use and uncontrollable tears can negatively affect pelvic floor function. In general, vaginal birth is advised for pregnant IBD patients with light-to-moderate disease activity, whereas cesarean section is preferred for patients with IPAA or with fulminant or active perianal disease[102]. Performance of a cesarean section for reasons other than the above should be decided by the obstetrician for obstetric reasons.

Although there is a risk of complications caused by adhesions in patients who underwent previous pelvic or abdominal surgery or ileostomy or colostomy, vaginal birth is considered safe. Episiotomy can also be performed in such patients[96,116]. A questionnaire administered to 232 pregnant women with IPAA reported no difference in the rates of pouch-related complications or functional problems between vaginal birth and cesarean section[117]. The European Crohn's and Colitis Organization (ECCO) recommends cesarean section for patients with active perianal disease or active rectal involvement[114]. Furthermore, the presence of an ileo-anal pouch or ileo-rectal anastomosis is reported to be relative indications for cesarean section[114].

The delivery method should be decided through collaboration among the patient, obstetrician, gastroenterologist and colorectal surgeon.

CONCLUSION

Since active IBD can have negative effects on both the pregnant patient and the fetus, treatment should be performed in a conscious and energetic manner[118]. In the case of a planned pregnancy, disease remission should be maintained prior to conception. Most studies report increased rates of preterm, stillbirths, low birth weight and spontaneous abortions in pregnant patients with active disease during pregnancy[13,19]. For this reason, maintenance of disease remission is essential.

The drugs used to treat IBD are generally recognized as safe during both pregnancy and lactation, with the exception of methotrexate and thalidomide. Methotrexate and thalidomide should be discontinued in both men and women at least 3 mo prior to conception. Some clinicians tend to stop treatment during the first trimester. Moskovitz *et al*[30] evaluated 207 pregnancies and reported no significant difference in the effects of medication used during the first trimester *vs* any time during pregnancy on pregnancy outcomes. Although they are low risk, methotrexate and 6-MP should not be used in first pregnancies due to a possible risk of bone marrow suppression and pancreatitis. Cyclosporine can be used successfully during pregnancy but can cause preterm birth and low birth weight. As anti-TNF agents cross the placental barrier during the third trimester and might cause immunosuppression in newborns, the ECCO guidelines suggest discontinuing IFX and

adalimumab at 24-26 wk of gestation[114]. In cases in which discontinuing anti-TNF treatment can cause a disease flare-up, certolizumab can be used, as it has a low rate of transplacental transmission during the third trimester.

In the last decade, pregnancy outcomes in IBD patients who became pregnant during a remission period and maintained remission throughout pregnancy were reported to be normal. Patients should be informed of the importance of remission maintenance, and the risk to benefit ratio of continuing treatment during pregnancy should be discussed. The benefits of remission outweigh possible harm to the fetus caused by any potential drugs used.

Since malnutrition occurs more frequently in pregnant patients with IBD, nutritional supplements should be taken. Preventative measures for VTE should be implemented in hospitalized pregnant patients. Endoscopic retrograde cholangiopancreatography should be performed only if absolutely necessary. Surgical treatment indications are identical to those for non-pregnant patients with IBD but carry a high risk of fetal mortality. As previous surgical intervention can negatively affect fertility, laparoscopic methods should be used whenever possible.

The delivery method should be decided in collaboration with the patient. Vaginal birth is deemed safe in patients without perianal disease or severe active rectal involvement who have no complications.

The ECCO guidelines state that 5-ASA preparations, thiopurines, anti-TNF and corticosteroids carry a low risk for the infant[114]. When used during the third trimester, IFX can be transferred to the newborn through the placenta. Therefore, live vaccines are not advised during the first 6 mo after birth. IFX has not been detected in breast milk. However, IBD treatment planning in pregnant patients requires special attention, and decisions should be made on a case-by-case basis. Pregnant patients should be treated more aggressively than non-pregnant patients, as maintaining remission is crucial for pregnancy outcomes. The treatment method should be decided by consensus among the obstetrician, gastroenterologist and colorectal surgeon to reassure the patient.

