

Seymour Katz, M.D., Series Editor

The Safety of Thiopurines in Patients with IBD at Conception, During Pregnancy and Nursing



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An area of concern for many patients with Inflammatory Bowel Disease (IBD) and providers who care for patients with IBD is the issue of conception and pregnancy, and the use of thiopurines during this time. Women with IBD have an increased risk of adverse pregnancy outcomes compared to those of the general population, and active disease seems to increase these risks. In women with IBD, thiopurines do not appear to increase the risk of low birth weight or congenital abnormalities, and may even have a protective effect on neonatal and pregnancy outcomes. However, women taking thiopurines may have an increased risk of preterm delivery, but this association may be confounded by disease activity. Men taking thiopurines do not appear to have an increased risk of offspring with congenital abnormalities. In lactating mothers, small amounts of 6-MP metabolites have been measured in breast milk though little concentration has been measured in neonatal blood. For women with IBD, we recommend achieving and maintaining remission prior to conception and throughout pregnancy and continuing thiopurines when required. Close follow up, with individually tailored management plans is recommended when planning conception and throughout pregnancy.

INTRODUCTION

Inflammatory bowel disease (IBD) commonly affects patients during their reproductive years, and questions regarding the safety of medications during pregnancy frequently arise. Thiopurines, azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP), are purine analogues that interfere with ribonucleoside

synthesis. These medications are commonly used in the management of patients with Inflammatory Bowel Disease (IBD), including those with Crohn's disease (CD) and ulcerative colitis (UC). The greatest controversy has surrounded the use of thiopurines during pregnancy and by males prior to conception. Patients and providers often struggle with the decision whether or not to continue thiopurines during conception and pregnancy. In order to best counsel patients, the risks of active IBD on pregnancy outcomes must be weighed against the potential risks and benefits of medications.

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This review outlines the effects of IBD and active disease on pregnancy outcomes, pregnancy outcomes for female and male patients taking thiopurines, and thiopurine use during breast feeding.

Early Studies on Thiopurines and Pregnancy

Based on investigational and post-marketing experiences and early case reports, AZA and 6-MP are considered FDA class D, which indicates that while there is positive evidence of human fetal risk, the potential benefits may warrant their use during pregnancy despite the potential risks.¹ However, physicians and patients are frequently hesitant to use class D medications during pregnancy.

