

# World Journal of *Clinical Cases*

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## Pregnancy and medications for inflammatory bowel disease: An updated narrative review

Shintaro Akiyama, Joshua M Steinberg, Mariko Kobayashi, Hideo Suzuki, Kiichiro Tsuchiya

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### Abstract

Inflammatory bowel disease (IBD) is often diagnosed during the peak reproductive years of young women. Women with active IBD around conception are at a significantly increased risk of disease relapse during pregnancy, which is associated with poor pregnancy and neonatal outcomes. Given these substantial risks, it is prudent that disease remission should ideally be achieved before conception. Unfortunately, some patients may experience a disease flare-up even if they are in a state of remission before pregnancy. Patients must continue their IBD medications to reduce the risk of disease flare and subsequent poor outcomes during the gestational and postpartum periods. When treating IBD flare-ups during pregnancy, the management is quite similar to the therapeutic approach for non-pregnant patients with IBD, including 5-aminosalicylate, steroids, calcineurin inhibitors (CNIs), and biologic therapies. While the data regarding the safety of CNIs in pregnant women with IBD is limited, the findings in our recent meta-analysis suggest that CNIs may be safer to use in those with IBD than in solid organ transplant recipients. There are several types of biologics and small-molecule therapies currently approved for IBD, and physicians should thoroughly understand their clinical benefits and safety profiles when utilizing these treatments in the context of pregnancy. This review highlights recent studies, including our systematic review and meta-analysis, and discusses the clinical advantages and safety considerations of biologics and small molecules for pregnant women with IBD.

**Key Words:** Inflammatory bowel disease; Pregnancy; Safety; Biologics; Small molecules

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**Core Tip:** Anti-tumor necrosis factor monotherapy is safe during pregnancy in women with Inflammatory bowel disease (IBD). However, their use in combination with thiopurines may be associated increased risk of neonatal prematurity and infection, although these data are conflicting. According to meta-analyses, vedolizumab and ustekinumab may be associated with early pregnancy loss; however, these data might be biased by IBD activity or small sample sizes. Recent prospective studies have demonstrated these biologics are generally safe during pregnancy. Janus kinase inhibitors are contraindicated during pregnancy as animal studies have demonstrated harmful effects. Calcineurin inhibitors may be considered for pregnant women with IBD who develop clinical relapse.

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## INTRODUCTION

Pregnancy is a critical period requiring coordinated, specialized health care for many women during their reproductive years. As most women with inflammatory bowel disease (IBD) experience the onset of the disease in their 20s and 30s, physicians should understand the clinical benefits and safety profiles of biologics and small molecules as they apply to pregnant women with IBD.

In general, patients with IBD have a higher incidence of adverse pregnancy outcomes, including miscarriage, preterm delivery (a live birth before 37 wk of pregnancy), low birth weight (LBW: A birth weight of < 2500 g), poor maternal weight gain, and complications of labor and delivery (*e.g.*, preeclampsia, placental abruption, increased probability of delivery by cesarean section)[1-3]. Many studies have previously confirmed that active or flaring IBD around conception increases the risk of disease relapse and is associated with several poor outcomes, including increased risk of LBW, preterm birth, small for gestational age, spontaneous abortion, and stillbirth[4]. These data imply that proactive family planning with the goal of sustained disease remission before conception should be practiced routinely. However, up to one-third of the patients with IBD in remission before pregnancy experience flare-ups during pregnancy[5]. Given these findings and subsequent risks, patients should continue their IBD medications throughout pregnancy, as there may be a clinical benefit in reducing the risk of disease flare-ups during both the gestational and postpartum periods[6-9]. A prospective study evaluating women with quiescent IBD at the time of conception reported that 38% of the patients experienced clinical relapse during pregnancy and that disease flare-up was significantly associated with higher rates of preterm delivery, hospitalization during pregnancy, and a lower gestational age at delivery. This study further analyzed the contributing factors to disease relapse during pregnancy, and reported that the use of biological therapies at the time of conception was negatively associated with the risk of disease flare-up, suggesting that biologics may be protective against clinical relapse during pregnancy[5].