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REFERENCES

1 **Binder V**. Epidemiology of IBD during the twentieth century: an integrated view. *Best Pract Res Clin Gastroenterol* 2004; **18**: 463-479 [PMID: 15157821 DOI: 10.1016/j.bpg.2003.12.002]

2 **Orholm M**, Fonager K, Sørensen HT. Risk of ulcerative colitis and Crohn's disease among offspring of patients with chronic inflammatory bowel disease. *Am J Gastroenterol* 1999; **94**: 3236-3238 [PMID: 10566721 DOI: 10.1111/j.1572-0241.1999.01526.x]

3 **Bennett RA**, Rubin PH, Present DH. Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease. *Gastroenterology* 1991; **100**: 1638-1643 [PMID: 2019369]

4 **Laharie D**, Debeugny S, Peeters M, Van Gossum A, Gower-Rousseau C, Bélaïche J, Fiasse R, Dupas JL, Lerebours E, Piotte S, Cortot A, Vermeire S, Grandbastien B, Colombel JF. Inflammatory bowel disease in spouses and their offspring. *Gastroenterology* 2001; **120**: 816-819 [PMID: 11231934 DOI: 10.1053/gast.2001.22574]

5 **Malgarinos G**, Gikas A, Delicha E, Stamataki A, Georgopoulos F, Papadimitriou A, Stanciu C, Triantafillidis JK. Pregnancy and inflammatory bowel disease: a prospective case-control study. *Rev Med Chir Soc Med Nat Iasi* 2007; **111**: 613-619 [PMID: 18293689]

6 **Ferguson CB**, Mahsud-Dornan S, Patterson RN. Inflammatory bowel disease in pregnancy. *BMJ* 2008; **337**: a427 [PMID: 18599468 DOI: 10.1136/bmj.39566.681458.BE]

7 **Khosla R**, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. *Gut* 1984; **25**: 52-56 [PMID: 6140209 DOI: 10.1136/gut.25.1.52]

8 **Mogadam M**, Dobbins WO, Korelitz BI, Ahmed SW. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. *Gastroenterology* 1981; **80**: 72-76 [PMID: 6108894]

9 **Miller JP**. Inflammatory bowel disease in pregnancy: a review. *J R Soc Med* 1986; **79**: 221-225 [PMID: 2871190]

10 **Mahadevan U**, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007; **133**: 1106-1112 [PMID: 17764676 DOI: 10.1053/j.gastro.2007.07.019]

11 **Hosseini-Carroll P**, Mutyala M, Seth A, Nageeb S, Soliman D, Boktor M, Sheth A, Chapman J, Morris J, Jordan P, Manas K, Becker F, Alexander JS. Pregnancy and inflammatory bowel diseases: Current perspectives, risks and patient management. *World J Gastrointest Pharmacol Ther* 2015; **6**: 156-171 [PMID: 26558150 DOI: 10.4292/wjgpt.v6.i4.156]

12 **Nielsen OH**, Andreasson B, Bondesen S, Jarnum S. Pregnancy in ulcerative colitis. *Scand J Gastroenterol* 1983; **18**: 735-742 [PMID: 6669937 DOI: 10.3109/00365528309182088]

13 **Cornish J**, Tan E, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007; **56**: 830-837 [PMID: 17185356 DOI: 10.1136/gut.2006.108324]

14 **Dominitz JA**, Young JC, Boyko EJ. Outcomes of infants born to mothers with inflammatory bowel disease: a population-based cohort study. *Am J Gastroenterol* 2002; **97**: 641-648 [PMID: 11926208 DOI: 10.1111/j.1572-0241.2002.05543.x]

15 **Nørgård B**, Puho E, Pedersen L, Czeizel AE, Sørensen HT. Risk of congenital abnormalities in children born to women with ulcerative colitis: a population-based, case-control study. *Am J Gastroenterol* 2003; **98**: 2006-2010 [PMID: 14499779 DOI: 10.1111/j.1572-0241.2003.07578.x]

16 **Bortoli A**, Saibeni S, Tatarella M, Prada A, Beretta L, Rivolta R, Politi P, Ravelli P, Imperiali G, Colombo E, Pera A, Daperno M, Carnovali M, de Franchis R, Vecchi M. Pregnancy before and after the diagnosis of inflammatory bowel diseases: retrospective case-control study. *J Gastroenterol Hepatol* 2007; **22**: 542-549 [PMID: 17376049 DOI: 10.1111/j.1440-1746.2006.04754.x]

17 **Moser MA**, Okun NB, Mayes DC, Bailey RJ. Crohn's disease, pregnancy, and birth weight. *Am J Gastroenterol* 2000; **95**: 1021-1026 [PMID: 10763954 DOI: 10.1111/j.1572-0241.2000.01852.x]