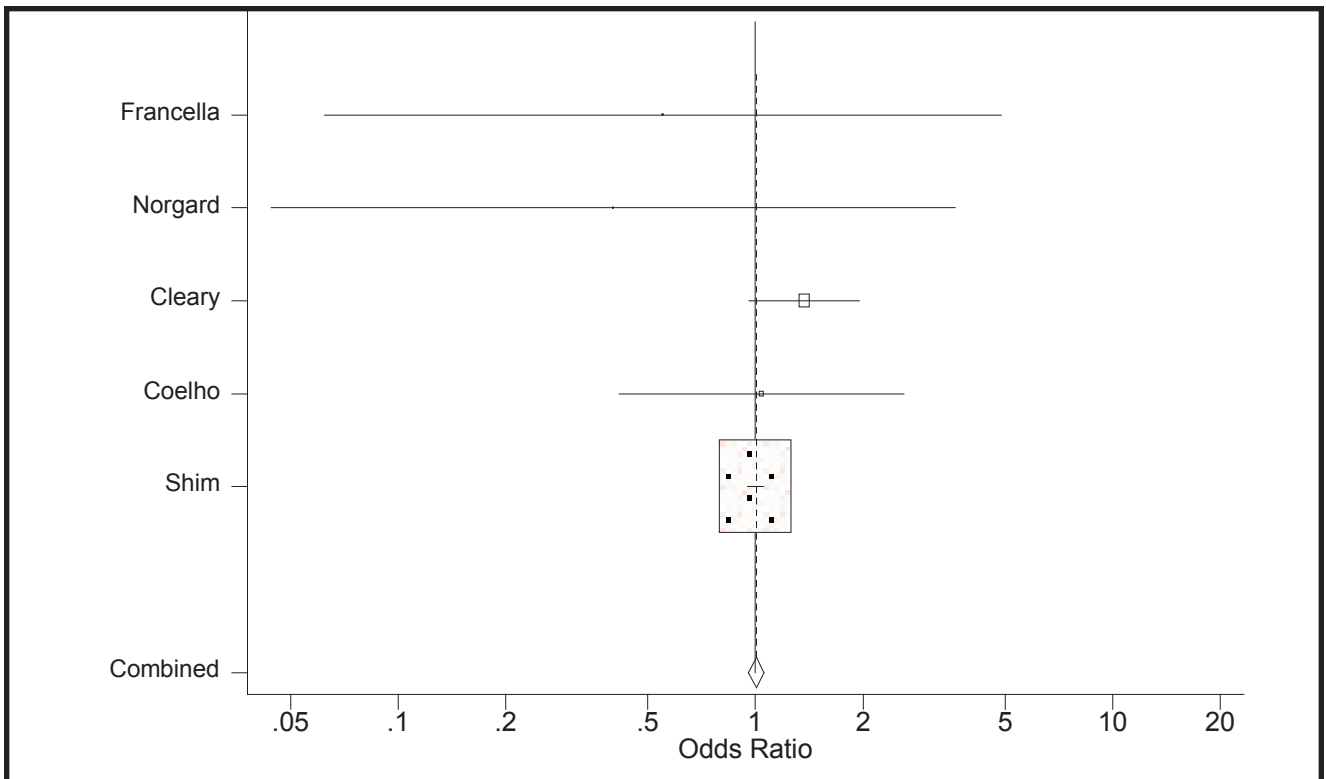
These safety concerns are drawn from early case reports in the non-IBD population that described adverse pregnancy outcomes for patients on thiopurines.²⁻⁷ Studies in animal models have demonstrated conflicting results of congenital malformations in offspring exposed to AZA or 6-MP. Congenital malformation and growth inhibition were found to occur in rat embryos with

increasing exposure to AZA or 6-MP⁸; and high doses of 6-MP impaired male mice reproduction.⁹ However, a more recent mouse study did not demonstrate an increased malformation rate related to 6-MP exposure.¹⁰

Case control studies, comparing pregnancies from mothers exposed to thiopurines to those of the general population, demonstrated that AZA and 6-MP use was associated with greater preterm births,^{11, 12} perinatal mortality,¹² and congenital abnormalities.^{11, 12} However, these studies had several methodological concerns. Namely, patients taking thiopurines for any indication, such as renal transplant and liver disease, were included in the exposed group. Moreover, the control groups consisted of women in the general population. In fact, the increased risk of preterm birth,¹² perinatal mortality,¹² and congenital abnormalities^{11, 12} was no longer significant when the control group was limited to include only women with similar diseases to the exposed group. Therefore, underlying disease is an important confounder that must be considered when interpreting these studies. This appears particularly true for IBD.

Figure 1. Forrest Plot for Maternal Thiopurine Use and Low Birth Weight*

The odds ratio, 95% confidence intervals, and pooled analysis from a random-effects model are shown.



Test for heterogeneity: Q = 3.949, df = 4 (p value = 0.413), I² = 0%

From *Inflammatory Bowel Diseases*, 2013

IBD and Pregnancy Outcomes

Compared to the general population, women with IBD have been shown to have increased adverse pregnancy outcomes.^{13, 14} Many studies have demonstrated that women with CD¹⁴⁻¹⁸ and UC^{14, 15, 17, 19} appear to be at a greater risk of preterm birth compared to women in the general population. However, this has not been shown in all studies.²⁰ Similarly, increased risk of low birth weight (LBW) infants from women with UC^{14,21} and CD^{14, 16} has been reported. Data regarding the risk of congenital abnormalities in women with IBD compared to the general population is conflicting. In one population based study, women with UC, but not CD, were found to have an increased risk of pregnancies that resulted in congenital abnormalities.¹⁶ However, other studies did not reveal an increased risk of congenital abnormalities for women with UC.^{19, 22} In studies that compared pregnancies from women before and after the diagnosis of IBD, the risk of congenital abnormalities was not increased after IBD diagnosis.^{23-25, 25} A meta-analysis of twelve studies did suggest that the risk of