There are several types of biologics and small molecules currently approved for treating IBD. While tumor necrosis factor (TNF) inhibitors, including infliximab, adalimumab, golimumab, and certolizumab, have been used for patients with immune-mediated inflammatory diseases (IMiDs) for several decades[10], vedolizumab, an  $\alpha_4\beta_7$  integrin inhibitor, and ustekinumab, an interleukin- (IL-) 12/IL-23 inhibitor, are newer treatments for IBD[11,12]. In addition, Janus kinase (JAK) inhibitors, including tofacitinib, filgotinib, and upadacitinib[13-15], calcineurin inhibitors (CNIs), including tacrolimus and cyclosporine[16], as well as a sphingosine-1 phosphate receptor modulator, ozanimod[17], are small-molecule therapies that can be used for treating moderate-to-severe ulcerative colitis (UC). It should be noted that all biologics other than certolizumab pegol are actively transported across the placenta[18] and theoretically could affect pregnancy and neonatal outcomes.

While there are concerns regarding the potential negative effects of IBD medications on pregnancy and fetal development, previous retrospective studies with large sample sizes demonstrated that pregnant women with IBD who continued their biologic therapy during pregnancy did not have increased adverse fetal outcomes. A multicenter retrospective European TEDDY study including 841 children, 46% of whom had been exposed to anti-TNF agents, found that the incidence rate of severe infection was similar between anti-TNF exposed and non-exposed children (2.8% *vs* 1.6% per person-year)[19]. Also, another retrospective cohort study that evaluated 8726 pregnant women with IBD using data from the French national health system database demonstrated no increased risk of infection in children born to mothers exposed to anti-TNF agents during pregnancy. While this study concluded that anti-TNF agents during pregnancy increased the risk of overall maternal complications, particularly infections, compared to non-exposed patients, discontinuing anti-TNF agents before week 24 increased the risk of a disease flare[8]. Several prospective studies published in the United States, France, Israel,

and the Czech Republic have recently demonstrated the safety of IBD medications during pregnancy [20-24]. The Pregnancy and Inflammatory Bowel Disease and Neonatal Outcome (PIANO) registry [20], a national United States registry that prospectively enrolled pregnant women with IBD, demonstrated that biologics and thiopurines do not increase the risk of maternal and neonatal outcomes in patients with IBD.

The American Gastroenterological Association (AGA) IBD Parenthood Project Working Group highlighted that most IBD medications, including aminosalicylates, biologics, and thiopurines, can be safely continued during pregnancy and through delivery [18]. The European Crohn's and Colitis Organization (ECCO) guideline published in 2022 recommended the continuation of TNF inhibitors before the third trimester for women in remission because discontinuation can increase the risk of relapse and lead to unfavorable outcomes [25]. Regarding newer therapies such as ustekinumab and vedolizumab, the decision to discontinue treatment should be individualized for women in remission on these therapies. Importantly, the continuation of biologics for patients in an active IBD disease flare just before or during pregnancy is recommended throughout the pregnancy in these guidelines [18,25]. The ECCO guidelines also highlight that if a pregnant woman with IBD develops a flare, a multidisciplinary care team, including a gastroenterologist, an obstetrician, a pediatrician, and an experienced surgeon, should be sought out to optimize outcomes [25].

In this review, we introduce recent investigations using large-scale national registry databases, prospective studies, and updated systematic reviews and meta-analyses, including our research findings, and discuss the clinical advantages and safety profiles of IBD medications during pregnancy.

## SAFETY OF BIOLOGICS AND THIOPURINES FOR PREGNANCY IN IBD

The PIANO registry is the most extensive prospective observational multicenter study in the United States, having enrolled 1712 pregnant women with IBD. In this registry, 1490 patients completed pregnancies with 1431 Live births, and 869 patients were exposed to biologics (predominantly TNF inhibitors) or combination therapies with thiopurines. Although the risk of cesarean section was higher in patients exposed to biologics or combination therapies than that in the unexposed population, there were no observed differences between the two groups in the rates of the following pregnancy-related complications: spontaneous abortion, preterm delivery, LBW, intrauterine growth restriction, small for gestational age, neonatal intensive care unit stay, and congenital malformations [20]. While combination therapy of biologics and immunomodulators may be discouraged by some providers due to concerns of an increased risk of infection, the PIANO registry data showed that the use of biologics, thiopurines, or combination therapy was not associated with an increased risk of any infection in the first year of life [20]. A recent systematic review and meta-analysis, including 48 studies with 6963 patients with IBD exposed to biologics, showed their pooled prevalence of adverse outcomes, including early pregnancy loss, preterm birth, stillbirth, LBW, and congenital malformations, was comparable with those found in the general population [26]. This meta-regression analysis showed no significant association between concomitant thiopurine use and adverse outcomes [26]. These data suggest that biologics and immunomodulators can be safely continued throughout pregnancy in women with IBD.

