**TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF ULCERATIVE COLITIS**
*TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN ÜLSERATİF KOLİT İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ*

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# Safety of drugs used in cases with ulcerative colitis during pregnancy and lactation

*Ülseratif kolitli hastalarda gebelik ve laktasyonda kullanılan ilaçların güvenilirliği*

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## INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic inflammatory processes that show a peak incidence in the childbearing ages (between ages 15-25). There are studies about ulcerative colitis (UC) reporting that the risks of pregnancy complications increase in patients with active disease during conception or during their pregnancy. Therefore, control of the disease activity during pregnancy is of utmost importance (1,3). Safe medical treatment both during pregnancy and lactation in cases with UC is an important issue concerning the mother, baby and doctor in charge. On the other hand, performing randomized controlled studies in pregnant patients is a constraint due to ethical issues. Nevertheless, the safety of the drugs used during pregnancy and lactation has been classified by the US Food and Drug Administration (FDA) (Table 1) (4).

In the guidelines published by ECCO (European Crohn's and Colitis Organisation) in 2008 for UC, there were no recommendations about "Pregnancy and Lactation", which should be under the topic of special situations, and it was stated that these recommendations would be published later (5).

In this study, we aimed to investigate the safety of IBD treatments used for UC in the pregnancy or lactation period in patients with UC.

## MATERIALS AND METHODS

We used the 3e systematic literature review method to determine answers to the questions "Which drug provides the least "odds ratio" (OR) value for gestational complications (abortion, *in utero* exitus, premature delivery, low birth weight (LBW), development of congenital malformations) with treatment for UC in pregnant patients?" and "Which drug provides the least OR value for side effects to infants of childbearing patients with ulcerative colitis?".

A systematic literature review was performed only through the PubMed database. Literature references were also reviewed in order to reach other studies. As key words, (Ulcerative colitis and pregnancy) or (Ulcerative colitis and lactation) were used, and only English literature was reviewed. For statistical analysis, we aimed to determine the hazard ratio (HR) values of the IBD drugs for gestational complications when used in pregnancy and for side effects to infants in lactation.

## RESULTS

Five studies related to the "Safety of drugs used for treatment of UC during pregnancy and lactation" were achieved as a result of the 3e systematic search. Determination of OR values of gestational complications and side effects to infants of childbearing patients with these drugs in patients with UC was targeted while evaluating the studies. The types of these five studies are stated in Table 2.

### A- Safety of drugs used in cases with ulcerative colitis during pregnancy

#### 1) Aminosalicylates

5-Aminosalicylic acid (ASA) compounds (mesalamine, olsalazine and balsalazide) are standard

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**Table 1.** Safety of IBD drugs in pregnancy and FDA rating

| Safe to use in pregnancy | Likely safe | Unlikely to be safe | Contraindicated |
|---|---|---|---|
| Oral 5-ASA (B) | Azathioprine (D) | Tacrolimus (C) | MTX (X) |
| Topical 5-ASA (B) | 6-Mercaptopurine (D) | | |
| Sulfasalazine (B) | Metronidazole (B) | | |
| Corticosteroids (C) | Fluoroquinolones (C) | | |
| | Infliximab (B) | | |
| | Adalimumab (B) | | |
| | Cyclosporine (C) | | |

5-ASA: 5-Aminosalicylic acid. MTX: Methotrexate.

drugs usually used in IBD as a first-step treatment. According to the FDA, they are category B drugs, except for olsalazine (category C). Both 5-ASA and its active metabolite N-acetyl 5-ASA can cross the placenta (6). However, studies in both animals and humans have not demonstrated any teratogenicity. Sulfasalazine is a sulfapyridine with an azo link to 5-ASA. Case reports about sulfasalazine have reported cardiovascular, genitourinary and neurologic defects (7). However, in a large scale series conducted among 181 pregnant women, there was no increase in the risk of having a baby with congenital anomaly (8). On the other hand, due to the potential anti-folate effect of sulfasalazine, ingestion of 2 mg folate in the prenatal period and during pregnancy is recommended (9).