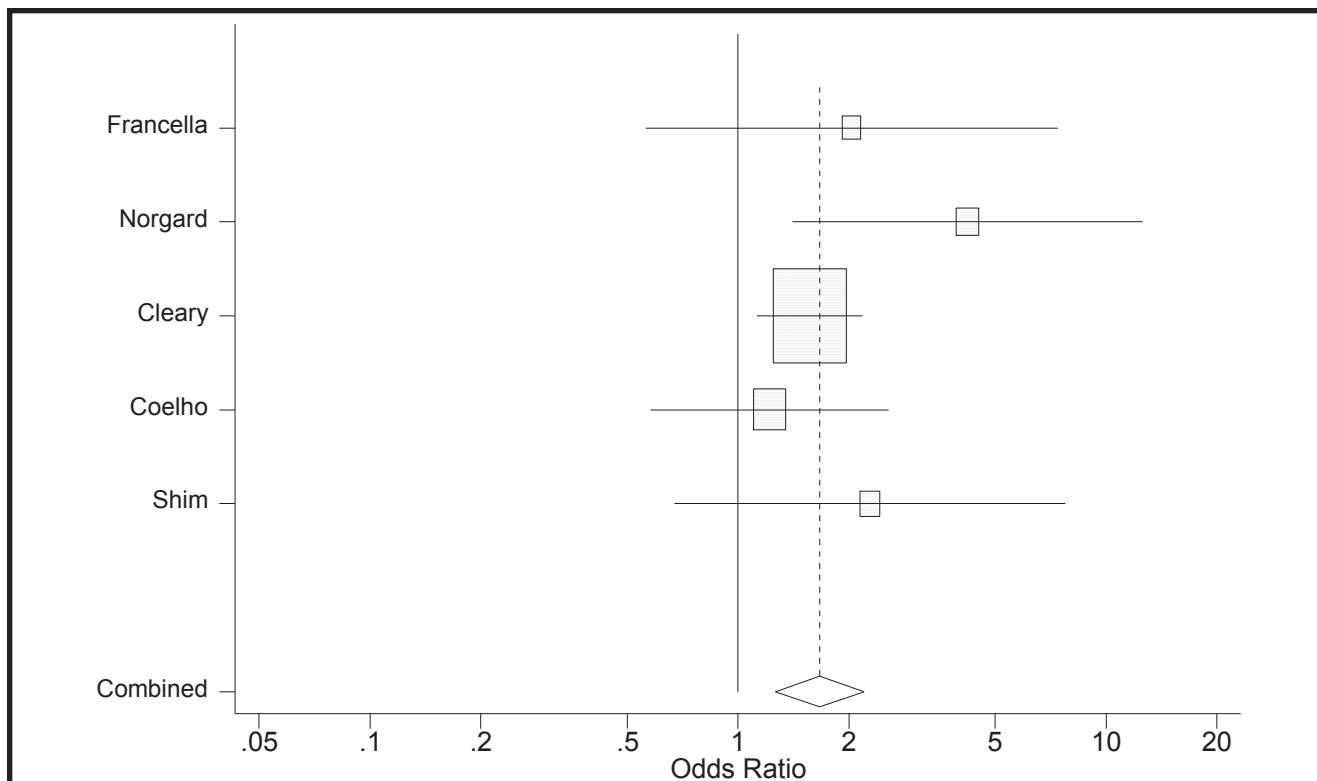
preterm birth and low birth weight, but not congenital abnormalities, was greater in IBD patients compared to the general population.²⁶ In subgroup analyses, preterm birth and LBW were greater in women with CD, but only preterm birth was greater in women with UC. The risk of congenital abnormalities appeared greater in births from women with UC, though this subgroup analysis pooled from only two studies, skewing and limiting interpretation of the results.

Numerous studies suggest that it is women with active IBD who seem to have an increased risk of pregnancy related complications.^{27, 28, 28, 29, 29, 30, 30, 30-32}

Though two studies failed to demonstrate an association between disease activity and adverse pregnancy outcomes, it is important to note that many of the women had quiescent IBD.^{13, 20} Given the potential risk of active IBD, maintaining remission prior to conception and during pregnancy is very important for maternal and fetal outcomes. The recommendation is that women wait until they are in remission to conceive.³³

Figure 2. Forest Plot for Maternal Thiopurine Use and Preterm Birth*

The odds ratio, 95% confidence intervals, and pooled analysis from a random-effects model are shown.