### *TNF inhibitors and immunomodulators*

A recent nationwide emulation trial utilizing a French population-based database demonstrated the clinical benefits of continuing TNF inhibitors during pregnancy in patients with IBD [7]. This study included 5293 pregnancies with subsequent births exposed to TNF inhibitors between conception and week 24 of pregnancy. Among this group, TNF inhibitors were discontinued before 24 wk in 2890 pregnancies and continued beyond 24 wk in 2403 pregnancies [7]. This analysis revealed that patients who continued TNF inhibitors after week 24 of pregnancy had decreased risks of maternal IBD relapse [adjusted risk ratio (aRR) 0.93, 95% confidence interval (CI): 0.86-0.99] and neonatal prematurity (aRR 0.82, 95% CI: 0.68-0.99). Continuation of TNF inhibitors showed no differences in rates of stillbirths, small for gestational age, or serious infection, supporting the recommendation of maintaining TNF inhibitor therapy throughout pregnancy in patients with IBD [7].

Regarding the potential risks of TNF inhibitors in pregnancy and neonatal outcomes, a recent systematic review and meta-analysis assessing the outcomes in women with IMiDs showed an increased risk of preterm births and neonatal infections in those treated with TNF inhibitors compared with diseased controls [27]. No significant differences in cesarean section, miscarriage, LBW, small for gestational age, or congenital malformation were identified between the two groups. However, subgroup analysis did show an increased risk of preterm births, LBW, and cesarean section in patients with IBD treated with TNF inhibitors [27]. In this meta-analysis, diseased controls were usually exposed to other medications, including azathioprine. Overall, the data regarding the effects of combination therapy of TNF inhibitors with thiopurines on pregnancy outcomes are limited, and more studies are needed to elucidate such risks further.

A recent French nationwide study compared pregnancy and neonatal outcomes among patients with IBD treated with thiopurine monotherapy ( $n = 3554$ ), anti-TNF monotherapy ( $n = 3525$ ), combination



therapy ( $n = 839$ ), and unexposed controls ( $n = 19811$ ). No significant differences in the risk of adverse pregnancy outcomes were observed between pregnant women exposed to anti-TNF monotherapy and unexposed controls. In contrast, those exposed to combination therapy were more likely to have preterm birth[21]. Furthermore, a French nationwide study using the same data source included 26561 children born to women with IBD (3392 exposed to thiopurine monotherapy, 3399 exposed to anti-TNF monotherapy, 816 exposed to combination, and 18954 unexposed controls) and showed no significant difference in the risk of serious infection during the first five years of life between children exposed to thiopurine or anti-TNF monotherapies and the unexposed population. However, children exposed to combination therapies had a higher risk of serious infection during the first year of life (adjusted hazard ratio, 1.36, 95%CI: 1.04-1.79)[22]. Considering these findings, the ECCO guidelines suggest that when thiopurines are combined with biologics, discontinuation should be considered on an individualized basis if the patient is in sustained, long-term remission. Testing for and ensuring adequate serum anti-TNF levels may be helpful in this setting[25].

The PIANO registry predominantly included patients treated with TNF inhibitors. This study found no increased risks of adverse maternal or fetal outcomes at birth or in the first year of life in pregnant women treated with biologics and/or thiopurines[20]. Given that the French nationwide studies suggest that combination therapy of TNF inhibitors and thiopurines is associated with the risk of neonatal prematurity and infection[21,22], further investigations are needed to more clearly understand whether combination therapy is beneficial or harmful in the context of maternal and fetal outcomes in patients with IBD (Tables 1 and 2).