Two prospective controlled studies have shown that mesalamine use during pregnancy does not have a teratogenic effect, even in the first trimester (10,11). In the larger scale study among these two, 165 cases with IBD who had used 5-ASA during pregnancy were investigated, and no increase in having a baby with major malformation was found when compared to the population in general. On the other hand, an increased risk was established in preterm labor (13% vs 5%) and LBW (3.2 vs. 3.4 kg) (10). However, in that study, the control cases did not have IBD; therefore, it could be debated whether this effect was due to IBD instead of 5-ASA.

The result of our systematic literature review showed that in a meta-analysis comprising seven different studies published between 1980-2007, no increase was found in pregnant patients using 5-ASA for the risks of complications such as congenital anomaly (odds ratio [OR]: 1.16, 95% confidence interval [CI]: 0.76-1.77, p=0.9), preterm labor (OR: 1.35, 95%CI: 0.85-2.13, p=0.07), LBW (OR: 0.93, 95%CI: 0.46-1.85, p=0.7), spontaneous abortion (OR: 1.14, 95%CI: 0.65-2.01, p=0.2), and stillbirth (OR: 2.38, 95%CI: 0.65-8.72, p=0.9) (12).

**Table 2.** The types of studies analyzed

| Types of the Study | Number of the studies |
|---|---|
| Retrospective cohort | 2 |
| Population-based cohort study | 1 |
| Meta-analysis | 1 |

Although data about topical use are scant, in 19 pregnants, 5-ASA suppository or enema was used, and all of them completed their pregnancy without any complications and gave birth to healthy children (13).

### 2) Corticosteroids

Corticosteroids (CS) are in category C. CS can cross the placenta and pass into breast-milk in different doses depending on the CS subgroup (14). A very strong relationship between CS exposure in the first trimester and the development of cleft lip/palate has been established in animal studies. Although many hypotheses regarding the relationship between various fetal malformations and first trimester exposure to CS have been launched, no constant malformations except for cleft lip and cleft palate have been established (15,16). In three small scale controlled cohort studies, an increased risk of cleft lip/palate was established in newborns exposed to CS in the first trimester. However, as this complication is relatively rare and is not life-threatening, many authors accept that the possible benefits they may bring to the mother outweigh the potential risks to the fetus. Also, in a prospective controlled study with 311 cases, no increase in the risk for major anomalies was found in women who had used glucocorticoids in the first trimester, and there were also no cases of cleft lip or cleft palate (16). The possible relationships between exposure to CS and premature membrane rupture, preterm labor risk, and adrenal insufficiency in the newborn have been mentioned in stu-

dies regarding organ transplantation (17). In the meta-analysis of IBD literature, no increases were found in the risks for stillbirth, premature labor, LBW, and spontaneous abortion due to CS use. Relative risk values for gestational complications of other drugs in comparison with 5-ASA are shown in Table 3 (18).

The effect of budesonide upon the fetus has not been thoroughly investigated in IBD literature. However, in a large scale (2968 pregnants) retrospective cohort study performed among women who had used budesonide inhalation during their pregnancies because of allergy or asthma, no increase was established in the risks for LBW, preterm labor, stillbirth, or fetal malformation (19). In a series comprising 8 CD (Crohn's disease) cases of IBD, no relationship was found between budesonide and pregnancy complications (20).

Our systematic literature review revealed a meta-analysis by Park-Wyllie et al. (21) that evaluated the studies between 1962-2000 in which CS were used in pregnants, including those with IBD, and no increased risk of having a newborn with congenital malformation due to CS use could be established [OR (95%CI): 1.45 (0.81-2.6)].

**3) Thiopurines**

Azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) are drugs of FDA category D. These are purine analogues that interact with adenine and guanine ribonucleosides, which are important in the synthesis of DNA and RNA. These drugs are effective upon T lymphocytes and other rapidly dividing cells (22). AZA and its metabolites can pass from the mother to the fetus transplacentally and transamniotically, and the oral bioavailability of AZA (47%) and 6-MP (16%) is low. The enzyme that converts AZA to 6-MP, inosinate pyrophosphorylase, is absent in the early fetal liver; therefore, the toxic effect of AZA to the fetus is quite low in this most important period of organogenesis (23).