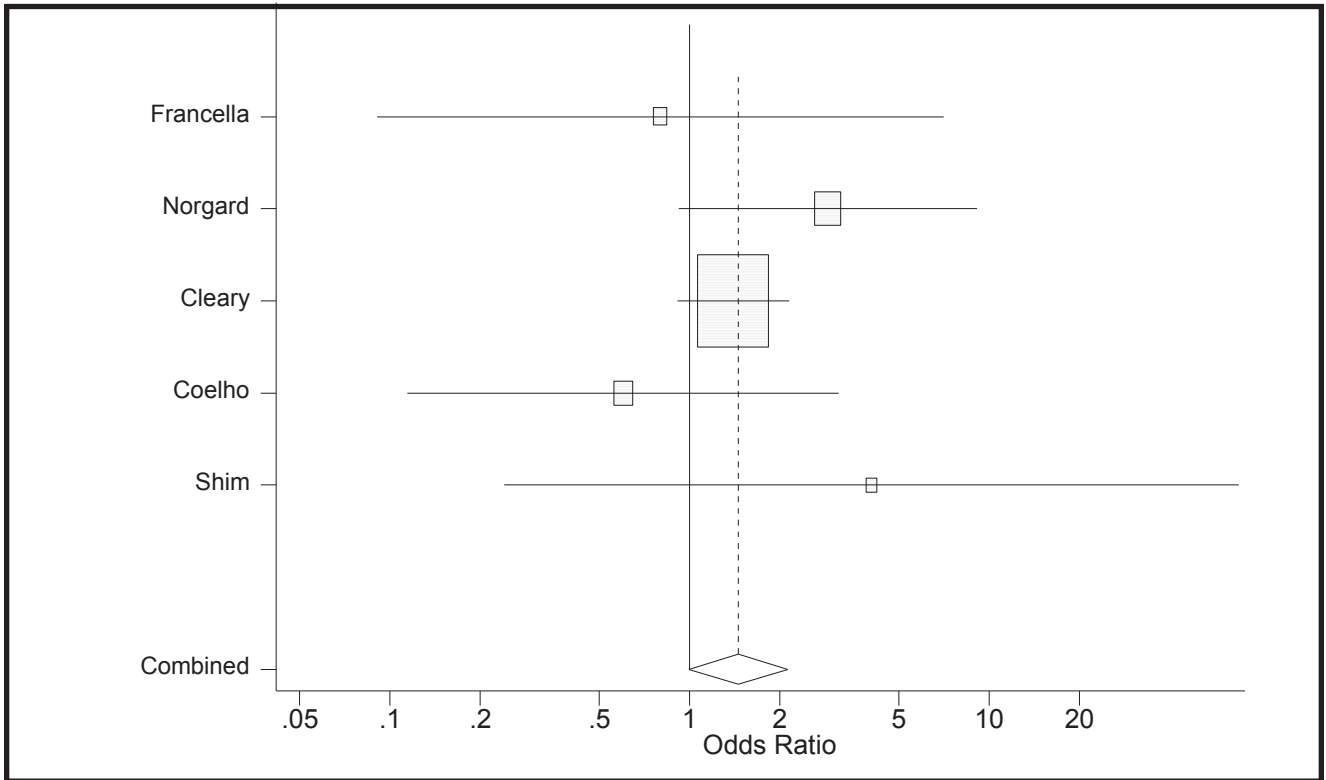


Test for heterogeneity: $Q = 3.949$, $df = 4$ (p value = 0.413), $I^2 = 0\%$

From *Inflammatory Bowel Diseases*, 2013

Figure 3. Forrest Plot for Maternal Thiopurine Use and Congenital Abnormalities*

The odds ratio, 95% confidence intervals, and pooled analysis from a random-effects model are shown.