18 **Naganuma M**, Kunisaki R, Yoshimura N, Nagahori M, Yamamoto H, Kimura H, Sako M, Kawaguchi T, Takazoe M, Yamamoto S, Matsui T, Hibi T, Watanabe M. Conception and pregnancy outcome in women with inflammatory bowel disease: A multicentre study from Japan. *J Crohns Colitis* 2011; **5**: 317-323 [PMID: 21683301 DOI: 10.1016/j.crohns.2011.02.003]

19 **Nguyen GC**, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol* 2009; **7**:

329-334 [PMID: 19027089 DOI: 10.1016/j.cgh.2008.10.022]
20 **Morales M**, Berney T, Jenny A, Morel P, Extermann P. Crohn's disease as a risk factor for the outcome of pregnancy. *Hepatogastroenterology* 2000; **47**: 1595-1598 [PMID: 11149010]
21 **Bush MC**, Patel S, Lapinski RH, Stone JL. Perinatal outcomes in inflammatory bowel disease. *J Matern Fetal Neonatal Med* 2004; **15**: 237-241 [PMID: 15280131 DOI: 10.1080/14767050410001668662]
22 **Nørgård B**, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007; **102**: 1947-1954 [PMID: 17573787 DOI: 10.1111/j.1572-0241.2007.01355.x]
23 **Bortoli A**, Pedersen N, Duricova D, D'Inca R, Gionchetti P, Panelli MR, Ardizzone S, Sanroman AL, Gisbert JP, Arena I, Riegler G, Marrollo M, Valpiani D, Corbellini A, Segato S, Castiglione F, Munkholm P. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-2006. *Aliment Pharmacol Ther* 2011; **34**: 724-734 [PMID: 21815900 DOI: 10.1111/j.1365-2036.2011.04794.x]
24 **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [PMID: 21122489 DOI: 10.1016/j.crohns.2009.12.002]
25 **Rahimi R**, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod Toxicol* 2008; **25**: 271-275 [PMID: 18242053 DOI: 10.1016/j.reprotox.2007.11.010]
26 **Khan AK**, Truelove SC. Placental and mammary transfer of sulphasalazine. *Br Med J* 1979; **2**: 1553 [PMID: 43760 DOI: 10.1136/b mj.2.6204.1553]
27 **Branski D**, Kerem E, Gross-Kieselstein E, Hurvitz H, Litt R, Abrahamov A. Bloody diarrhea--a possible complication of sulfasalazine transferred through human breast milk. *J Pediatr Gastroenterol Nutr* 1986; **5**: 316-317 [PMID: 2870147 DOI: 10.1097/00005176-198605020-00028]
28 **Järnerot G**, Into-Malmberg MB, Esbjörner E. Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. *Scand J Gastroenterol* 1981; **16**: 693-697 [PMID: 6119765 DOI: 10.3109/00365528109182032]
29 **Nørgård B**, Fonager K, Pedersen L, Jacobsen BA, Sørensen HT. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003; **52**: 243-247 [PMID: 12524407 DOI: 10.1136/gut.52.2.243]
30 **Moskovitz DN**, Bodian C, Chapman ML, Marion JF, Rubin PH, Scherl E, Present DH. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. *Am J Gastroenterol* 2004; **99**: 656-661 [PMID: 15089898 DOI: 10.1111/j.1572-0241.2004.04140.x]
31 **Nørgård B**, Pedersen L, Christensen LA, Sørensen HT. Therapeutic drug use in women with Crohn's disease and birth outcomes: a Danish nationwide cohort study. *Am J Gastroenterol* 2007; **102**: 1406-1413 [PMID: 17437503 DOI: 10.1111/j.1572-0241.2007.01216.x]
32 **Habal FM**, Hui G, Greenberg GR. Oral 5-aminosalicylic acid for inflammatory bowel disease in pregnancy: safety and clinical course. *Gastroenterology* 1993; **105**: 1057-1060 [PMID: 8405849]
33 **Marteau P**, Tennenbaum R, Elefant E, Lémann M, Cosnes J. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. *Aliment Pharmacol Ther* 1998; **12**: 1101-1108 [PMID: 9845399 DOI: 10.1046/j.1365-2036.1998.00417.x]
34 **Trallori G**, d'Albasio G, Bardazzi G, Bonanomi AG, Amorosi A, Del Carlo P, Palli D, Galli M, Pacini F. 5-Aminosalicylic acid in pregnancy: clinical report. *Ital J Gastroenterol* 1994; **26**: 75-78 [PMID: 8032081]
35 **US Food and Drug Administration.** Asacol (mesalamine) delayed release tablets. May 2010