The strongest evidences regarding the safety of AZA come from transplantation studies. In these studies, congenital anomaly rates were between 0.0%-11.8%, and congenital anomalies that showed a recurrent pattern were not established (24). In a large scale study comparing 189 cases using AZA with 230 cases that did not use any teratogenic drugs during their pregnancy, there was no difference between groups regarding the development of congenital anomalies (OR (95% CI): 1.17 (0.37-3.69), p=0.7) (25).

During our systematic literature review, we evaluated the data of the cohort study among IBD cases using thiopurines, performed by the French CESAME Pregnancy Working Group. In that study, 55 cases treated with thiopurine during pregnancy, 56 cases treated with other drugs and 27 cases receiving no treatment were compared. No increased risk was established regarding LBW, congenital malformations and preterm delivery in both thiopurine users and those treated with other drugs (26). Further, Norgard et al. (27) compared cases treated with AZA or 6-MP during pregnancy with a control group in a population-based cohort study, following readjustments for mother age, smoking status and parity number, and no significant increase was found in the risks for preterm labor (OR: 2.8, 95%CI: 0.4-19.4), perinatal mortality (OR: 3.2, 95%CI: 0.2-56.4), LBW (OR: 2.3, 95%CI: 0.4-13.6), or congenital malformations (OR: 7.7, 95%CI: 0.6-102.1).

Table-4 shows effect of 5-ASA, AZA and CS on pregnancy outcomes.

**4) Cyclosporine**

Cyclosporine is a FDA category C drug. It is used in bone marrow, liver and kidney transplantations and rheumatic diseases. Cyclosporine is an effective alternative to colectomy in serious UC cases. Colectomy in the third trimester of pregnancy has serious morbidity and mortality rates. Therefore, the use of cyclosporine during pregnancy becomes more important (28).

**Table 3.** Relative risk values for gestational complications of other drugs in comparison with 5-ASA

| | AZA | CS | Anti-TNF-α |
|---|---|---|---|
| SA (RR-95%CI, p value) | 1.03 (0.141-7.629), 0.9 | 0.6 (0.146-2.697), 0.5 | 4.8 (2.319-10.108), <0.0001 |
| Stillbirth (RR-95%CI, p value) | 1.8 (0.098-32.905), 0.6 | 1.2 (0.141-11.144), 0.8 | 0.7 (0.042-14.286), 0.8 |
| LBW (RR-95%CI, p value) | 4.1 (0.475-36.285), 0.1 | 5.0 (1.272-19.827), p=0.02 | 1.7 (0.199-15.584), 0.6 |
| Preterm delivery (RR-95%CI, p value) | 11.8 (3.945-35.697), <0.0001 | 2.1 (0.564-8.215), 0.2 | 3.0 (0.794-11.468), 0.1 |
| CA (RR-95%CI, p value) | 3.3 (0.753-14.648), 0.1 | 7.0 (3.194-15.483), <0.0001 | 1.4 (0.313-6.328), 0.6 |

SA: Spontan Abortus, RR: Relative risk, LBW: Low Birth Weight, CA: Congenital abnormality, AZA: Azathiopurine, CS: Corticosteroids.

**Table 4.** Effect of drugs for inflammatory bowel disease on pregnancy outcomes

| Complication | 5-ASA | CS | AZA |
|---|---|---|---|
| CA (OR, p value) | 1.1 (0.9) | 2.4 (0.5) | 0.9 (0.9) |
| Stillbirth (OR, p value) | 2.3 (0.9) | 2.4 (0.5) | - |
| SA (OR, p value) | 1.1 (0.2) | 1.2 (0.8) | - |
| Preterm delivery (OR, p value) | 1.3 (0.07) | 4.8 (0.1) | 1.6 (0.4) |
| LBW (OR, p value) | 0.93 (0.7) | 2.4 (0.5) | 2.1 (0.3) |

5-ASA: 5-Aminosalicylic acid. CS: Corticosteroids. AZA: Azatiopurine. CA: Congenital abnormality. SA: Spontaneous abortion. LBW: Low birth weight.

Many of the human data come from organ transplantation studies. In a meta-analysis comprising 15 small scale studies, in which a total of 410 pregnants were investigated regarding the use of cyclosporine in pregnancy, no significant increase was found in the risk for fetal malformations (OR: 3.83, 95%CI: 0.75–19.6) (29). Although most of the data from gynecology and obstetric literature are favorable, small increases in preterm labor rates and pregnancy wastage rates have been reported (30). Another aspect about the use of cyclosporine during pregnancy is its toxic effects upon the bone marrow, kidneys and liver. However, interestingly enough, many studies have shown that cyclosporine exposure does not affect the fetal bone marrow, liver or kidneys (31).