Test for heterogeneity: $Q = 3.315$, $df = 4$ (p value = 0.506), $I^2 = 0\%$

From *Inflammatory Bowel Diseases*, 2013

Women with IBD, Pregnancy, and Thiopurines

Before counseling IBD patients on AZA or 6-MP use prior to conception and during pregnancy, it is important to review the literature on thiopurines in pregnant women with IBD. The placenta acts as a relative barrier to the metabolites of AZA, 6-thioguaninenucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP). The level of 6-TGN from newborns with intrauterine exposure to thiopurines has been reported to be less than that detected of the mothers with IBD.^{34, 35} Little to no 6-MMP has been detected in infants born to mothers receiving thiopurines during pregnancy.^{34, 35} In a study of 41 female patients with IBD, maternal level of 6-TGN and 6-MMP were similar between mothers with full term pregnancies and spontaneous abortions. Similarly, levels of 6-TGN were not different for mothers with full term pregnancies (106 pmol/8x10⁸ RBCs) and first trimester miscarriages (96 pmol/8x10⁸ RBCs). Levels of 6-MMP levels were greater in women with full term pregnancies (2140 pmol/8x10⁸ RBCs) compared to first trimester miscarriages (340 pmol/8x10⁸ RBCs). The authors of this study concluded that miscarriages and

spontaneous abortions observed in their patients were not related to toxic levels of thiopurine metabolites.³⁵

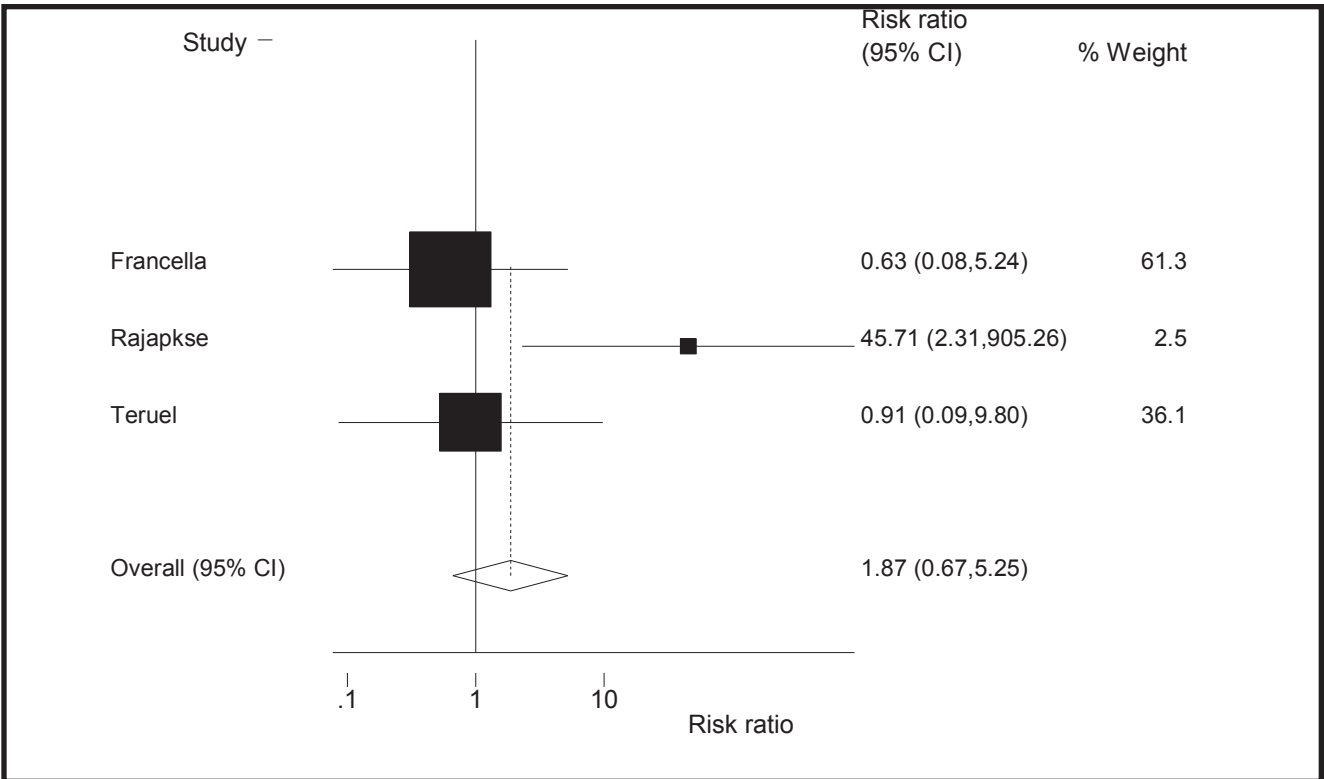
There are several observational studies that examine pregnancy outcomes specifically in women with IBD on thiopurines at conception and during pregnancy. Women exposed to AZA or 6-MP at the time of conception and/or during pregnancy did not have an increased risk of low birth weight when compared to unexposed pregnancies.³⁶⁻³⁹ However, preterm birth has been shown to be higher in thiopurine exposed pregnancies in some,^{36, 38} but not all,^{37, 39} studies. Thiopurine exposure was not associated with small for gestational age delivery.³⁶ Similarly, the risk of congenital abnormality was not significantly increased in pregnancies exposed to thiopurines.³⁶⁻³⁹ In a meta analysis, which pooled five studies of birth outcomes from women with IBD, thiopurine use was not associated with low birth weight or congenital abnormalities (figure 1-2).⁴⁰ There was an increased risk of preterm birth (OR 1.67 95% CI 1.26, 2.20, p -value <0.001) though only two of the studies adjusted for disease activity using hospitalization as a