### **Vedolizumab**

A prospective multicenter study in Denmark and Canada examined vedolizumab levels in neonates' umbilical cord blood, the rates of clearance after birth, and the risk of infection and delayed developmental milestones. This study identified 50 vedolizumab-exposed pregnancies and found that the rates of live births, miscarriages, and congenital malformations were 86%, 14%, and 0%, respectively. The mean period of vedolizumab clearance was 3.8 mo, and the newborns' developmental milestones were found to be normal or above average. No association was observed between the infants' vedolizumab level and the risk of infection during the first year of life, suggesting that vedolizumab is generally safe during pregnancy[28]. Another prospective comparison study including 24 pregnant women with IBD treated with vedolizumab, 82 with TNF inhibitors, and 224 with conventional therapy showed that the rate of spontaneous abortion was higher (21%) in the vedolizumab group than in the other groups. However, conception in the setting of active disease flare-ups occurred in more than 30% of the vedolizumab group, which was higher than the rates in the other groups, suggesting that disease activity at conception may affect outcomes[29].

Systematic reviews and meta-analyses, including four studies, showed that women treated with vedolizumab had an increased risk of preterm births and early pregnancy loss compared with those not exposed to vedolizumab during pregnancy[26,30]. No differences were observed in the number of live births or congenital abnormalities. However, there is concern regarding the number of included studies having small sample sizes and that disease activity may have confounded these findings. Meanwhile, a recent prospective multicenter observational study in the Czech Republic, including 39 pregnant women with IBD exposed to vedolizumab during pregnancy, reported that 90% of pregnancies resulted in a live birth, 5% in spontaneous abortion, and 5% in therapeutic abortion. However, no significant differences in the risk of pregnancy outcomes were observed between the vedolizumab- and TNF inhibitor-exposed populations[24].

Further prospective studies and meta-analyses with updated data are needed to confirm the safety of vedolizumab in pregnant patients with IBD (Tables 1 and 2).

### **Ustekinumab**

A previous systematic review and meta-analysis, including two case studies, showed that female patients with IBD treated with ustekinumab had an increased risk of early pregnancy loss compared with those treated with TNF inhibitors[26]. However, this meta-analysis's small number of studies may have overestimated the prevalence of adverse pregnancy-related events. Recently, several prospective studies focusing on ustekinumab safety during pregnancy have been published. A Czech prospective study including 54 pregnant women treated with ustekinumab showed that 80% and 20% of pregnancies resulted in live births and spontaneous abortions, respectively. No significant difference in the risk of pregnancy outcomes was observed between ustekinumab- and anti-TNF-exposed controls [24]. Furthermore, an Israeli prospective multicenter cohort study recruited 129 pregnant patients (27 pregnant women exposed to ustekinumab, 52 exposed to TNF inhibitors, and 50 unexposed controls) and showed no significant differences among these groups in the rates of maternal obstetrical complications, preterm delivery, LBW, or newborn hospitalization during the first year of life[23]. These findings are consistent with those of the Czech study and support the relative safety of ustekinumab in the setting of pregnancy.

An investigation using the drug manufacturer's global safety database prospectively identified 408 ustekinumab-exposed pregnant women with IMIDs, such as Crohn's disease, UC, psoriasis, and psoriatic arthritis. For the 408 prospective ustekinumab-exposed pregnancies, 420 pregnancy outcomes

**Table 1 Summary of prospective and nationwide studies regarding the safety of biologics and small molecules for pregnant women with inflammatory bowel disease**