In our systematic literature review, we analyzed a retrospective study regarding the safety of cyclosporine use during pregnancy. GETAID (Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif) collected the data of pregnant UC patients who had been treated with cyclosporine between 2001 and 2007, from 35 different centers, and in total 8 cases were reported. All cases received 7 days intravenous (IV) steroid therapy, following an approximately 14-day oral steroid trial. Cyclosporine was given for 7 days IV, with a starting dose of 2 mg/kg in 7 patients and of 4 mg/kg in 1 patient. In 1 case refractory to 17 days IV cyclosporine, a clinical improvement was achieved with infliximab, and in 2 cases, treatment was switched to oral cyclosporine and AZT was added to the treatment. In 1 out of the 8 cases, fetal demise occurred at 22 weeks of pregnancy. There was no maternal side effect or any fetal malformation in the other 7 cases (32).

**5) Tacrolimus**

Tacrolimus is another fungus-derived calcineurin inhibitor used in organ transplantation for immunosuppression. It is FDA pregnancy category C. Tacrolimus is still used in an experimental level in the treatment of UC, and is not used off-label (33). The first experiences with this drug's use in pregnancy were reported in 1977. Twenty-seven patients who had used tacrolimus during pregnancy were reported. Two fetuses were lost in the 23$^{rd}$ and 24$^{th}$ weeks, and the mean gestational period was reported as 36.6 weeks. Transient perinatal hyperkalemia was reported at a rate of 36%. Unilateral polycystic renal disease was established in one newborn (34). In another study reported later from Germany, 100 transplant recipient pregnants were followed from 1992-1998. The live birth rate was 68%, and spontaneous abortion rate was 12%. The stillbirth rate was reported as 3%, whereas premature labor was 59%. Inconsistent malformations were reported in 4 of the newborns (35). In a unicenter study investigating 37 women receiving tacrolimus treatment, among 49 pregnancies, 2 resulted in premature labor. One newborn was lost due to Alagille syndrome, while the rest of the newborns lived with no diagnosed congenital anomaly. Birth weights were registered in 78% of the infants (36). In the literature, in a 31-year-old refractory case of UC who refused surgical treatment, oral tacrolimus was tried (beginning at a dose of 0.1 mg/kg, and adjusted to obtain a serum level of 4-6 ng/ml) during her second pregnancy, and this case gave birth to a healthy child (40 wks, 3500 g, 51 cm) (37).

**6) Antibiotics**

Metronidazole is used primarily in protozoal and anaerobic infections, and it is FDA category B. Its use in IBD is usually for pouchitis and abscess treatment. In animal studies, exposure to metronidazole was related to a possible development of breast, pulmonary and hepatic tumors. Human studies have shown rare occasions of cleft lip and cleft palate (38,39). In a large scale, prospective cohort study, comparing 250 women exposed to metronidazole in the first trimester with a control group of 608 women similar in age, there was no difference between groups regarding the pregnancy data, major birth defects, and birth weights (40). In a

meta-analysis, in which Caro-Paton et al. (41) evaluated five epidemiological studies, dated 1997, no relationship was found between metronidazole use and birth defects. In a population-based case-control study, the risk of teratogenicity was reported to be low for metronidazole, in all pregnancy stages, but an increase was reported in the rates of cleft lip and/or cleft palate when used in the second or third trimester. However, it was emphasized that this increase was mild and had no clinical significance (42).