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Figure 4. Forrest Plot for Paternal Thiopurine Use and Congenital Abnormalities*

The odds ratio, 95% confidence intervals, and pooled analysis from a random-effects model are shown.



Test of heterogeneity: χ^2 5.76, df = 2 (p-value 0.056)

From *Inflammatory Bowel Diseases*, 2013

marker (figure 3).⁴⁰ The two studies that adjusted for disease activity failed to show a significant association between thiopurine use and LBW or congenital abnormalities. One demonstrated an increased risk in preterm birth³⁸ while the second did not.³⁹ However, it is likely that mild-moderate and even some moderate-severe flares of IBD were not captured in either of these studies, as these exacerbations are often treated as an outpatient. Therefore, the use of hospitalization as a marker of active IBD likely underestimated disease activity in these studies.

Since the publication of this meta-analysis, a multicenter study from 24 Spanish hospitals assessed pregnancy outcomes, defined as Global Pregnancy Outcome (GPO), in women with IBD taking thiopurines or anti-TNF.⁴¹ GPO consisted of both pregnancy and neonatal outcomes. The rate of unfavorable GPO was lower for women treated with thiopurines compared to non-exposed IBD women (21.9% vs. 31.8% p-value 0.01). In fact, in multivariate analysis, thiopurine exposure was the only predictor of favorable GPO

(OR 0.6 95% CI 0.4, 0.9, p-value 0.02). The prevalence of congenital abnormalities in the thiopurine exposed and un-exposed groups was similar, 0.6 and 0.4% respectively. The exact mechanism of thiopurine's protective effect observed in this study is not clear. Interestingly, women taking thiopurines were more likely to have CD as well as IBD activity at conception and/or pregnancy in comparison to control women. Overall, however, 70% of active IBD females had only mild disease, and no women had severe disease. Future results from a large registry of pregnant women with IBD followed prospectively in the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) study should reveal further information on medication exposures and pregnancy and neonatal outcomes.

Given the available evidence, we advocate achieving remission prior to conception and maintaining disease inactivity throughout pregnancy. We do not recommend stopping azathioprine or 6-MP during pregnancy or

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around the time of conception in women who require this drug to maintain remission. The European Crohn's and Colitis Organization (ECCO) and American Gastroenterological Association (AGA) Institute similarly suggest that thiopurines may be continued during pregnancy.^{33, 42} Initiating azathioprine or 6-MP for the first time during pregnancy is not recommended because of the risk of bone marrow suppression and pancreatitis.⁴³