36 **Aparajita S**, Martin CF, Kane SV, Dubinsky M, Nguyen DD, McCabe RP, Rubin DT, Scherl EJ, Mahadevan U. Is Asacol use associated with congenital anomalies? Results from a nationwide prospective pregnancy registry. *Gastroenterology* 2013; **5**: S-379 [DOI: 10.1016/S0016-5085(13)61398-0]
37 **Habal FM**, Huang VW. Review article: a decision-making algorithm for the management of pregnancy in the inflammatory bowel disease patient. *Aliment Pharmacol Ther* 2012; **35**: 501-515 [PMID: 22221203 DOI: 10.1111/j.1365-2036.2011.04967.x]
38 **Carmichael SL**, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999; **86**: 242-244 [PMID: 10482873 DOI: 10.1002/(SICI)1096-8628(19990917)86:3<242: : AID-AJMG9>3.0.CO; 2-U]
39 **Tegethoff M**, Pryce C, Meinlschmidt G. Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review. *Endocr Rev* 2009; **30**: 753-789 [PMID: 19837868 DOI: 10.1210/er.2008-0014]
40 **Beaulieu DB**, Ananthakrishnan AN, Issa M, Rosenbaum L, Skaros S, Newcomer JR, Kuhlmann RS, Otterson MF, Emmons J, Knox J, Binion DG. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. *Inflamm Bowel Dis* 2009; **15**: 25-28 [PMID: 18680195 DOI: 10.1002/ibd.20640]
41 **Källén B**, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 1999; **93**: 392-395 [PMID: 10074986 DOI: 10.1097/00006250-199903000-00016]
42 **Norjavaara E**, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. *J Allergy Clin Immunol* 2003; **111**: 736-742 [PMID: 12704351 DOI: 10.1067/mai.2003.1340]
43 **McKenzie SA**, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. *Arch Dis Child* 1975; **50**: 894-896 [PMID: 1211963 DOI: 10.1136/adc.50.11.894]
44 **Ng SW**, Mahadevan U. Management of inflammatory bowel disease in pregnancy. *Expert Rev Clin Immunol* 2013; **9**: 161-173; quiz 174 [PMID: 23390947 DOI: 10.1586/eci.12.103]
45 **Polifka JE**, Friedman JM. Teratogen update: azathioprine and 6-mercaptopurine. *Teratology* 2002; **65**: 240-261 [PMID: 11967923 DOI: 10.1097/00007890-200104270-00006]
46 **Nielsen OH**, Bjerrum JT, Herfarth H, Rogler G. Recent advances using immunomodulators for inflammatory bowel disease. *J Clin Pharmacol* 2013; **53**: 575-588 [PMID: 23408468 DOI: 10.1002/jcph.2]
47 **Jharap B**, de Boer NK, Stokkers P, Hommes DW, Oldenburg B, Dijkstra G, van der Woude CJ, de Jong DJ, Mulder CJ, van Elburg RM, van Bodegraven AA. Intrauterine exposure and pharmacology of conventional thiopurine therapy in pregnant patients with inflammatory bowel disease. *Gut* 2014; **63**: 451-457 [PMID: 23424097 DOI: 10.1136/gutjnl-2012-303615]
48 **Nørgård B**, Pedersen L, Fonager K, Rasmussen SN, Sørensen HT. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. *Aliment Pharmacol Ther* 2003; **17**: 827-834 [PMID: 12641505 DOI: 10.1046/j.1365-2036.2003.01537.x]
49 **Cleary BJ**, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res A Clin Mol Teratol* 2009; **85**: 647-654 [PMID: 19343728 DOI: 10.1002/bdra.20583]
50 **McConnell RA**, Mahadevan U. Use of Immunomodulators and Biologics Before, During, and After Pregnancy. *Inflamm Bowel Dis* 2016; **22**: 213-223 [PMID: 26444103 DOI: 10.1097/MIB.0000000000000596]
51 **Bröms G**, Granath F, Linder M, Stephansson O, Elmberg M, Kieler H. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. *Inflamm Bowel Dis* 2014; **20**: 1091-1098 [PMID: 24810137 DOI: 10.1097/MIB.0000000000000060]
52 **Goldstein LH**, Dolinsky G, Greenberg R, Schaefer C, Cohen-Kerem R, Diav-Citrin O, Malm H, Reuvers-Lodewijks ME, Rost

van Tonningen-van Driel MM, Arnon J, Ornoy A, Clementi M, Di Gianantonio E, Koren G, Braunstein R, Berkovitch M. Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res A Clin Mol Teratol* 2007; **79**: 696-701 [PMID: 17847119 DOI: 10.1002/bdra.20399]