Quinolones (ciprofloxacin, levofloxacin, norfloxacin) are pregnancy category C drugs. Quinolones have a high affinity for bones and cartilage, and they can cause arthropathies in children (43). In immature rats and dogs, exposure to quinolones was reported to result in cartilage damage in joints under pressure. Nevertheless, in a population-based cohort study investigating 57 women who had used quinolones, no increase was established in the risk for congenital malformations. Also, in a prospective controlled study comparing 200 women exposed to quinolones during pregnancy to 200 women exposed to non-teratogenic antibiotics, there was no increase in the risks for congenital malformations (RR: 0.85, 95%CI: 0.21-3.49, p=0.5), spontaneous abortion (RR: 1.80, 95%CI: 0.85-3.80, p=0.1), premature labor (RR: 0.92, 95%CI: 0.42-2.00, p=0.99), or LBW (RR: 0.85, 95%CI: 0.32-2.22, p=0.93) compared to the control group (44,45). However, the treatment period in that study was short (1-14 doses). Therefore, even though ciprofloxacin seems to be safe in pregnancy, nonetheless, alternative antibiotics should be used for long-term therapies in IBD, if possible. For example, amoxicillin-clavulanate can be an alternative in the treatment of pouchitis. This drug is in FDA category B, and there is a population-based case-control study and a prospective controlled study showing its safety (46,47).

**7) Anti-tumor necrosis factor (TNF)-α antibodies**

Infliximab is a chimeric immunoglobulin (Ig)G1 anti-TNF-alpha antibody used in the treatment of CD and UC, with FDA category B. Due to its large molecular size and the fact that the antibodies cannot cross the placenta until late in pregnancy, it would be rational to use during the first trimester of pregnancy (48,49). However, the first data regarding anti-TNF treatment from various case series show poor obstetrical outcomes, including a premature infant with intracerebral and intrapulmonary hemorrhage, lost 3 days following birth (50). However, other large case studies did not show similar results. In the large scale prospective TREAT study, no fetal malformation was observed in 36 pregnancies exposed to infliximab. While the spontaneous abortion rate was 11.1%, the neonatal complication rate was 8.3%, and this rate was no different than in the general US population (51). The Infliximab Safety Database is a larger database, in which 96 pregnancy periods resulting in 100 live births were reported. There was no difference in the obstetric outcome of pregnants exposed to infliximab in comparison to pregnancies in the general population (52). Although it is a known fact that large molecules like infliximab do not cross the placenta in early pregnancy, it has been detected in fetal serum during birth, bringing into mind that it might cross the placenta in the third trimester by diffusion (53). It has been shown that the measurable infliximab levels in the newborn do not have a negative effect upon the immune system. Traditionally, the first live virus vaccines (varicella, mumps-measles-rubella) are applied at 1 year of age, when the serum infliximab levels have decreased to unmeasurable levels. However, nowadays, rotavirus live vaccine is applied at 2 months. Although this vaccine is given orally and is seriously attenuated, its safety is still an unknown issue (54).

Adalimumab (ADA) is FDA category B. Animal studies have found no evidence of increased obstetric risk or teratogenicity. Human data are scant; there are only case reports about IBD (55). In one case, ADA was started before pregnancy and was used throughout pregnancy, and the result was successful. In another infliximab-resistant case, there was serious active disease during conception and a moderate degree of activity in the third trimester, but the pregnancy terminated without any complications (56,57). More data are needed in order to recommend ADA use in pregnancy, but early results show that it would be safe.

**8) Methotrexate (MTX)**

The FDA category of MTX is X. MTX is certainly teratogenic in animal and human models. It causes spontaneous abortion and neural tube defects. It causes “MTX embryopathy”, characterized by intrauterine growth retardation, cranial anomalies, hypoplastic supraorbital ridges, low-set ears, micrognathia, and extremity anomalies. As MTX can last for 3 months in the liver, it is recommended not to conceive during the 3-4 months follo-

wing treatment. If conception does occur during MTX treatment, 5 mg folate intake daily, or preferably, termination of the pregnancy, is recommended (58,59).

## B- Safety of drugs used in cases with ulcerative colitis during lactation

Data regarding the use of UC drugs during lactation are very limited. These data usually consist of metabolite levels in breast-milk and anecdotal records (60).

### 1) Aminosalicylates

The use of 5-ASA preparations during lactation is usually safe, but there are case reports about serious reversible diarrhea in the infants of mothers using 5-ASA. It is recommended that breast- feeding mothers using 5-ASA should follow their children's bowel habits more carefully. Similarly, sulfasalazine is a safe drug in breast-feeding women (61,62).

### 2) Corticosteroids (CS)

It is thought that prednisone and prednisolone are the safest CS in breast-feeding mothers. These two steroid compounds show the least passage into breast-milk. However, with doses above 20 mg, it is recommended to postpone breast-feeding for 4 hours in order to minimize passage to the milk (63).