Biologics/small molecules	ECCO's guideline[25]	Summary of recent prospective and nationwide studies
TNF inhibitors (monotherapy)	Low risk	The PIANO registry predominantly including patients treated with TNF inhibitors found no increased risks of adverse maternal or fetal outcomes at birth or in the first year of life in pregnant women with IBD treated with biologics[20]. Two French nationwide studies reported no significant differences in the risk of pregnancy outcomes between pregnancies exposed to anti-TNF monotherapy and unexposed controls[21]. The risk of serious infection during the first 5 yr of life was not significantly different between children exposed to anti-TNF monotherapy and the unexposed population[22]
TNF inhibitors with thiopurines	Thiopurine discontinuation may be considered	The PIANO registry predominantly including patients treated with TNF inhibitors found no increased risks of adverse maternal or fetal outcomes at birth or in the first year of life in pregnant women with IBD treated with biologics combined with thiopurines[20]. Two French nationwide studies reported that patients on combination therapy were more likely to have preterm birth than unexposed controls[21]. Children exposed to combination therapies had a higher risk of serious infection during the first year of life[22]
Vedolizumab	Low risk, limited data	In 50 vedolizumab-exposed pregnancies, the rates of live birth, miscarriage, and congenital malformations were 86%, 14%, and 0%, respectively. Infant vedolizumab level was not associated with the risk of infection during the first year of life[28]. The first prospective study comparing 24 pregnant women treated with vedolizumab, 82 with TNF inhibitors, and 224 with conventional therapy showed that the rate of spontaneous abortion (21%) was higher in the vedolizumab group than in the other groups[29]. In this study, disease activity at conception may affect the result. A Czech prospective study including 39 pregnant women with IBD exposed to vedolizumab during pregnancy showed that 90% of pregnancies ended in a live birth, 5% in spontaneous abortion, and 5% in therapeutic abortion. No significant differences in the risk of pregnancy outcomes were observed between vedolizumab- and TNF inhibitor-exposed populations[24]
Ustekinumab	Low risk, limited data	A Czech prospective study including 54 pregnant women treated with ustekinumab showed that 80% and 20% of patients resulted in live births and spontaneous abortions, respectively. The risk of pregnancy outcomes was not significantly different between ustekinumab- and anti-TNF-exposed controls[24]. An Israeli prospective study including 27 pregnancies exposed to ustekinumab, 52 exposed to TNF inhibitors, and 50 unexposed controls showed no significant differences in the rates of obstetrical maternal complications, preterm delivery, LBW, and first-year newborn hospitalization[23]. The manufacturer's global safety database including 408 ustekinumab-exposed pregnancies with IMIDs showed that the rates of adverse pregnancy outcomes were comparable to those of United States general population[31]
JAK inhibitors	Contraindicated (no mention of upadacitinib)	Data from interventional studies of tofacitinib identified 11 patients with UC exposed to tofacitinib before/at the time of conception or during pregnancy and showed that 36% of patients delivered healthy newborns, 18% had a medical termination, and no cases of neonatal death, fetal death, or congenital malformation were reported[33]
Ozanimod	Contraindicated	N/A
Calcineurin inhibitors	Low risk, limited data	N/A

ECCO: European Crohn's and Colitis Organization; IBD: Inflammatory bowel disease; IMIDs: Immune-mediated inflammatory diseases; JAK: Janus kinase; LBW: Low birth weight; TNF: Tumor necrosis factor; UC: Ulcerative colitis; N/A: Not applicable.

were reported. The rates of live births, spontaneous abortions, elective/induced abortions, stillbirths, and fetal congenital anomalies were 81%, 12%, 6%, 0.7%, and 0.2%, respectively. Among 340 Live births, the percentage of preterm deliveries was 9.7%. The overall rates of pregnancy outcomes were consistent across disease indications. These data suggest that the rates of adverse pregnancy outcomes in women with IMIDs exposed to ustekinumab were comparable to those of the United States general population [31].

Recent prospective studies have supported the safety of ustekinumab in relation to pregnancy and neonatal outcomes in patients with IBD. However, further investigations are needed to validate the safety profile of ustekinumab for pregnant women with IBD (Tables 1 and 2).

## SAFETY OF SMALL MOLECULES FOR PREGNANCY IN IBD

### JAK inhibitors

Tofacitinib is a JAK1/3 inhibitor approved for UC[13]. Studies on rats and rabbits showed that tofacitinib is fetocidal and teratogenic[32]. The teratogenic effects included external and soft tissue malformations (*e.g.*, anasarca and membranous ventricular septal defects) and skeletal malformations [32]. Therefore, current recommendations suggest that tofacitinib be discontinued in female patients with IBD who plan to start a family. However, human data regarding the safety profile of tofacitinib for pregnant women with IBD is generally limited. Data from interventional studies of tofacitinib in patients with UC identified 11 cases of maternal exposure to tofacitinib (5 mg or 10 mg twice daily) before or at the time of conception or during pregnancy. Among these cases, 36% of patients delivered healthy newborns, and 18% had a medical termination. While 18% of the patients experienced