53 **Ban L**, Tata LJ, Fiaschi L, Card T. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. *Gastroenterology* 2014; **146**: 76-84 [PMID: 24126096 DOI: 10.1053/j.gastro.2013.09.061]

54 **Beaugerie L**, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, Hébuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadié M, Hermine O, Faivre J, Carrat F. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009; **374**: 1617-1625 [PMID: 19837455 DOI: 10.1016/S0140-6736(09)61302-7]

55 **Coelho J**, Beaugerie L, Colombel JF, Hébuterne X, Lerebours E, Lémann M, Baumer P, Cosnes J, Bourreille A, Gendre JP, Seksik P, Blain A, Metman EH, Nisard A, Cadiot G, Veyrac M, Coffin B, Dray X, Carrat F, Marteau P. Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study. *Gut* 2011; **60**: 198-203 [PMID: 21115547 DOI: 10.1136/gut.2010]

56 **Akbari M**, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 15-22 [PMID: 22434610 DOI: 10.1002/ibd.22948]

57 **Casanova MJ**, Chaparro M, Domènech E, Barreiro-de Acosta M, Bermejo F, Iglesias E, Gomollón F, Rodrigo L, Calvet X, Esteve M, García-Planella E, García-López S, Taxonera C, Calvo M, López M, Ginard D, Gómez-García M, Garrido E, Pérez-Calle JL, Beltrán B, Piqueras M, Saro C, Botella B, Dueñas C, Ponferrada A, Mañosa M, García-Sánchez V, Maté J, Gisbert JP. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013; **108**: 433-440 [PMID: 23318480 DOI: 10.1038/ajg.2012.430]

58 **Mahadevan U**, Martin CF, Sandler RS, Kane SV, Dubinsky M, Lewis JD, Sands B E. 865 PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. *Gastroenterology* 2012; **142**: 149

59 **Lin K**, Martin CF, Chambers C, Kane SV, Dubinsky M, Sandborn W, Sands BE. Achievement of developmental milestones among offspring of women with inflammatory bowel disease: the PIANO registry. *Gastroenterology* 2014; **5**: S-1 [DOI: 10.1016/S0016-5085(14)60002-0]

60 **de Meij TG**, Jharap B, Kneepkens CM, van Bodegraven AA, de Boer NK. Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **38**: 38-43 [PMID: 23675854 DOI: 10.1111/apt.12334]

61 **Ng SW**, Mahadevan U. My treatment approach to management of the pregnant patient with inflammatory bowel disease. *Mayo Clin Proc* 2014; **89**: 355-360 [PMID: 24582194 DOI: 10.1016/j.mayocp.2013.11.012]

62 **Christensen LA**, Dahlerup JF, Nielsen MJ, Fallingborg JF, Schmiegelow K. Azathioprine treatment during lactation. *Aliment Pharmacol Ther* 2008; **28**: 1209-1213 [PMID: 18761704 DOI: 10.1111/j.1365-2036.2008.03843.x]

63 **Gardiner SJ**, Gearry RB, Roberts RL, Zhang M, Barclay ML, Begg EJ. Exposure to thiopurine drugs through breast milk is low based on metabolite concentrations in mother-infant pairs. *Br J Clin Pharmacol* 2006; **62**: 453-456 [PMID: 16995866 DOI: 10.1111/j.1365-2125.2006.02639.x]

64 **Angelberger S**, Reinisch W, Messerschmidt A, Miehsler W, Novacek G, Vogelsang H, Dejaco C. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. *J Crohns Colitis* 2011; **5**: 95-100 [PMID: 21453877 DOI: 10.1016/j.crohns.2010.10.005]

65 **Milunsky A**, Graef JW, Gaynor MF. Methotrexate-induced congenital malformations. *J Pediatr* 1968; **72**: 790-795 [PMID: 5652604]

66 **Briggs GG**, Wan SR. Drug therapy during labor and delivery, part 1. *Am J Health Syst Pharm* 2006; **63**: 1038-1047 [PMID: 16709890]