### 3) Thiopurines

In a study investigating four cases that took AZA during breast feeding, 6-MP was not detected in breast-milk in samples taken at different intervals. There was also no side effect in the infants (64). In another study, breast-milk samples were taken from 8 breast-feeding mothers. The samples taken at the first 30 and 60 minutes and every hour thereafter for 5 hours showed that most of the 6-MP in breast-milk was excreted in the first 4 hours. Even in the maximum concentration period measured, the 6-MP level passing into the infant was reported as <0.008/mg/kg/24 hours (65). Breast-feeding women should be warned about waiting 4 hours after drug ingestion before feeding.

### 4) Cyclosporine

It is contraindicated due to its high concentration in breast-milk. There are risks of immunosuppression and neutropenia (54).

### 5) Tacrolimus

It is seen in high concentrations in breast-milk. The effect upon the infant is still unknown; therefore, its use during lactation is contraindicated (66).

### 6) Methotrexate (MTX)

MTX passes into breast-milk in high concentrations. It has been shown to accumulate in neonatal tissues. It is contraindicated during lactation (67).

### 7) Antibiotics

Metronidazole is found in high concentrations in breast-milk. If possible, it should be avoided during lactation. The American Pediatric Society has recommended that infants should not be fed for 24-48 hours after ingestion of the drug (68).

Ciprofloxacin is secreted by breast-milk, and is thus not safe during lactation (69).

### 8) Anti-TNF-α antibodies

Theoretically, infliximab treatment should be safe during lactation because large protein molecules such as infliximab would be degraded or inactivated by digestive enzymes during their passage through the gastrointestinal tract. Also, two case reports have demonstrated that the infliximab levels in breast-milk were below the measurable limits (70,71).

Human data regarding the use of adalimumab during lactation are insufficient.

## CONCLUSION

The results of our systematic literature review show that, in UC cases, the use of IBD drugs, except MTX, which is contraindicated, during conception and pregnancy seems to have a low risk. On the other hand, during lactation, in addition to MTX, tacrolimus, cyclosporine and quinolones are also absolutely contraindicated. The facts that the disease activity during conception affects the disease course during pregnancy and that the disease becomes active mostly during the first trimester justify the use of drugs during pregnancy. We thus conclude that, except for MTX, the other drugs can be used, keeping in mind the benefit/damage equilibrium to the mother and fetus.

***Recommendation:***

***Which is the optimal safe treatment in pregnant UC cases?***

*Medical treatment should be continued during pregnancy, because the risk of active disease is more compared to the risks of the drugs.* ***(EL 1a, RG A)***

*MTX treatment during pregnancy is absolutely contraindicated.* ***(EL 2a, RG B)***

*5-ASA (except olsalazine) treatment during pregnancy is safe.* ***(EL 1a, RG A).***

*Infliximab treatment can be given until the 30$^{th}$ week.* ***(EL 4, RG C)***

*Steroid and AZA/6-MP can be used keeping in mind the benefit/damage rates.* ***(EL 5, RG D)***

*As for antibiotics;*

*Metronidazole can be used.* ***(EL 5, RG D)***

*For ciprofloxacin, data for long-term use are inadequate.* ***(EL 5, RG D)***

*Adalimumab, cyclosporine and tacrolimus treatment in UC cases resistant to treatment can be used, as the benefit to the mother outweighs the possible damage to the fetus. However, wide scale prospective studies are still needed for the safe use of these drugs.* ***(EL 5, RG D)***

***Recommendation:***

***Which is the optimal safe treatment in UC cases during the lactation period?***

*The use of ASA, sulfasalazine, prednisone, prednisolone, and AZA/6-MP is safe in lactation.* ***(EL 5, RG D)***

*The infants of the mothers using 5-ASA should be watched carefully for changes in bowel habits. Mothers using AZA/6-MP and high doses of prednisone/prednisolone should wait 4 hours before breastfeeding their child.* ***(EL5, RG D)***

*Cyclosporine, tacrolimus, MTX, quinolones, and metronidazole use during lactation is contraindicated.* ***(EL 5, RG D)***

*It is thought that infliximab use during lactation is safe.* ***(EL 5, RG D)***

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