Males on Thiopurines Prior to Conception

In addition to the use of AZA and 6-MP in pregnancy, another concern has been the use of thiopurines in males attempting to conceive. There is less data available regarding the use of thiopurines and pregnancy outcomes in this situation. An early retrospective study showed that men taking 6-MP within 3 months of conception had greater complications (spontaneous abortions and congenital abnormalities) compared to men who discontinued 6-MP more than 3 months prior to conception and men who did not take 6-MP prior to conception (OR 19.6 95% CI 3.1, 122, p -value < 0.002).⁴⁴ This study, however, relied on interviews to obtain outcomes and exposure, where recall bias becomes an issue. Moreover, given the small number of pregnancies included in the two groups, the confidence interval around the risk estimate is very wide and introduces uncertainty to the exposure's effect. In another retrospective analysis that included 79 men and 76 women with IBD, 6-MP exposure was not associated with lower conception success rates (including spontaneous abortions, ectopic pregnancy, birth defect) (RR 0.85 95% CI 0.47, 1.55 p -value 0.59).⁴⁵ Major congenital abnormalities were observed from one of 37 (2.7%) pregnancies from fathers taking 6-MP at the time of conception compared to two of 73 (2.7%) pregnancies from fathers who conceived prior to treatment with 6-MP. Another multicenter study of 134 conceptions from 84 fathers with IBD, demonstrated that thiopurine use did not decrease the risk of a successful pregnancy.⁴⁶ Moreover, fertility impairment (15.2% exposed group vs. 8.3% unexposed group, p 0.596) and congenital abnormality (2.2% exposed group vs. 2.4% unexposed group, p 0.872) were similar for men taking a thiopurine compared to those not taking one. In a meta-analysis, pooling these studies, thiopurine use in males at conception was not associated with congenital abnormalities (figure 4).⁴⁰

Based on these results, it does not appear that AZA or 6-MP use around the time of conception increases the risk of congenital abnormalities and that they may be safely continued in men with IBD.

Breastfeeding and Thiopurines

There is limited data on thiopurine use and breastfeeding. Levels of 6-MMP and 6-TGN have been undetectable in infants exposed through breast milk of four mothers with wildtype TPMT genotypes⁴⁷ as well as in a single case report.⁴⁸ In another study that analyzed thirty one breast milk samples from ten women taking azathioprine, low concentrations of 6-MP was detected in only two milk samples from one woman and 6-MMP and 6-TGN were undetectable in neonatal blood. Only one infant had a borderline low neutrophil count and there were no signs of immunosuppression in any of the neonates.⁴⁹ Results from another study that included eight women with IBD breastfeeding while on AZA (at daily doses of 0.75-2mg/kg), demonstrated that concentrations of 6-MP in breast milk displayed wide variability and peaked within the first 4 hours after drug intake.⁵⁰ The maximum exposure of the drug to the infant was estimated to be less than 1% of the maternal dose. Moreover, there does not appear to be an increased rate of infection or hospitalizations for offspring breastfed by mothers while on AZA therapy.⁵¹ Therefore, it appears to be acceptable to breast-feed while on AZA or 6-MP. To minimize the infant's exposure to thiopurines, we advise that patients use the breast pump 4 hours after taking thiopurine and discard this milk. We also recommend that women discuss breast-feeding with their pediatrician, and caution should be advised for breast-feeding infants with known immunocompromised states.

CONCLUSION

IBD commonly affects patients during their reproductive years, and questions regarding the safety of medications during pregnancy frequently arise. Women with IBD have an increased risk of adverse pregnancy outcomes compared to those of the general population, and active disease seems to increase these risks. Therefore we recommend achieving and maintaining remission prior to conception and throughout pregnancy. In women with IBD, thiopurines do not appear to increase the risk of low birth weight or congenital abnormalities. The potential increased risk for preterm delivery with

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maternal thiopurines exposure may be confounded by IBD disease activity and has not been reproduced in all studies. Close monitoring of women throughout pregnancy is recommended to ensure ongoing remission. Thiopurine use in men around the time of conception similarly appears safe and not associated with an increase risk of congenital abnormalities. Though the data regarding 6-MP and AZA use while breast-feeding is limited, it does appear to be acceptable. Counseling patients on the risks and benefit of thiopurine therapy before, during, and after pregnancy and individualizing treatment decisions is recommended. ■

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