67 **Del Campo M**, Kosaki K, Bennett FC, Jones KL. Developmental delay in fetal aminopterin/methotrexate syndrome. *Teratology* 1999; **60**: 10-12 [PMID: 10413333]

68 **Gisbert JP**. Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. *Inflamm Bowel Dis* 2010; **16**: 881-895 [PMID: 19885906 DOI: 10.1002/ibd.21154]

69 **Nielsen OH**, Maxwell C, Hendel J. IBD medications during pregnancy and lactation. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 116-127 [PMID: 23897285 DOI: 10.1038/nrgastro.2013.135]

70 **Johns DG**, Rutherford LD, Leighton PC, Vogel CL. Secretion of methotrexate into human milk. *Am J Obstet Gynecol* 1972; **112**: 978-980 [PMID: 5042796]

71 **van der Aa EM**, Peereboom-Stegeman JH, Noordhoek J, Gribnau FW, Russel FG. Mechanisms of drug transfer across the human placenta. *Pharm World Sci* 1998; **20**: 139-148 [PMID: 9762726]

72 **Paziana K**, Del Monaco M, Cardonick E, Moritz M, Keller M, Smith B, Coscia L, Armenti V. Ciclosporin use during pregnancy. *Drug Saf* 2013; **36**: 279-294 [PMID: 23516008 DOI: 10.1007/s40264-013-0034-x]

73 **Bar Oz B**, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation* 2001; **71**: 1051-1055 [PMID: 11374400]

74 **Branche J**, Cortot A, Bourreille A, Coffin B, de Vos M, de Saussure P, Seksik P, Marteau P, Lemann M, Colombel JF. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. *Inflamm Bowel Dis* 2009; **15**: 1044-1048 [PMID: 19137604 DOI: 10.1002/ibd.20858]

75 **Ecevit Ç**, Ünal F, Baran M, Aydoğdu S. Parenthood in pediatric liver transplant patients. *Pediatr Transplant* 2012; **16**: 346-349 [PMID: 22404458 DOI: 10.1111/j.1399-3046.2012.01671.x]

76 **Baumgart DC**, Sturm A, Wiedenmann B, Dignass AU. Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. *Gut* 2005; **54**: 1822-1823 [PMID: 16120758 DOI: 10.1136/gut.2005.078972]

77 **O'Donnell S**, O'Morain C. Review article: use of antitumour necrosis factor therapy in inflammatory bowel disease during pregnancy and conception. *Aliment Pharmacol Ther* 2008; **27**: 885-894 [PMID: 18284649 DOI: 10.1111/j.1365-2036.2008.03648.x]

78 **Mahadevan U**, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, Sandborn WJ, Colombel JF. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 2011; **106**: 214-223; quiz 224 [PMID: 21157441 DOI: 10.1038/ajg.2010.464]

79 **Mahadevan U**, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, Ullman T, Glover S, Valentine JF, Rubin DT, Miller J, Abreu MT. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013; **11**: 286-292; quiz e24 [PMID: 23200982 DOI: 10.1016/j.cgh.2012.11.011]

80 **Katz JA**, Lichtenstein GR, Keenan GF, Healy D, Jacobs SJ. Outcome of pregnancy in women receiving REMICADE® (Infliximab) for the treatment of Crohn's disease or rheumatoid arthritis. *Gastroenterology* 2001; **120**: A69 [DOI: 10.1016/S0016-5085(08)80343-5]

81 **Friedman S**, Regueiro MD. Pregnancy and nursing in inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 265-273, xii [PMID: 12122737 DOI: 10.1016/S0889-8553(01)00015-2]

82 **Srinivasan R**. Infliximab treatment and pregnancy outcome in active Crohn's disease. *Am J Gastroenterol* 2001; **96**: 2274-2275 [PMID: 11467677 DOI: 10.1111/j.1572-0241.2001.03987.x]

83 **Lichtenstein GR**, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and

mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; **4**: 621-630 [PMID: 16678077 DOI: 10.1016/j.cgh.2006.03.002]

84 **Katz JA**, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004; **99**: 2385-2392 [PMID: 15571587 DOI: 10.1111/j.1572-0241.2004.30186.x]

85 **Dubinsky M**, Abraham B, Mahadevan U. Management of the pregnant IBD patient. *Inflamm Bowel Dis* 2008; **14**: 1736-1750 [PMID: 18626967 DOI: 10.1002/ibd.20532]