**Table 2 Summary of systematic review and meta-analyses regarding the safety profiles of biologics and small molecules for pregnant women with inflammatory bowel disease**

Biologics/small molecules	ECCO's guideline[25]	Summaries of recent systematic review and meta-analysis
TNF inhibitors (monotherapy)	Low risk	There was an increased risk of preterm births, LBW, and cesarian section in patients with IBD treated with TNF inhibitors[27]. This study was limited in its understanding of whether anti-TNF monotherapy or its combination with thiopurines is associated with these risks
TNF inhibitors with thiopurines	Thiopurine discontinuation may be considered on an individualized basis	Meta-analyses including recent prospective studies that assess the risk of combination therapy for pregnant women with IBD are lacking
Vedolizumab	Low risk, limited data	Women treated with vedolizumab had an increased risk of preterm births and early pregnancy loss compared with those unexposed to vedolizumab during pregnancy. No differences were observed in the number of live births or congenital abnormalities[26,30]. The systematic review and meta-analyses' results may be biased by disease activity
Ustekinumab	Low risk, limited data	A meta-analysis including two case studies showed that women treated with ustekinumab had an increased risk of early pregnancy loss compared with those treated with TNF inhibitors[26]. The prevalence of adverse pregnancy events was likely to be overestimated due to the small number of studies in this meta-analysis
JAK inhibitors	Contraindicated (no mention of upadacitinib)	N/A
Ozanimod	Contraindicated	N/A
Calcineurin inhibitors	Low risk, limited data	A meta-analysis including 4450 CNI-treated patients (4372 solid organ transplant recipients and 78 patients with IMIDs including IBD) showed that the rates of preterm delivery, LBW, and preeclampsia were 3–4 times greater than the rates in the general population. The risk of neonatal prematurity was higher in solid organ transplant recipients than in patients with IMIDs due to the higher risk of preeclampsia in solid organ transplant recipients. CNIs may be safer for pregnant women with immune-mediated diseases than for solid organ transplant recipients[38]

CNI: Calcineurin inhibitor; ECCO: European Crohn's and Colitis Organization; IBD: Inflammatory bowel disease; IMIDs: Immune-mediated inflammatory diseases; JAK: Janus kinase; LBW: Low birth weight; TNF: Tumor necrosis factor; UC: Ulcerative colitis; N/A: Not applicable.

spontaneous abortion, no cases of neonatal death, fetal death, or congenital malformations were reported[33]. Although these study sizes are small, these findings suggest that pregnancy and neonatal outcomes in UC studies of tofacitinib are similar to those in the general population and clinical studies of other indications (such as rheumatoid arthritis, psoriatic arthritis, and psoriasis). Regardless, current best practice recommendations, including the ECCO guideline and the product labeling, state that tofacitinib use is contraindicated in pregnancy due to the very limited data on pregnant women with IBD[25].

Filgotinib is a small molecule that preferentially inhibits JAK1 and is approved for moderately to severely active UC in Europe and Japan[14]. Animal studies have shown that filgotinib is associated with decreased male fertility and impaired spermatogenesis. However, filgotinib exposure was not associated with decreased female fertility[34]. The MANTA study is currently being conducted to confirm the impact of filgotinib on male fertility[34]. Since filgotinib is considered harmful to the fetus, according to animal studies findings, both the ECCO guideline and the product labeling state that this drug is contraindicated during pregnancy[25] (Tables 1 and 2).

Upadacitinib is a selective JAK1 inhibitor approved for moderately to severely active UC in Europe, the US, and Japan[35]. Although no human studies have assessed the safety of upadacitinib for pregnancy, this drug was also found to be teratogenic in animal studies. Therefore, the product labeling recommends against using upadacitinib during pregnancy[36].

### ***Sphingosine-1 phosphate receptor modulators***

Ozanimod is the first oral agonist of the sphingosine-1 phosphate receptor subtypes 1 and 5, which was approved for moderately to severely active UC in the United States and Europe[17]. There is only very limited data regarding the safety of ozanimod during pregnancy from the trials of multiple sclerosis[37] and UC[17]. Due to the lack of human data, ozanimod is contraindicated during pregnancy according to the ECCO guideline[25].