86 **Ben-Horin S**, Yavzori M, Kopylov U, Picard O, Fudim E, Eliakim R, Chowers Y, Lang A. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis* 2011; **5**: 555-558 [PMID: 22115374 DOI: 10.1016/j.crohns.2011.05.006]

87 **Vasiliauskas EA**, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. *Clin Gastroenterol Hepatol* 2006; **4**: 1255-1258 [PMID: 17045211 DOI: 10.1016/j.cgh.2006.07.018]

88 **Zelinkova Z**, van der Ent C, Bruin KF, van Baalen O, Vermeulen HG, Smalbraak HJ, Ouwendijk RJ, Hoek AC, van der Werf SD, Kuipers EJ, van der Woude CJ. Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. *Clin Gastroenterol Hepatol* 2013; **11**: 318-321 [PMID: 23103819 DOI: 10.1016/j.cgh.2012.10.024]

89 **Osting VC**, Carter JD. A safety assessment of tumor necrosis factor antagonists during pregnancy. *Expert Opin Drug Saf* 2010; **9**: 421-429 [PMID: 20367495 DOI: 10.1517/14740330903578639]

90 **Wolf D**, Mahadevan U. Certolizumab pegol use in pregnancy: low levels detected in cord blood. *Arthritis Rheu* 2010; **62**: 718 [DOI: 10.1002/art.28486]

91 **Mahadevan U**, Nazareth M, Cristiano L, Kooijmans M, Hogge G. Natalizumab use during pregnancy. *Am J Gastroenterol* 2008; **103**: S449-S450 [DOI: 10.1111/j.1572-0241.2008.02139_9.x]

92 **Lau AG**, Clark M, Harrison DD, Geldho A, Nissinen R, Sanders M. Pregnancy outcomes in women exposed to golimumab. *Arthritis Rheum* 2013; **65**: S870-S871 [DOI: 10.1002/art.38216]

93 **Lewis JH**, Weingold AB. The use of gastrointestinal drugs during pregnancy and lactation. *Am J Gastroenterol* 1985; **80**: 912-923 [PMID: 2864852]

94 **Briggs GG**, Freeman R K, Yaffe S J. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. USA: Lippincott Williams & Wilkins, 2012

95 **Acs N**, Bánhidy F, Puhó EH, Czeizel AE. No association between severe constipation with related drug treatment in pregnant women and congenital abnormalities in their offspring: A population-based case-control study. *Congenit Anom* (Kyoto) 2010; **50**: 15-20 [PMID: 20201964 DOI: 10.1111/j.1741-4520.2009.00252.x]

96 **Tilson RS**, Friedman S. Inflammatory Bowel Disease During Pregnancy. *Curr Treat Options Gastroenterol* 2003; **6**: 227-236 [PMID: 12744822 DOI: 10.1007/s11938-003-0004-y]

97 **Nguyen GC**, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008; **103**: 2272-2280 [PMID: 18684186 DOI: 10.1111/j.1572-0241.2008.02052.x]

98 **Pomp ER**, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost* 2008; **6**: 632-637 [PMID: 18248600 DOI: 10.1111/j.1538-7836.2008.02921.x]

99 **Bröms G**, Granath F, Linder M, Stephansson O, Elmberg M, Kieler H. Complications from inflammatory bowel disease during pregnancy and delivery. *Clin Gastroenterol Hepatol* 2012; **10**: 1246-1252 [PMID: 22922307 DOI: 10.1016/j.cgh.2012.08.018]

100 **Leung YP**, Kaplan GG, Coward S, Tanyingoh D, Kaplan BJ, Johnston DW, Barkema HW, Ghosh S, Panaccione R, Seow CH. Intrapartum corticosteroid use significantly increases the risk of gestational diabetes in women with inflammatory bowel disease. *J Crohns Colitis* 2015; **9**: 223-230 [PMID: 25576754 DOI: 10.1093/ecco-jcc/jjv006]

101 **Zachos M**, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2001; **(3)**: CD000542 [PMID: 11686966 DOI: 10.1002/14651858.cd000542.pub2]

102 **Habal FM**, Ravindran NC. Management of inflammatory bowel disease in the pregnant patient. *World J Gastroenterol* 2008; **14**: 1326-1332 [PMID: 18322943 DOI: 10.3748/wjg.14.1326]

103 **Rossi E,** Costa M. Fish oil derivatives as a prophylaxis of recurrent miscarriage associated with antiphospholipid antibodies (APL): a pilot study. *Lupus* 1993; **2**: 319-323 [PMID: 8305926 DOI: 10.1177/096120339300200508]

104 **Cappell MS**, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. *Dig Dis Sci* 1996; **41**: 2353-2361 [PMID: 9011442 DOI: 10.1007/BF02100127]

105 **Ferrero S**, Ragni N. Inflammatory bowel disease: management issues during pregnancy. *Arch Gynecol Obstet* 2004; **270**: 79-85 [PMID: 12721680 DOI: 10.1007/s00404-003-0489-6]

106 **Visser BC**, Glasgow RE, Mulvihill KK, Mulvihill SJ. Safety and timing of nonobstetric abdominal surgery in pregnancy. *Dig Surg* 2001; **18**: 409-417 [PMID: 11721118 DOI: 10.1159/000050183]

107 **Hill J**, Clark A, Scott NA. Surgical treatment of acute manifestations of Crohn's disease during pregnancy. *J R Soc Med* 1997; **90**: 64-66 [PMID: 9068432 DOI: 10.1177/014107689709000203]

108 **Watson WJ**, Gaines TE. Third-trimester colectomy for severe ulcerative colitis. A case report. *J Reprod Med* 1987; **32**: 869-872 [PMID: 3430496]

109 **Bohe MG**, Ekelund GR, Genell SN, Gennser GM, Jiborn HA, Leandoer LJ, Klaus GL, Svanberg LK. Surgery for fulminating colitis during pregnancy. *Dis Colon Rectum* 1983; **26**: 119-122 [DOI: 10.1007/BF02562590]

110 **Boulton R**, Hamilton M, Lewis A, Walker P, Pounder R. Fulminant ulcerative colitis in pregnancy. *Am J Gastroenterol* 1994; **89**: 931-933 [PMID: 8198108]

111 **Kornfeld D**, Cnattingius S, Ekbom A. Pregnancy outcomes in women with inflammatory bowel disease--a population-based cohort study. *Am J Obstet Gynecol* 1997; **177**: 942-946 [PMID: 9369849 DOI: 10.1016/S0002-9378(97)70298-9]

112 **Ilnyckyji A**, Blanchard JF, Rawsthorne P, Bernstein CN. Perianal Crohn's disease and pregnancy: role of the mode of delivery. *Am J Gastroenterol* 1999; **94**: 3274-3278 [PMID: 10566729 DOI: 10.1111/j.1572-0241.1999.01537.x]

113 **Beniada A**, Benoist G, Maurel J, Dreyfus M. [Inflammatory bowel disease and pregnancy: report of 76 cases and review of the literature]. *J Gynecol Obstet Biol Reprod* (Paris) 2005; **34**: 581-588 [PMID: 16208201]

114 **van der Woude CJ**, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, Kolacek S, Juillerat P, Mulders AG, Pedersen N, Selinger C, Sebastian S, Sturm A, Zelinkova Z, Magro F. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2015; **9**: 107-124 [PMID: 25602023 DOI: 10.1093/ecco-jcc/jju006]

115 **Brandt LJ**, Estabrook SG, Reinus JF. Results of a survey to evaluate whether vaginal delivery and episiotomy lead to perineal involvement in women with Crohn's disease. *Am J Gastroenterol* 1995; **90**: 1918-1922 [PMID: 7484992 DOI: 10.1097/00006254-199606000-00006]

116 **Biedermann L**, Rogler G, Vavricka SR, Seibold F, Seirafi M. Pregnancy and breastfeeding in inflammatory bowel disease. *Digestion* 2012; **86** Suppl 1: 45-54 [PMID: 23051726 DOI: 10.1159/000341941]

117 **Hahnloser D**, Pemberton JH, Wolff BG, Larson D, Harrington J, Farouk R, Dozois RR. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: immediate and long-term consequences and outcomes. *Dis Colon Rectum* 2004; **47**: 1127-1135 [PMID: 15164253 DOI: 10.1007/s10350-004-0569-0]

118 **Mountifield RE**, Prosser R, Bampton P, Muller K, Andrews JM. Pregnancy and IBD treatment: this challenging interplay from a patients' perspective. *J Crohns Colitis* 2010; **4**: 176-182 [PMID: 21122502 DOI: 10.1016/j.crohns.2009.10.001]

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