### ***CNIs***

Many studies have demonstrated the safety of CNIs for solid organ transplant (SOT) recipients during pregnancy[38]. However, safety data for pregnant women with IMIDs are scarce[38]. A case series assessed the clinical outcomes in 8 pregnant women with steroid-refractory UC who were started on CNIs. All patients received oral steroid therapy and were treated with cyclosporine for UC. Of the eight

patients treated with cyclosporine, 7 (88%) clinically improved, and the remaining patient who did not respond to cyclosporine was started on infliximab and subsequently improved. Half of the patients continued steroids at the time of delivery, and the other half stopped steroids. No patient underwent colectomy during pregnancy. As for pregnancy outcomes, 7 (88%) out of 8 pregnancies were carried to term, and one (13%) in-utero death occurred at 22 wk of gestation. Among the two premature newborns, one had LBW (1820 g), and the other newborn's weight was 3340 g[39]. This report suggests that cyclosporine is effective and safe for pregnant women with UC. No prospective studies assessing the safety of CNIs for IBD have been performed to date.

## INTRODUCTION OF OUR CURRENT RESEARCH

### *How to manage IBD flare-ups during pregnancy*

When pregnant women present with symptoms such as hematochezia, frequent bowel movements, or rectal urgency, laboratory tests (*e.g.*, fecal calprotectin), diagnostic imaging studies (*e.g.*, magnetic resonance imaging or ultrasound), and endoscopy may be considered for the assessment of IBD recurrence. A flexible sigmoidoscopy should be considered and readily performed without sedation or preparation, especially when the findings might change disease management[18]. The ECCO guideline highlights that IBD flare-ups during pregnancy should be managed according to current guidelines for non-pregnant patients with IBD using 5-aminosalicylate, steroids, cyclosporine, anti-TNF agents, ustekinumab, or vedolizumab[25].

In the setting of pregnancy, physicians should be aware that there are several exceptions when treating women with IBD flare-ups[18]. For instance, thiopurine initiation during pregnancy is not recommended, particularly in thiopurine-naïve patients, due to the potential risks of pancreatitis or leukopenia, which can be devastating[18]. Furthermore, JAK inhibitors, including tofacitinib, filgotinib, and upadacitinib, methotrexate, and ozanimod, cannot be used during pregnancy. As described above, animal data have demonstrated an increased risk of congenital malformation with tofacitinib[18]. Methotrexate should be stopped at least three months before conception due to its well-described teratogenic effects[40]. Ozanimod is also contraindicated due to the lack of human data on its safety during pregnancy[25].

### *Our research findings*

When treating pregnant women who develop acute severe UC, we must consider early hospitalization and the initiation of rapid-acting therapies, including IV steroids, infliximab, or CNIs, to induce remission. While previous investigations demonstrated the efficacy and safety of IV steroids[39] and infliximab[41] in pregnant women with IBD flares, the number of studies focusing on the safety of CNIs in this population is still limited, as previously described. CNIs are often used in SOT recipients to prevent allograft rejection and to control disease activity in patients with IMIDs[38]. In general, CNIs are indicated for patients with acute severe UC who fail to adequately respond to IV steroids within 3-5 d [42]. CNIs can cause arteriolar vasoconstriction and endothelial injury, and CNI-associated hypertension is a well-described adverse effect of this therapy[43]. Previous studies have shown that cyclosporine has a more substantial vasoconstrictive effect than tacrolimus[44,45]. CNI-associated hypertension can be managed by dose reduction and the addition of anti-hypertensive medications[38]. We recently conducted a systematic review and meta-analysis to evaluate the effects of CNIs on pregnancy and neonatal outcomes in SOT recipients and those with IMIDs, including IBD.

Our systematic review identified a total of 5355 pregnancies in 4450 CNI-treated patients (4372 SOT recipients and 78 patients with IMIDs such as IBD, systemic lupus erythematosus, and rheumatoid arthritis). Our meta-analysis showed that the rates of preterm delivery (33.2%, 95%CI: 29.2%-37.5%), LBW (35.8%, 95%CI: 27.7%-44.8%), and preeclampsia (13.5%, 95%CI: 9.4%-19.2%) in CNI-treated patients were 3-4 times greater than the rates in the general population[38]. The subgroup analysis revealed that the rates of gestational hypertension and preeclampsia in SOT recipients were higher than in patients with IMIDs. Furthermore, the pooled rate of LBW in SOT recipients was higher than that in patients with IMIDs. Notably, the meta-regression analysis showed a significant association between preeclampsia and the risks of preterm delivery and LBW. These findings suggest that the risk of neonatal prematurity with CNIs is higher in SOT recipients than in patients with IMIDs, due to the higher risk of preeclampsia in SOT recipients[38].

Additionally, our meta-regression analysis showed that pre-pregnancy hypertension and cyclosporine use significantly increased the risk of preeclampsia. The development of pre-pregnancy hypertension in SOT recipients may be attributed to CNI use and other risk factors, including allograft dysfunction, steroid use, volume overload, and particularly kidney transplantation[46]. On the other hand, patients with IMIDs may have a lower risk of pre-pregnancy hypertension, as this population is less likely to have such risk factors. Therefore, we suggest that risk stratification based on clinical indications for CNIs may help enable and subsequently inform discussions around appropriate preconception counseling and proactive blood pressure management in CNI-treated pregnant women. Moreover, given the stronger vasoconstriction effect of cyclosporine as compared with tacrolimus, our



findings also support that the vasoconstrictive effects of CNIs could be associated with the risk of preeclampsia and suggest that tacrolimus may be the preferred CNI to use in pregnant patients, particularly for those with a high risk of gestational hypertensive disorders (such as SOT recipients)[38].

Overall, our data support that CNIs may be safer in patients with IBD than SOT recipients. Due to the limited number of patients with IBD in our study, further studies with larger IBD sample sizes are needed to validate our findings (Tables 1 and 2).

## CONCLUSION

The PIANO registry demonstrated that biologics and thiopurines are generally safe and do not increase the risk of adverse maternal and neonatal outcomes in patients with IBD. Recent prospective data have also revealed that anti-TNF monotherapy is safe during pregnancy. However, their combination with thiopurines may increase the risk of neonatal prematurity and infection. Nonetheless, the impact of this risk is still unclear, given the conflicting data reported among these studies. Although meta-analyses of a small number of studies showed that vedolizumab and ustekinumab could be associated with early pregnancy loss, recent prospective studies have demonstrated that these biologics are relatively safe to use in pregnant women with IBD.

On the other hand, there is a paucity of prospective data assessing the clinical benefits of the continuation of biologics during pregnancy. For example, while a French nationwide emulation study demonstrated that the continuation of TNF inhibitors after 24 wk of pregnancy decreased the risks of maternal IBD relapse and neonatal prematurity[7], the clinical benefits of non-TNF biologics during pregnancy remain to be elucidated. Further investigations are also needed to understand whether biologics are to be used preemptively among patients in remission on conventional therapies before pregnancy to reduce the risk of clinical relapse during pregnancy. Such analyses may provide meaningful information to strengthen the current evidence that supports the continuation of biological therapies during pregnancy in patients with IBD.

Regarding small-molecule therapies, JAK inhibitors are contraindicated for pregnancy as animal studies have demonstrated harmful fetal effects. Due to the lack of human data, ozanimod should not be used during pregnancy. Our meta-analysis assessing pregnancy and neonatal outcomes in CNI-treated patients found a significant association between preeclampsia and neonatal prematurity in exposed patients. The rate of preeclampsia was higher in SOT recipients than in patients with IMIDs, suggesting that CNIs may be safer in patients with IBD. To better understand the efficacy and safety of CNIs in pregnant women with IBD, our future research will include prospective and/or multicenter studies that facilitate more significant numbers of patients to participate and enroll, strengthening the validity of our findings further.

## FOOTNOTES

**Author contributions:** Akiyama S designed the research; Akiyama S and Kobayashi M performed the research and analyzed the data; Akiyama S, Steinberg JM, Kobayashi M, Suzuki H, and Tsuchiya K wrote the paper.

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